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Cobalt-Catalyzed Enantioselective Reductive α-Chloro-Carbonyl Addition of Ketimine to Construct the β-Tertiary Amino Acid Analogues

Tingting Xia,[a] Wenwen Wu,[a] Xianqing Wu,[a]* Jingping Qu,[a] and Yifeng Chen*[a][b]

[a] T. Xia, W. Wu, Dr. X. Wu, Prof. Dr. J. Qu, Prof. Dr. Y. Chen
Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, Frontiers Science Center for Materiobiology and Dynamic Chemistry, School of Chemistry and Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai, 200237, China.

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P R China.
E-mail: xianqingwu@ecust.edu.cn; yifengchen@ecust.edu.cn

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Abstract: β-Tertiary amino acid derivatives constitute one of the most frequently occurring units in natural products and bioactive molecules. However, the efficient asymmetric synthesis of this motif still remains a significant challenge. Herein, we disclose a cobalt-catalyzed enantioselective reductive addition reaction of ketimine using α-chloro carbonyl compound as a radical precursor, providing expedient access to a diverse array of enantioenriched β-quaternary amino acid analogues. This protocol exhibits outstanding enantioselectivity and broad substrate scope with excellent functional group tolerance. Preliminary mechanism studies rule out the possibility of Reformatsky-type addition and confirm the involvement of radical species in stereoselective addition process. The synthetic utility has been demonstrated through the rapid assembly of iterative amino acid units and oligopeptide, showcasing its versatile platform for late-stage modification of drug candidates.

Chiral β-amino acid is widely found in numerous natural products, pharmaceuticals and bioactive molecules.[1] As a consequence, significant endeavors have been dedicated to the pursuit of asymmetric construction of these motifs.[2] In particular, synthetic methods targeting chiral β-secondary amino acid scaffolds are extensively explored, such as the century-old catalytic asymmetric Mannich reaction of aldimines,[3] as well as asymmetric reduction of enamines.[4] In striking contrast, strategies for the manufacture of sterically encumbered β-tertiary amino acids with structural diversity remain scarce, yet highly desirable for advancing the new drug development. Enantioselective addition of α-carbonyl carbanion or radical to ketimine is a straightforward and appealing approach for assembling this structure framework (Scheme 1a). However, the less acidic α-C−H site of ester or amide functionality largely suppressed the development of asymmetric Mannich reaction of ketimine. Kanai and Shibasaki seminally presented the only case of copper-catalyzed asymmetric nucleophilic addition of ketimines with preformed silyl ketene acetal species at 2007, delivering the β-amino ester in high enantioselectivities.[5a] Therefore, the utilization of versatile α-carbonyl electrophiles for the radical addition to ketimines offers an advantageous strategy to tackle this longstanding synthetic challenges, thus providing an opportunity for synthesizing various β-amino carbonyl skeletons.[6-9]

The utilization of readily accessible α-halo carbonyl compounds in transition metal-catalyzed asymmetric reductive addition to the carbon-heteroatom double bonds still poses a formidable challenge. This is mainly attributed to the intrinsic

(a) Chiral β-tertiary amino ester synthesis enabled by the stereoselective addition

(Kanai, Shibasaki, 2007)

β-amino esters

highly active short-lived

unexploited
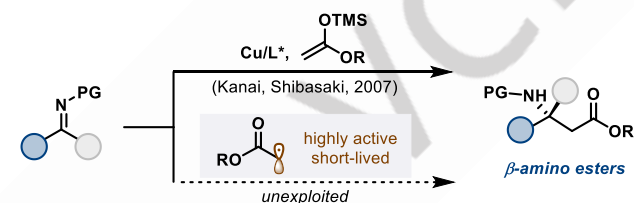
(b) Enzyme-catalyzed intramolecular asymmetric reductive addition of ketimine with α-chloro amide (Hyster, 2021)

