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Catalytic Asymmetric Hydroalkylation of α , β -Unsaturated Amides Enabled by Regio-Reversed and Enantiodifferentiating syn-Hydronickellation

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T o improve the clinical success in drug discovery, an attractive approach is to increase $C(sp^3)$ fraction of drug candidates to avoid flat molecules.¹ Construction of the most common $C(sp^3)-C(sp^3)$ bond with stereochemical control has long been a goal in organic synthesis.² As a catalyst, low-cost nickel has many advantages, such as its easy access to diverse oxidation states and its ability to allow facile oxidative addition with alkyl electrophiles. Over the past two decades, it has emerged as a powerful catalyst in enantioselective $C(sp^3)$ cross-coupling reactions.³

Generation of alkyl organometallic reagents in situ by catalytic hydrometalation of alkenes with metal hydrides is an attractive strategy that avoids the special preparation of organometallic reagents.⁴ It also circumvents 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. Recently, nickel hydride⁵⁻⁹ has proved to be an efficient catalyst for enantioselective reductive hydrofunctionalization,⁸ especially in hydroalkylation reactions (Figure 1a). In this process, chiral induction could occur in one of two possible steps: (i) enantioconvergent alkylation with racemic 2° or 3° alkyl halide to form enantioenriched Ni(III) intermediates, constructing stereocenter at the carbon originating from racemic electrophile;^{8a-d} or (ii) enantioselective synhydrometalation of NiH with an alkene to form enantioenriched alkylnickel species, constructing a stereocenter at the carbon originating from achiral olefin.^{8e-p}

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 limited the subsequent functionalization to the α -position (Figure 1b, left).^{10,11} To overcome the electronic effect and reverse the classical regioselectivity of hydrometalation, we questioned if the coordination effect of a certain metal hydride with a carbonyl group could predominate and whether the stereoselectivity could be simultaneously controlled.^{8h-o} 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-hydronickellation and then form a five-membered nickellacycle.^{8h-o} In terms of enantiomeric control, such a hydrometalation step with an appropriate chiral ligand could be enantioselective producing enantioenriched β -alkylnickel intermediates, which could undergo subsequent stereospecific cross-coupling with alkyl iodides to produce the enantioenriched β -alkylation product.¹² 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.^{8f,g,i,j,p} This is essential, because, otherwise, a loss of

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a) Previous work: enantioselective NiH-catalyzed reductive hydroalkylation



Figure 1. Enantioselective regio-reversed hydroalkylation of $\alpha_{,\beta}$ -unsaturated amides.

/o homolvsis

ΟA

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 hydrometalation step (Figure 1c).

This catalytic regio-reversed hydroalkylation was first evaluated by using α,β -unsaturated amide (1a) and 1iodohexane (2a) as model substrates (see Table 1). After examination of the reaction parameters and evaluation of different ligands, it was determined that Ni(NO₃)₂•6H₂O and the C6-substituted PyrOx ligand (L1)^{8b,13} 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 (Table 1, entry 1). Other nickel sources such as NiI₂•xH₂O led to significantly lower yields and a moderate rr (Table 1, entry 2). Screening of ligands revealed that ligands lacking the C4-methoxy substituent gave similar results (Table 1, entry 3), while a ligand with a *tert*-butyl group on its oxazoline ring shown the highest ee (Table 1, entry 3 vs entries 4 and 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 (Table 1, entry 3 vs entries 6 and 7). Evaluation of other hydride sources showed that diethoxy(methyl)silane (DEMS) and pinacolborane (HBpin) were equally effective (Table 1, entries 8 and 9). Polymethylhydrosiloxane (PMHS), which is an inexpensive, environmentally friendly, and common silicone industry byproduct was used in subsequent investigations. NaF was shown to be an unsuitable base (Table 1, entry 10) and DME was shown to be an unsuitable solvent (Table 1, entry 11). Similar

Table 1. Variation of Reaction Parameters

1a (α,β-unsa	0 + 7 mol% Ni 10.5 10.5 NHPh 2.5 eq 1.2 equiv) 2a aturated amide alkyl iodide	(NO ₃)₂ • 6H₂(mol% L1 uiv PMHS quiv KF 2 M), −10 °C i8 h	ⁿ Hex 3 β-chiral	O NHPh a amide
entry	variations from above conditions	yie l d 3a (%) ^a rr ^b	ee (%) ^c
1	None	99 (90)	>99:1	98
2	Nil ₂ ·xH ₂ O instead of Ni(NO ₃) ₂ ·6H ₂ O	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) ₂ MeSiH 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 DMA	5	>99:1	93
12	0 °C instead of -10 °C	95	>99:1	98
13	1-bromohexane instead of 2a	16	>99:1	97
14	(<i>Z</i>)-1a used	11	88:12	-56
15	5 mol% catalyst	93	>99:1	96
16	1.0 equiv H ₂ O added	93	>99:1	97
17	under air in a closed vial	80	>99:1	98
Ph Ph	OMe Ph N PyrOx (S)-L1 Ph Ph Ph Ph N L2: R = 'Bu L3: R = 'Pr L4: R = Ph L4: R = Ph L4: R = Ph		5: R = Me 5: R = H	O //Bu

