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Hydroamination

Catalyst-Controlled Regiodivergent and Enantioselective Formal Hydroamination of *N,N*-Disubstituted Acrylamides to α-Tertiary-α-Aminolactam and β-Aminoamide Derivatives

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Dedicated to Professor Guo-Qiang Lin on the occasion of his 80th birthday

Abstract: Enantioenriched α-tertiary-α-aminoacid and α-chiral-β-aminoacid derivatives play an important role in biological science and pharmaceutical chemistry. Thus, the development of methods for their synthesis is highly valuable and yet remains challenging. Herein, an unprecedented catalyst-controlled regiodivergent and enantioselective formal hydroamination of *N,N*-disubstituted acrylamides with aminating agents has been developed, accessing enantioenriched α-tertiary-α-aminolactam and α-chiral-β-aminoamide derivatives. Sterically-disfavored and electronically-disfavored enantioselective hydroamination of electron-deficient alkenes have been successfully tuned using different transition metals and chiral ligands. Notably, extremely hindered aliphatic α-tertiary-α-aminolactam derivatives were synthesized by Cu–H catalyzed asymmetric C–N bond forming with tertiary alkyl species. Enantioenriched α-chiral-β-aminoamide derivatives have been accessed by Ni–H catalyzed anti-Markovnikov-selective formal hydroaminations of alkenes. This set of reactions tolerates a wide range of functional groups to deliver diverse α-tertiary-α-aminolactam and α-chiral-β-aminoamide derivatives in good yields with high levels of enantioselectivity.

Introduction

Enantiopure unnatural α-aminoacid and β-aminoacid derivatives constitute an important class of molecules, which serve as pervasive key substructures in peptides, pharmaceuticals, agrochemicals, and biologically active natural products (Figure 1).[1] Thus, general and selective methods for their synthesis have been a long-term goal to achieve.[2] In particular, enantioenriched α-tertiary-α-aminoacids represent the most challenging ones due to their peculiar and congested stereochemistry, stimulating great effort to developing methods for their stereoselective synthesis over the past decades.[3–5] Classic methods to α-tertiary-α-aminoacids include the asymmetric addition to ketimines with carbon nucleophiles (Scheme 1a, path 1).[6] However, it remains an unmet challenge to achieve high enantioselectivity for dialkyl ketimines. Asymmetric α-carbofunctionalizations of α-aminoacids derivatives could lead to α-tertiary-α-aminoacids, which limited to Schiff-base and azalactone derivatives (Scheme 1a, path 2).[7]

Recently, Fu developed a ground-breaking work on Cu-catalyzed C–N coupling of α-tertiary α-haloamides/nitriles with anilines to afford α-tertiary-α-aminonitriles/amides in good enantioselectivities (Scheme 1a, path 3).[8] General and straightforward methods to enantioenriched α-tertiary-α-aminoacid derivatives are still challenging and highly desirable. We envisioned the possibility of the relay reaction of sterically congested α-substituted-electron deficient alkenes with metal-hydrides with aminating agents to couple the newly-formed tertiary alkyl-metal species with asymmetric C–N bond formation (Scheme 1a, path 4). Olefins play an important role in synthesizing value-added targets due to their easy accessibility and orthogonal reactivity profiles.[9,10] Buchwald and Miura developed a seminal work on Cu–H-catalyzed asymmetric hydroamination of alkenes to con-

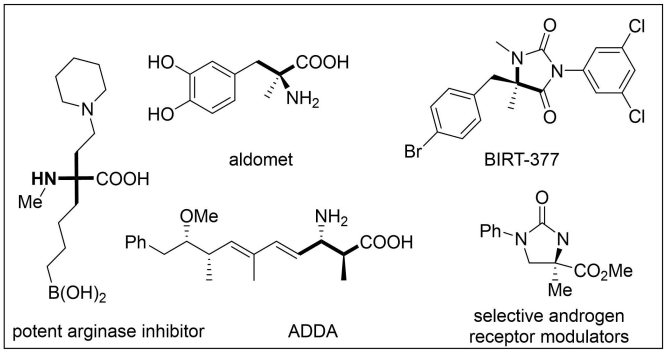

Figure 1. Selected molecules containing chiral α-tertiary-α-aminoacid, β-aminoacid derivatives.