'Ene'-Reductase
cyan light
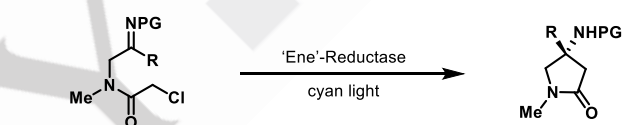
(c) Cobalt-catalyzed intermolecular asymmetric reductive addition of ketimine with unactivated alkyl halides (previous work)

reductant
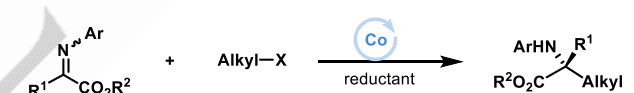
(d) Cobalt-catalyzed intermolecular asymmetric reductive addition of ketimine with the reactive α-chloro carbonyl compound (This work)

R = NR₂, OR, C

reductant

up to 92% yield
up to 98% ee
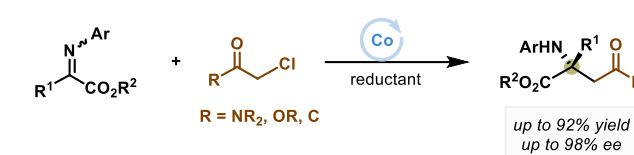
● transition metal-catalyzed stereoselective addition of α-carbonyl radical
● convenient synthesis of enantioenriched tertiary β-amino acid analogues
● excellent enantioselectivity with broad substrate scope under mild condition

Scheme 1. Enantioselective reductive addition of α-carbonyl radical with ketimine.

high reactivity and short lifetime of α-carbonyl radicals, thus resulting in the difficulties of realizing the precise control over the stereoselectivity and the reactivity, such as dehalogenative side reaction pathway.[10] Recent studies have witnessed impressive advancements in asymmetric enzymatic catalysis, which offers a complementary arsenal of small organic molecular synthesis.[11-14] Particularly, Hyster and coworkers have elegantly reported a photoenzyme-catalyzed intramolecular cyclization of α-chloroamide bearing an imine moiety, affording valuable and diverse chiral lactam fragments in good yields and enantioselectivity (Scheme 1b).[12] We recently reported the cobalt-catalyzed asymmetric aza-Barbier reaction of α-imino

COMMUNICATION

ester and the unactivated organoelectrophiles to construct the α-tertrasubstituted amino ester in presence of stochiometric amount of metal as terminal reductant. (Scheme 1c).[15] The utilization of chiral NPN ligand enabled the high enantioselectivity. Particularly, the reaction of unactivated alkyl halides allows for the selective formation of alkyl radical intermediate to participate the stereoselective addition process.[15a] Intriguingly, we are wondering if this asymmetric reductive addition process could be suitable for the more reactive α-halo carbonyl compounds, as the highly reactive α-halo carbonyls could easily generate the nucleophilic Reformatsky reagent in the presence of a metal reductant, which often proceeds the classic Reformatsky-type background reaction with ketimine, thus inevitably diminishing the enantioselectivities in the realm of stereoselective addition process.[16] We envision that the leverage of α-halocarbonyl compounds with moderate activity might circumvent the formation of Reformatsky reagent to generate an α-carbonyl radical, and allow the subsequent engagement of the radical species in the addition process towards C=N bond[17] The cobalt-catalyzed reductive cross-coupling reactions between electrophiles have received growing interest as a valuable synthetic tool for the facile construction of C-C bonds.[18-26] In addition to our work,[15] Xiao and coworkers accomplished the cobalt/photo-cocatalyzed asymmetric reductive Grignard-type addition of aldehydes with aryl iodides to construct various chiral benzyl alcohols.[23a] Very recently, Shi and coworkers uniquely disclosed a Co-catalyzed enantioselective reductive arylation of cyclic N-sulfonyl aldimine to furnish diarylmethylamines derivatives.[24a] Based on our continuous interest in catalytic asymmetric reductive transformations,[15, 27] herein, we set a protocol for cobalt-catalyzed enantioselective reductive addition of ketimine with reactive α-chloro carbonyl compound, to afford the β-tertiary amino acid derivatives with excellent yields and broad functional group tolerance (Scheme 1d).