^{*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*}Regioisomeric ratio represents 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. ND = not determined. PMHS, polymethylhydrosiloxane; DMA, *N*,*N*-dimethylacetamide; DME, dimethoxyethane.

results were obtained when the reaction was conducted at 0 °C (Table 1, entry 12). An alkyl bromide was less reactive when 1bromohexane was used (Table 1, entry 13). The *E*,*Z*configuration of the α , β -unsaturated amide governs the stereochemistry of the product. When (*Z*)-1a was used, the opposite enantiomer was obtained, albeit in significantly lower yield and with only moderate ee (Table 1, entry 14). A slightly diminished yield was obtained when the catalyst loading was reduced to 5 mol % (Table 1, entry 15), and the reaction was found to be not highly sensitive to small amounts of water and air (Table 1, entries 16 and 17).

With these optimal conditions in hand, we examined the scope of the alkyl iodide reaction partner. As shown in Table 2, both primary (2a-2d') and secondary (2e'-2i') 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, 2w), a phosphonate (2i), ethers (2j-2l, 2z, 2b', 2f'), an acetal (2m), a N-Boc carbamate (2n), and a phthaloyl imide (2o) tolerated, but a trisubstituted alkene (2c') and easily reduced ketones (2p, 2x) remained intact. Notably, the reaction is orthogonal to alkyl chlorides (2g) and aryl chlorides (2u), providing coupling handles that can be used for further derivatization. Various medicinally relevant heterocycles including furan (2v), thiophene (2w), pyrrole (2x), indole (2y), pyridine (2z), pyrazole (2a'), and benzothiazole (2b') were also found to be







compatible. However, for unsymmetrical racemic secondary alkyl iodide substrate (2i'), the stereocenter at the carbon originating from this alkyl electrophile could not be well-controlled in this protocol.

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 the case of the β -aryl acrylamide (1i), 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 synhydronickellation is the enantio-determining step. β , β -Disubstituted $\alpha_{i}\beta$ -unsaturated amide produced no desired product under the current reaction conditions. 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. $\alpha_{,\beta}$ -Unsaturated amides 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).

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). As illustrated in Scheme 1b, the obtained enantiopure β -substituted amides could be transformed to versatile enantioenriched motifs including an amine (5), a primary amide (6), an ester (7), or a ketone (8). To shed light on the hydrometalation process, an isotope labeling experiment was performed (Scheme 1c). With deuteropinacolborane as a hydride source, the desired deuteroalkylation product (3a-D) was obtained as only one diastereoisomer,¹⁴ together with the partial hydroalkylation product (3a), indicating the amide-directed regio-reversed synhydronickellation is the enantio-determining step, which is also consistent with previous reports.^{8e,h,k-n} This conclusion was also supported by the observation of diastereoisomerically pure products in the case of 4k or 4l (see Table 3). Finally, the amide directing group also plays an important role. As illustrated in Scheme 1d, α,β -unsaturated carbonyl compounds with a weak directing group such as α_{β} -unsaturated ester (4w) gave the desired β -alkylation product with poor selectivity and low yield. And a trace amount of desired product was obtained in the case of using $\alpha_{,\beta}$ -unsaturated ketone (4x) or $\alpha_{,\beta}$ -unsaturated aldehyde (4y) as a substrate.

In conclusion, we have developed an enantioselective reductive NiH-catalyzed strategy for regio-reversed hydrofunctionalization of α,β -unsaturated amides to form enantiopure β -alkylated carbonyl compounds. This reversed hydrometalation of nickel hydride 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*-hydrometalation 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

Scheme 1. Gram-Scale, Versatile Transformations, Isotopic Labelling, and Directing Group Experiments



directed toward the development of a migratory enantioselective version of this transformation are currently in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02299.

Full experimental data, details on methods and starting materials, copies of spectral data (PDF) Crystallographic data of **4c** (CIF) Crystallographic data of **4l** (CIF)

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Author Contributions

F.Z. and S.Z. designed the project. F.Z. performed the experiments. All authors cowrote the manuscript, analyzed the data, discussed the results and commented on the manuscript.

Notes

The authors declare no competing financial interest.

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