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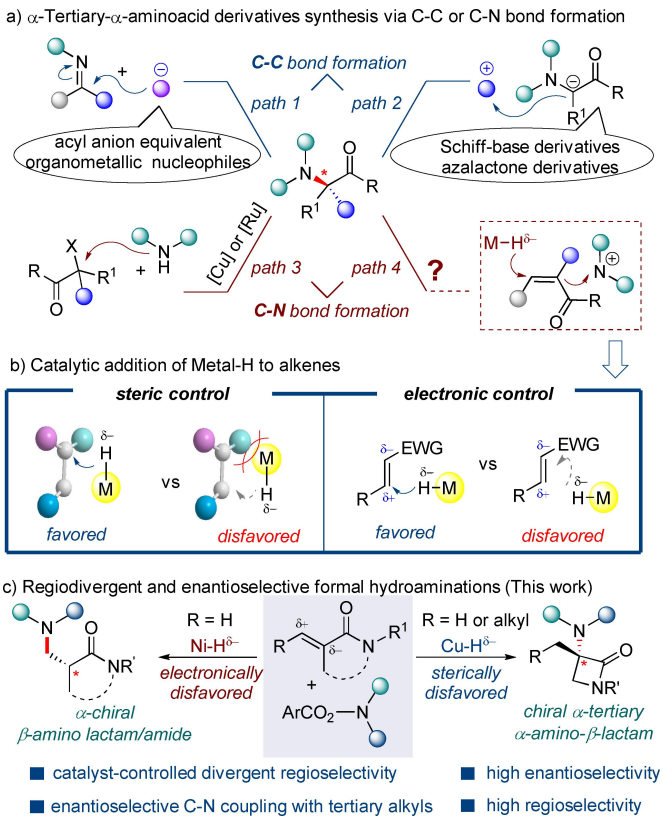


Scheme 1. Enantioselective construction of α-tertiary-α-amino and β-aminoacid derivatives.

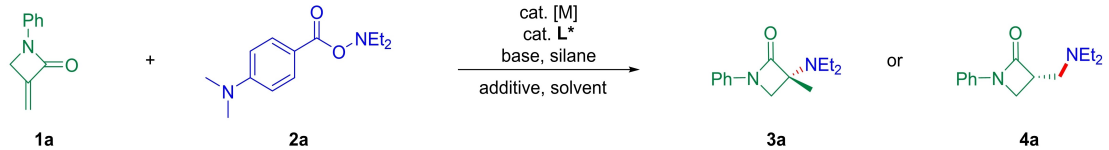
struct C–N bonds, followed by the flourish of metal-H catalyzed C–N coupling reaction.[11] However, the known protocols can only lead to C–N bond formation on primary or secondary carbons (Scheme 1b).[12] Metal-H catalyzed hydroamination of alkenes to construct C–N bond with tertiary carbon center remains unknown due to the kinetic and thermodynamic challenges as well as difficulties in regio- and enantioselectivity control (Scheme 1b). Catalytic hydrometallation of 1,1-disubstituted alkenes favors anti-Markovnikov selectivity due to the repulsion of ligated metal center with substituents on olefins (Scheme 1b, left).[11c,13,14] Thus, the pathway leading to enantioenriched α-tertiary amines is sterically disfavored. In addition, hydrometallation of unsaturated alkenes is electronically disfavored (Scheme 1b, right). To tackle these challenges, we reported a catalyst-controlled enantioselective regiodivergent formal hydroaminations of *N,N*-disubstituted acrylamides to furnish chiral α-tertiary-α-aminolactams and α-chiral-β-amino amide derivatives (Scheme 1c). The regio- and enantioselectivity is dictated by metal catalysts and ligands, allowing for the regio-switchable enantioselective formal hydroamination reaction of alkenes to undergo nontrivial sterically disfavored and electronically disfavored formal hydroamination reactions.

Results and Discussion

To test the feasibility of the reaction, we set out to identify the reaction parameters using 3-methylene-1-phenylazetidin-2-one **1a** with hydroxylamine ester **2a** as prototype substrates with a silane and base (Table 1 and Tables S1–S15). With extensive evaluation, sterically congested α-tertiary amine was not detected, proving the challenge in achieving asymmetric C–N bond-formation with tertiary carbon centers. To our surprise, desired sterically disfavored formal hydroamination product **3a** was obtained using $Cu(acac)_2$ as catalyst precursor in the presence of **L1**, albeit with very low efficiency (4% yield, Table 1, entry 1). Evaluation of ligand effect revealed **L2** gave optimal results, delivering the desired amination product **3a** in 8% yield with 83% *ee* (Table 1, entries 2–5). Other copper catalyst precursors and chiral ligand could catalyze the reaction, giving **3a** in lower yields or enantioselectivities (Tables S1 and S2). Fortunately, addition of H_2O or acetylacetone substantially increased the yields and enantioselectivity of **3a** (Table 1, entries 6 and 7). Further examination of catalyst loading and reaction time improved the yield of **3a** to 65% with 90% *ee*. We next turned to evaluate electronically disfavored asymmetric formal hydroamination of **1a** using Ni-catalysis. However, no desired product **4a** was observed under Cu-catalysis conditions (Table 1, entry 10). After preliminary evaluation, we found the use of Ph-Box ligand **L6** with nickel catalysis exclusively delivered anti-Markovnikov formal hydroamination, furnishing electronically disfavored product **4a** in 36% yield with 92% *ee* (Table 1, entry 11). Optimization of chiral ligands increased the yield of **4a** to 63% with 94% *ee* (Table 1, entries 12–14 and Table S10). Alternation of other parameters, such as silanes, bases, solvents, or additives led to inferior yields or enantiomeric excesses. (Table 1, entries 15–17, and Tables S10–15).