At the outset of our investigation, we selected ketimine **1a** as the prototype substrate with α-chloro amide **2a** as the radical precursor to test the feasibility of asymmetric reductive addition. The desired product **3a** could be obtained in 28% yield with 63% ee by the utilization of CoI$_2$ and NPN ligand **L1** as a catalyst,[28] Mn as a reductant and EtOH as an additive in MeCN at 35°C (Table 1, entry 1). To our delight, the yield and enantioselectivity could be dramatically improved (52%, 90% ee) when Zn powder was utilized as the terminal reductant (Table 1, entry 2). The screening of the chiral ligands was subsequently executed under the aforementioned conditions. Changing the *tert*-butyl group on the chiral oxazoline moiety to less bulky substituents such as cyclohexyl (**L2**) and *sec*-butyl (**L3**) groups could increase both the reaction yield (61–62%) and the enantioselectivity (95–96%) (Table 1, entries 3–4). Notably, the employment of the *iso*-butyl-substituted NPN ligand **L4** further improved the enantioselectivity to 98% ee with 62% yield (Table 1, entry 5), whereas the benzyl-substituted NPN ligand **L5** delivered the desired product **3a** in lower 92% ee (Table 1, entry 6). Screening the amount of LiI revealed that the addition of 20 mol% of LiI could improve the reaction yield to 71% without any erosion of the optical activity (Table 1, entries 7-9). Eventually the α-tertiary amino acid derivative **3a** was obtained in 80% isolated yield with 98% ee (Table 1, entry 10) by using MeCN/DMA (9/1) as a mixed solvent. Both lowering and raising the reaction temperature would be

harmful to the reaction efficiency (Table 1, entries 11-12). The reaction failed to deliver the target product when one equivalent of H$_2$O was added (Table 1, entry 13).

Table 1. Optimization of the reaction conditions.[a]
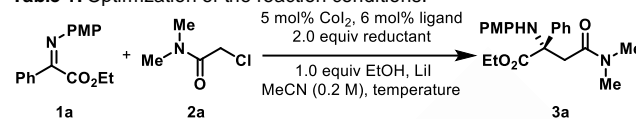
| entry	ligand	reductant	T (°C)	LiI	yield (%)[b]	ee (%)[c]
1	**L1**	Mn	35	--	28	63
2	**L1**	Zn	35	--	52	90
3	**L2**	Zn	35	--	61	95
4	**L3**	Zn	35	--	62	96
5	**L4**	Zn	35	--	62	98
6	**L5**	Zn	35	--	60	92
7	**L4**	Zn	35	10 mol%	67	98
8	**L4**	Zn	35	20 mol%	71	98
9	**L4**	Zn	35	50 mol%	71	97
10[d]	**L4**	Zn	35	20 mol%	80 (80)[e]	98
11[d]	**L4**	Zn	25	20 mol%	70	98
12[d]	**L4**	Zn	50	20 mol%	65	97
13[d, f]	**L4**	Zn	35	20 mol%	0	--
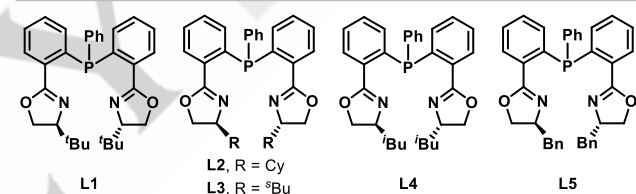
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv, 0.15 mmol), CoI$_2$ (5 mol%, 0.005 mmol), **L1** (6 mol%, 0.006 mmol), reductant (2.0 equiv, 0.2 mmol), EtOH (1.0 equiv, 0.1 mmol), MeCN (0.2 M, 0.5 mL), stirred at 35 °C for 18 h. [b] The yields were determined by ¹H NMR using mesitylene as an internal standard. [c] The ee values were determined by chiral HPLC analysis. [d] MeCN/DMA = 9/1. [e] isolated yield in parentheses on 0.2 mmol scale. [f] add 1.0 equiv H$_2$O. PMP = 4-methoxyphenyl.