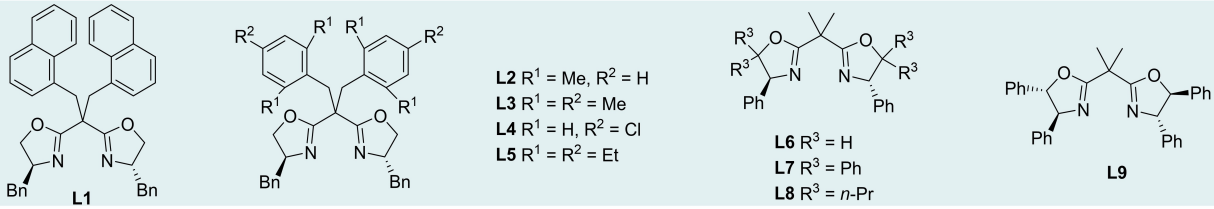
With the optimized conditions in hand, we turned to examine the scope of Cu-catalyzed sterically disfavored enantioselective formal hydroamination of β-lactams to give α-tertiary amines (Table 2). First, the scope of β-lactams was tested. To our delight, **3b** was obtained in 95% yield with 89% *ee* under standard conditions using 4-diethylaminobenzoate ester of dibenzylhydroxylamine. Moreover, N-aryl with electron-withdrawing (**3c–3e**) and electron-donating (**3f–3h**) groups were well-tolerated, producing corresponding α-tertiary-α-amino lactams in good yields (68–96% yields) with high levels of enantioselectivity (84–90% *ee*). Notably, chlorides, bromides and iodides were compatible in this copper catalytic process (**3c**, **3d** and **3e**), leaving chemical handles for further elaboration of α-tertiary-α-amino lactams. α-Methylene-β-lactam with a bulky substituent at C-4 position (**3i**) and 1,1,2-trisubstituted alkene (**3j**) were also suitable for this reaction to deliver corresponding α-tertiary-α-amino lactams in synthetic useful yields with good enantioselectivities. The absolute configuration of the α-tertiary-α-amino lactams was unambiguously confirmed by X-ray diffraction analysis of **3g**.[15] Next, the scope of aminating agents was evaluated (**3k–3ae**). Benzylhydroxylamine with primary alkyl group reacted well with **1a**,

Table 1: Evaluation of the reaction parameters for the metal-catalyzed enantioselective regiodivergent formal hydroamination.[a]



1a **2a** **3a** **4a**

entry	[M]/**L***	additive	solvent	**3a** yield (*ee*)[b]	**4a** yield (*ee*)[c]
1	[Cu]/**L1**	none	PhMe	4% (79%)	/
2	[Cu]/**L2**	none	PhMe	8% (83%)	/
3	[Cu]/**L3**	none	PhMe	8% (77%)	/
4	[Cu]/**L4**	none	PhMe	5% (54%)	/
5	[Cu]/**L5**	none	PhMe	8% (78%)	/
6	[Cu]/**L2**	H_2O (1.5 eq.)	PhMe	42% (89%)	/
7	[Cu]/**L5**	Hacac (1.5 eq.)	PhMe	45% (91%)	/
8[d]	[Cu]/**L2**	Hacac (1.5 eq.)	*o*-xylene	60% (91%)	/
9[d,e]	[Cu]/**L2**	Hacac (1.5 eq.)	*o*-xylene	65%[f] (90%)	/
10	[Ni]/**L2**	Hacac (1.5 eq.)	*o*-xylene	/	/
11	[Ni]/**L6**	*t*-BuOH (4.0 eq.)	Et_2O	/	36% (92%)
12	[Ni]/**L7**	*t*-BuOH (4.0 eq.)	Et_2O	/	40% (93%)
13	[Ni]/**L8**	*t*-BuOH (4.0 eq.)	Et_2O	/	46% (86%)
14	[Ni]/**L9**	*t*-BuOH (4.0 eq.)	Et_2O	/	63%[f] (94%)
15	[Ni]/**L9**	none	Et_2O	/	56% (94%)
16	[Ni]/**L9**	*t*-BuOH (4.0 eq.)	PhMe	/	23% (95%)
17	[Ni]/**L9**	*t*-BuOH (4.0 eq.)	DMF	/	N.D.



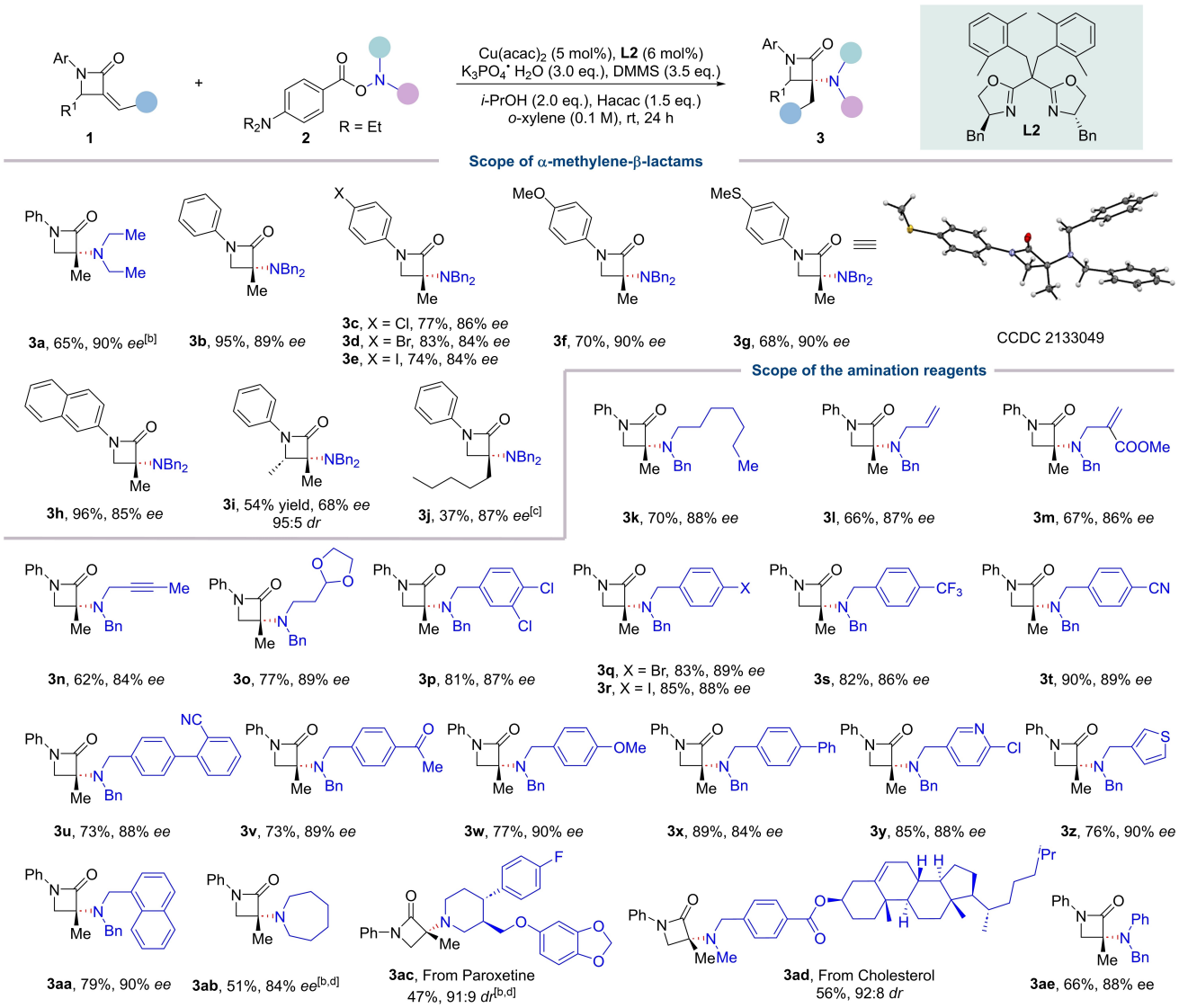
[a] Entries 1–9: The reaction was conducted using **1a** (0.10 mmol), **2a** (0.11 mmol), [Cu] (10 mol%), **L*** (12 mol%) in the presence of $K_3PO_4 \cdot H_2O$ (3.0 eq.), methyldimethoxysilane (3.5 eq.) and additive in solvent (1.0 mL) at room temperature for 12 h. Entries 10–17: The reaction was conducted using **1a** (0.15 mmol), **2a** (0.10 mmol), [Ni] (10 mol%), **L*** (12 mol%) in the presence of $NaHCO_3$ (2.0 eq.), trimethoxysilane (3.0 eq.) and additive in solvent (2.0 mL) at 40 °C for 12 h. [b] Yield was determined by ^1H NMR using CH_2Br_2 as internal standard. [c] Yield was determined by GC using *n*-dodecane as internal standard. Enantiomeric excess was determined by HPLC using a chiral stationary phase. [d] *i*-PrOH (2.0 eq.) was added. [e] $Cu(acac)_2$ (5 mol%) and ligand (6 mol%) were used and reaction time was 24 h. [f] Isolated yield. **L*** = chiral ligand. Hacac = acetylacetone. [Cu] = $Cu(acac)_2$, [Ni] = $NiBr_2 \cdot$glyme. DMF = *N,N*-dimethylformamide. N.D. = not detected.