With the optimized conditions in hand, we investigated the substrate scope of this cobalt-catalyzed enantioselective reductive radical addition to ketimine with α-chloro carbonyl compounds (Scheme 2). The reaction efficiency varied with different ester groups including methyl (**3b**), ethyl (**3a**) and isopropyl (**3c**) on imine substrate, giving the corresponding products in 72–90% yields with excellent 98% ees. Evaluation of substitution pattern of the aromatic ring on the nitrogen atom moiety revealed that both steric hindrance (**3d**) and electronic effect (**3e**) would not affect the enantioselectivity, although the inclusion of a methyl group at the *ortho*-position caused a slightly lower yield. Furthermore, we also explored the generality of the other functionalities on the aromatic ring adjacent to the carbonyl carbon of the ketimine. Encouragingly, the electron-donating group (-OMe) and electron-withdrawing halogen atom (-Cl) were successfully integrated into the substrate, leading to the corresponding products in moderate to good yields with excellent enantioselectivities (**3f**–**3g**). Moreover, heteroaryl substituents such as indolyl proved to be a compatible substrate, delivering the corresponding product **3h** in 65% yield with 98% ee. It should

COMMUNICATION

be noted that the methyl-substituted ketimine could also be a successful example, providing product **3i** with good optical activity, albeit in a moderate yield. The trifluoromethyl-substituted ketimine substrate was also compatible with this protocol, affording the β-amino acid derivative **3j** bearing a tetrasubstituted stereocenter with CF₃ group in 61% yield with 97% ee. Next, we focused on exploring the applicability of α-chloro carbonyl electrophiles. A diverse range of α-chloro-*N,N*-disubstituted amides could be applicable in this reaction with the standard conditions, including *N,N*-diisopropyl (**3k**), *N,N*-diphenyl (**3l**), *N*-aryl-*N*-alkyl with functionalities such as CN (**3m**) and CO₂Et (**3n**), as well as Weinreb amides (**3o**), providing the corresponding products in moderate to good yields with excellent enantioselectivity. The absolute configuration of **3k** was

assigned as *S* configuration, unambiguously confirmed by X-ray diffraction. Tertiary amides bearing pyrrolidine (**3p**) and morpholine (**3q**) moieties were satisfactorily tolerated in this reaction and furnished products **3p** and **3q** in 85–92% yields with 98% ee. Moreover, a secondary amide (**3r**) with a bulky adamantyl group was also a suitable substrate for this transformation. Significantly, this methodology demonstrated versatility in accommodating α-electron-withdrawing group substituted alkyl electrophiles, such as α-chloroalkyl ester (**3s–3t**), α-chloroalkyl ketone (**3u**), α-chloroalkyl sulfamide (**3v**), as reductive addition fragments. These reactions yielded the corresponding β-carbonyl α-amino ester products with exceptional enantioselectivity.
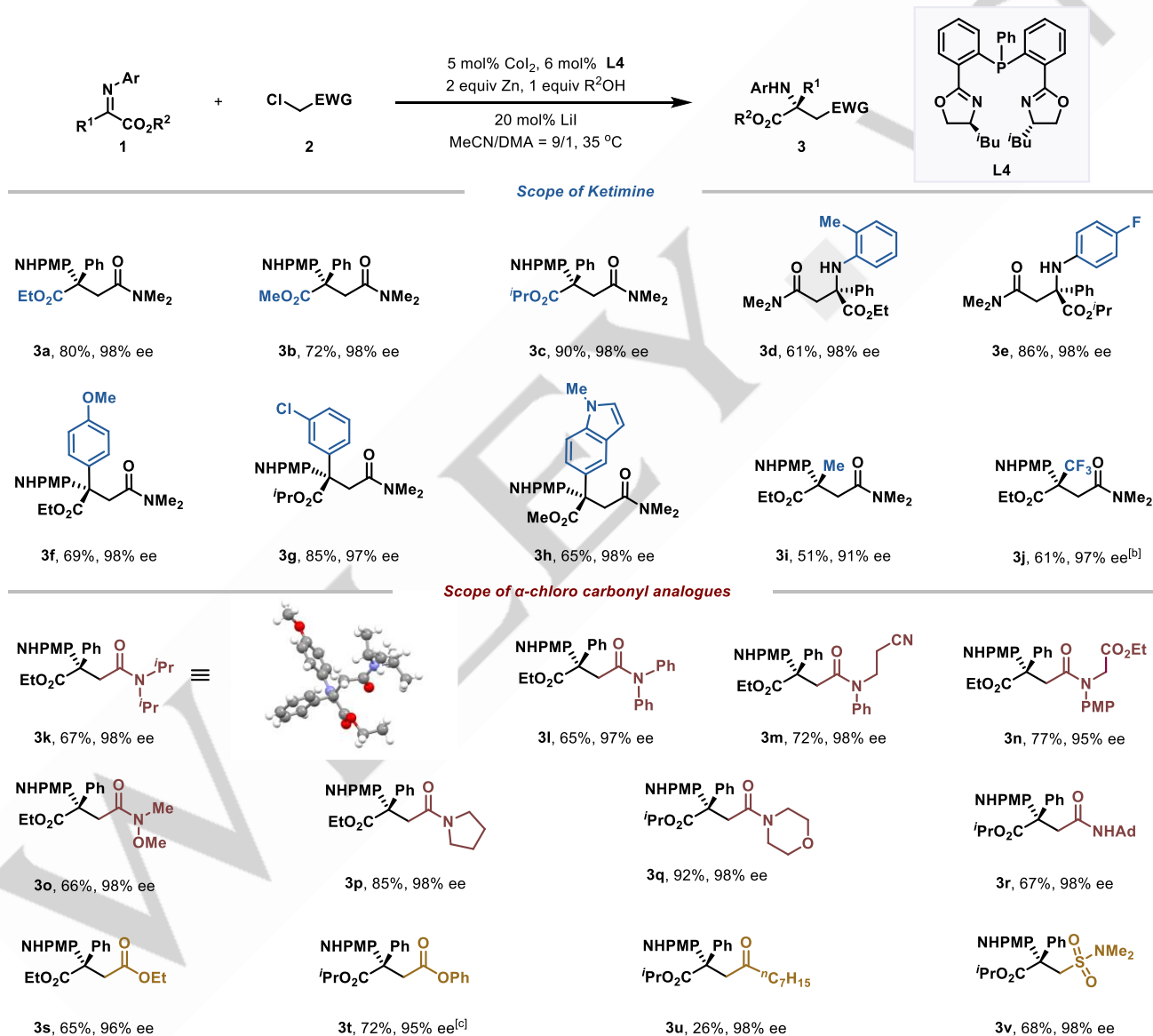
Scheme 2. Substrate scope of Co-catalyzed enantioselective reductive addition of ketimine with α-chloro carbonyl compounds.[a]