delivering **3k** in 70% yield with 88% *ee*. Amines containing alkenes (**3l**), methacrylates (**3m**), alkynes (**3n**) and acetals (**3o**) were all good substrates for this reaction, furnishing corresponding α-tertiary-α-amino lactams in 62–77% yields with 84–89% *ee*. Moreover, benzyl groups bearing chlorides (**3p**), bromides (**3q**) and iodides (**3r**) were suitable for this reaction. Both electron-poor (**3s**–**3u**) and electron-rich (**3v**–**3x**) substituents on the benzyl of amine electrophile could be transformed to corresponding α-tertiary-α-amino lactams in 73–90% yields with 86–90% *ee*. Furthermore, heteroaromatics and fused aromatics, such as pyridines (**3y**), thiophenes (**3z**) and naphthalenes (**3aa**), were tolerated in this reaction. Cyclic aliphatic amines could be installed to α-position of α-tertiary lactams in 51% yield with 84% *ee* (**3ab**). To demonstrate the robustness and usefulness of this protocol, this protocol was applied to late-stage functionalization of natural product derivatives. Paroxetine and cholesterol derived hydroxylamine esters could be transformed to desired α-tertiary amination products (**3ac**, **3ad**) in synthetic useful yields with 91:9 and 98:2 *dr*. In addition, aryl-substituted aminating agent was also good substrate under the reaction conditions (**3ae**).

Next, the scope for Ni-catalyzed enantioselective electronically disfavored formal hydroamination of the *N,N*-acrylamides to afford β-aminolactams was examined (Table 3). Under the optimized conditions, a wide range of α-chiral-β-aminolactam derivatives were obtained by Ni-catalyzed anti-Markovnikov asymmetric formal hydroamination. Hydroxylamine esters containing long-chain alkyls (**4b**), α-branched alkyls (**4c**) and benzyls (**4d**) were all well-tolerated in the reaction. Functional groups, such as ethers, esters, nitriles, acetals, amides, allyls, chlorides were compatible under the reaction conditions, producing corresponding α-chiral-β-aminolactams (**4e**–**4l**) in moderate yields (43–66%) with 91–95% *ee*.

Amines containing indoles (**4m**), thiophenes (**4n**), piperidines (**4o**) were also tolerated, delivering the desired β-amino lactams in moderate yields with 91%–92% *ee*. The absolute configuration of the α-chiral-β-aminolactams was unambiguously confirmed by X-ray diffraction analysis of **4o**.[15] Both natural products and drug molecules derivatives

Table 2: Scope for α-tertiary-α-aminoacid derivatives via Cu-catalyzed asymmetric formal hydroamination of β-lactams.[a]

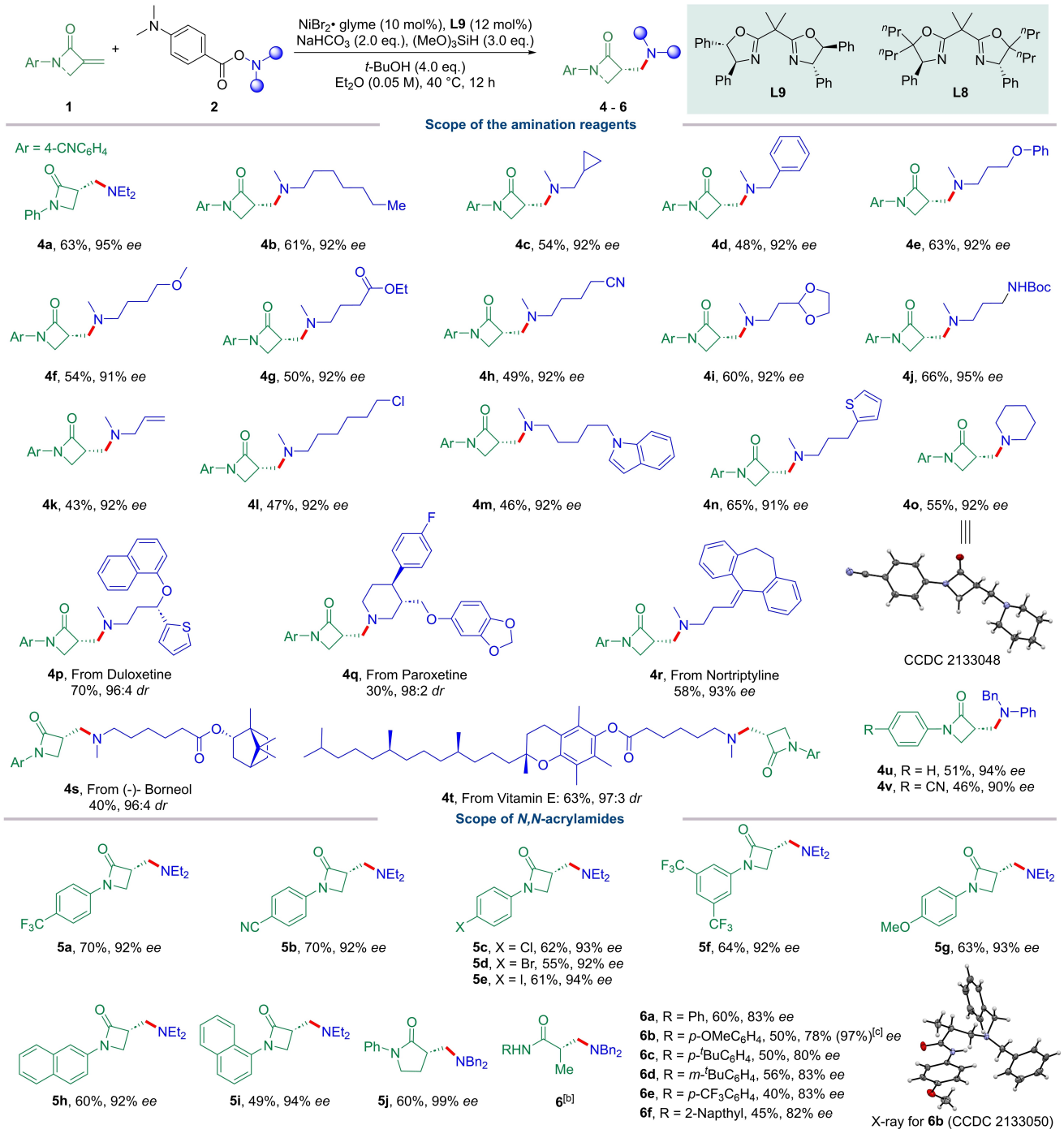


[a] The reaction was conducted using **1** (0.20 mmol), **2** (0.22 mmol), $Cu(acac)_2$ (5 mol%), **L2** (6 mol%) in the presence of $K_3PO_4 \cdot H_2O$ (3.0 eq.), methyldimethoxysilane (3.5 eq.), *i*-PrOH (2.0 eq.) and Hacac (1.5 eq.) in *o*-xylene (2.0 mL) at room temperature for 24 h. [b] R = Me. [c] **2** (1.5 eq.), $Cu(acac)_2$ (10 mol%), **L2** (12 mol%) and DMMS (5.0 eq.) was used, react for 40 h. [d] Hacac (0.5 eq.) was used.

were successfully applied to the reaction conditions (**4p**–**4t**). Amination agents derived from Duloxetine and Paroxetine were successfully transformed to the desired products (**4p** and **4q**) in moderate yields with 96:4 and 98:2 *dr*. Nortriptyline derivative could be tolerated to give corresponding chiral amine **4r** in 58% yield with 93% *ee*. (−)-Borneol and Vitamin E could be converted to corresponding β-amino lactam products in 40% and 63% yields with 96:4 and 97:3 *dr* (**4s** and **4t**). Aryl-substituted aminating agent also could be tolerated, delivering **4u** and **4v** in synthetic useful yields with excellent enantioselectivities.

In addition, the scope of *N*-aryl protected α-methylene-β-lactams (**5a**–**5i**) with different substitution patterns was evaluated under Ni-catalyzed conditions. *N*-Aryl with trifluoromethyls, nitriles and halides were tolerated, delivering corresponding α-chiral-β-aminolactam derivatives in 49–70% yields with 92–95% *ee*. In addition, α-methylene-γ-lactam was successfully transformed to the desired product **5j** in 60% yield with 99% *ee*. Furthermore, acyclic *N*-aryl-methacrylamides with *meta*- and *para*-substituents were also good substrates, delivering corresponding α-chiral-β-amino-lactam by Ni-catalyzed enantioselective electronically reversed formal hydroamination in moderate yields and good enantioselectivities (**6a**–**6f**). The absolute configuration of the **6a**–**6f** was unambiguously confirmed by X-ray diffraction analysis of **6b**.[15] To further demonstrate the potential of this enantioselective regiodivergent formal hydroaminations of *N,N*-acrylamides, Cu-catalyzed sterically disfavored and Ni-catalyzed electronically reversed formal hydroamination were both conducted on gram scale, leading to the formation of α-tertiary-α-amino lactam **3b** (1.67 g, 94% yield, 89% *ee*) and α-chiral-β-aminolactam **5b** (0.61 g, 72%

Table 3: Scope for β-chiral amines synthesis via Ni-catalyzed asymmetric formal hydroamination of *N,N*-acrylamides.[a]



[a] The reaction was conducted using **1** (0.30 mmol), **2** (0.20 mmol), $NiBr_2$·glyme (10 mol%), **L9** (12 mol%) in the presence of $NaHCO_3$ (2.0 eq.), Trimethoxysilane (3.0 eq.) and ^{t}BuOH (4.0 eq.) in Et_2O (4.0 mL) at 40 °C for 12 h. [b] **L8** was used instead of **L9** with addition of NMP (10.0 eq.). [c] Enantiomeric excess after recrystallization. NMP = *N*-methyl-2-pyrrolidone.

yield, 92 % *ee*) without erasing the yield or enantioselectivity (Figure 2a). Notably, α-tertiary-α-amino lactams serve as useful precursors for a wide range of chiral α-tertiary-α-amino compounds (Figure 2b). Enantioenriched α-amino-esters (**7**), α-aminoketones (**8**), and α-aminoacids (**9**) with a chiral α-tertiary center could be easily accessed in good yields (88 %-90 %) without racemization by simple transformations. Further transformation of **7** afforded **10** in 80 % yield for formal synthesis of **11** (Figure 2c), which can be used in the treatment of disorders and conditions modulated by the androgen receptor.[1e] Next, we carried out the reaction using deuterated silane (Ph_2SiD_2) under otherwise identical to standard conditions to shed light on the reaction process (Figure 2d). The Cu-catalyzed formal hydroamina-

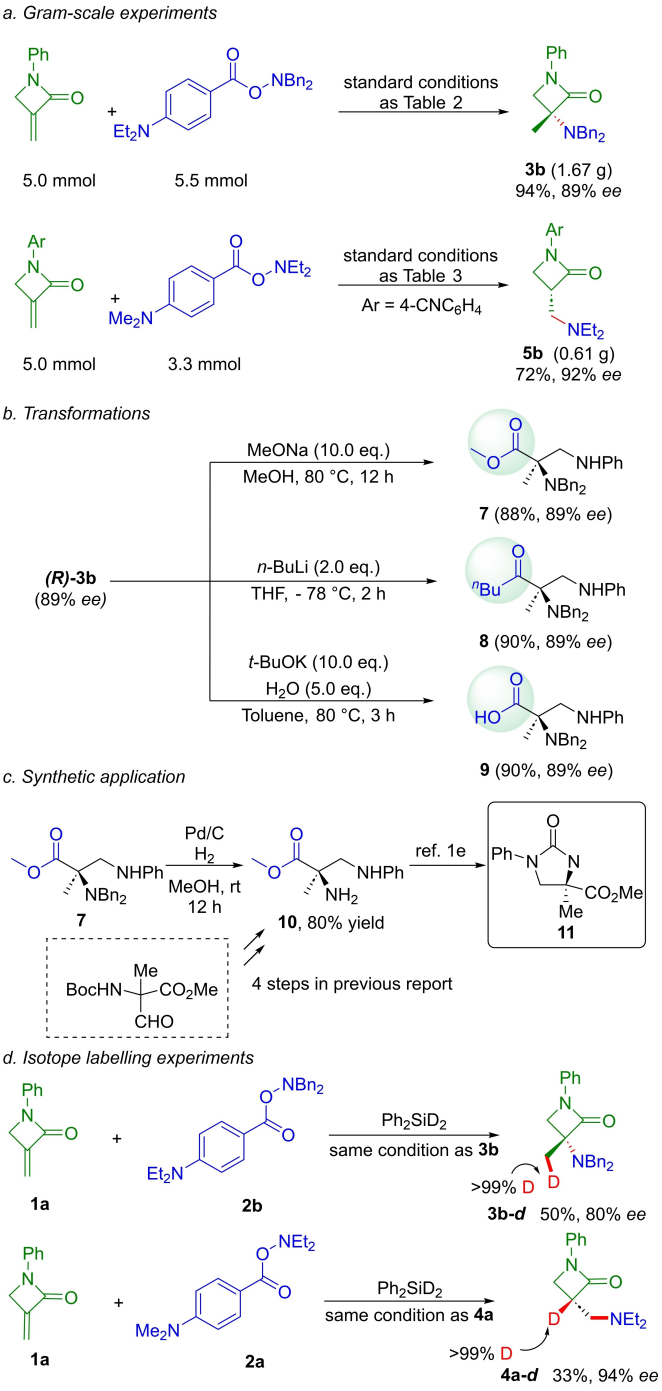


Figure 2. Synthetic applications and mechanistic studies.

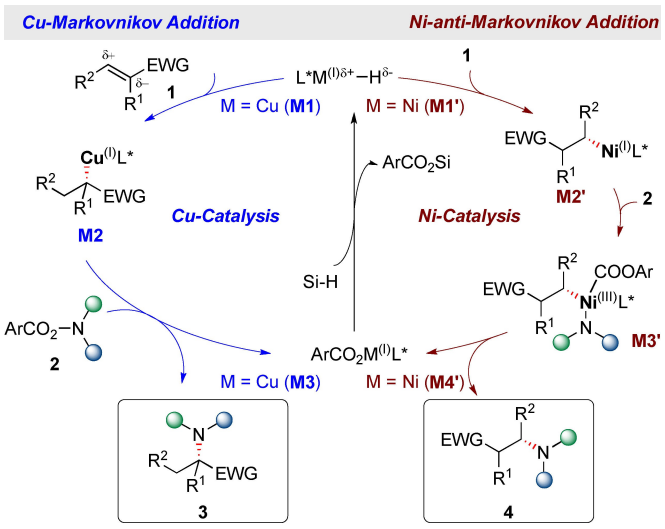


Figure 3. Proposed mechanism.

position to amide of **4a–d**, which is non- conclusive due to the formation of a α-tertiary alkyl-Ni species by hydrometallation.

Based on the mechanistic results and literature precedents,[11,12a,b,e–g] two tentative mechanistic pathways for Ni- and Cu-catalyzed reactions were proposed and depicted in Figure 3. In the case of Cu-catalyzed reactions (Figure 3, left), the **L***Cu–H catalyst **M1** generated in situ from Cu salt, chiral ligand, and silane underwent enantioselective hydrometallation with *N,N*-acrylamide **1** to generate alkyl copper intermediate **M2** with high Markovnikov regioselectivity. Interception of **M2** by amine electrophile **2** generated chiral amine **3** and copper(I) complex **M3**. Regeneration of **L***CuH from **M3** closed the catalytic cycle. In Ni-catalyzed reaction (Figure 3, right), nickel hydride species **M1′** generated from ligated Ni^{I} precursor in the presence of a silane and a base coordinate with *N,N*-acrylamide **1** and then underwent anti-Markovnikov hydrometallation to generate alkyl nickel intermediate **M2′**. **M2′** could oxidize an amine electrophile **2** to form Ni^{III} intermediate **M3′**, which could undergo reductive elimination to give the final product **4** and Ni^{I} complex **M4′**. Finally, regeneration of **L***NiH from **M4′** closed the catalytic cycle.

Conclusion

In summary, catalyst-controlled regiodivergent and enantioselective formal hydroaminations of *N,N*-acrylamides have been achieved to deliver enantioenriched α-tertiary-α-aminolactam and β-aminoamide derivatives in good yields and excellent levels of enantioselectivity. Notably, both sterically-disfavored and electronically-disfavored formal hydroaminations have been realized by catalyst regulation. In addition, sterically congested enantioenriched α-tertiary aliphatic amines have been obtained by formal hydroamination via C–N bond-forming from alkenes, opening the

tion reaction in the presence of Ph_2SiD_2 afforded deuterated product **3b–d** in 50 % yield with 80 % *ee*. Only one deuterium incorporation (>99 % D) was exclusively delivered to β- position of amide of **3b–d**. No H/D exchange was observed at the α-position to amide of **3b–d**. These results indicated that Cu–H insertion onto β-lactam **1a** to form alkyl-Cu species might be irreversible and enantio-determining with exclusive regioselectivity. In contrast, Ni-catalyzed formal hydroamination conditions gave **4a–d** in 33 % yield with 93 % *ee*. Deuterium was solely occurred at the α-

avenue for metal-catalyzed C–N bond construction to access α-tertiary chiral amines.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Acrylamides · Chiral Aminoacids · Hydroamination · Lactams · Regiodivergent

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