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.5 equiv), CoI₂ (5 mol%), **L4** (6 mol%), Zn (2.0 equiv), R²OH (1.0 equiv), LiI (20 mol%), MeCN/DMA (9/1, 0.2 M), 35 °C, isolated yields are shown after column chromatography. [b] CoI₂ (10 mol%), **L4** (12 mol%), Mn (2.0 equiv), EtOH (1.0 equiv), MeCN (0.2 M), 50 °C. [c] Without LiI. Ad = adamantyl.

Based on the promising results discussed above, we envisioned to realize the oligomerization of different α-amino

acid units, thus offering convenient access to some biologically active small molecules (Scheme 3). By subjecting α-chloroamide

3

COMMUNICATION

derived from methyl *L*-prolinate to the standard conditions, we successfully obtained product **4** featuring both α-tertiary and secondary amino ester units in 83% yield with 99:1 dr. Additionally, the utilization of α-chloro amide containing the methyl *L*-prolyl-*L*-leucinate moiety as an electrophile also yielded the corresponding product **5**, incorporating three α-amino ester units with promising diastereoselectivity and a moderate yield. Besides, when we employed α-chloroamide **2p** derived from the product **3p** as an addition partner, reaction with ketimine **1k** under the standard conditions also worked successfully to give a product **6** in moderate yield with>20:1 dr, which could not only realize the synthesis of iterative α-amino acid units, but also

provide a rapid approach to achieve the prolongation of peptide chain. Removal of p-methoxyphenyl group of **6** by using CAN provided product **7** in 91% yield. We also employed unnatural α-tertrasubstituted amino ester **8** as the starting material. Remarkably, through the derivatization to α-chloroamide followed by asymmetric reductive addition with ketimine **1c** under this Co/NPN-catalyzed protocol, products **9** and **10** could be stereodivergently synthesized in good yield with excellent diastereoselectivity by the switching the absolute configuration of chiral ligand **L4**. These results collectively showcase the advantage over the classic nucleophilic addition under basic conditions, thus allowing the tolerance of peptide functionality.
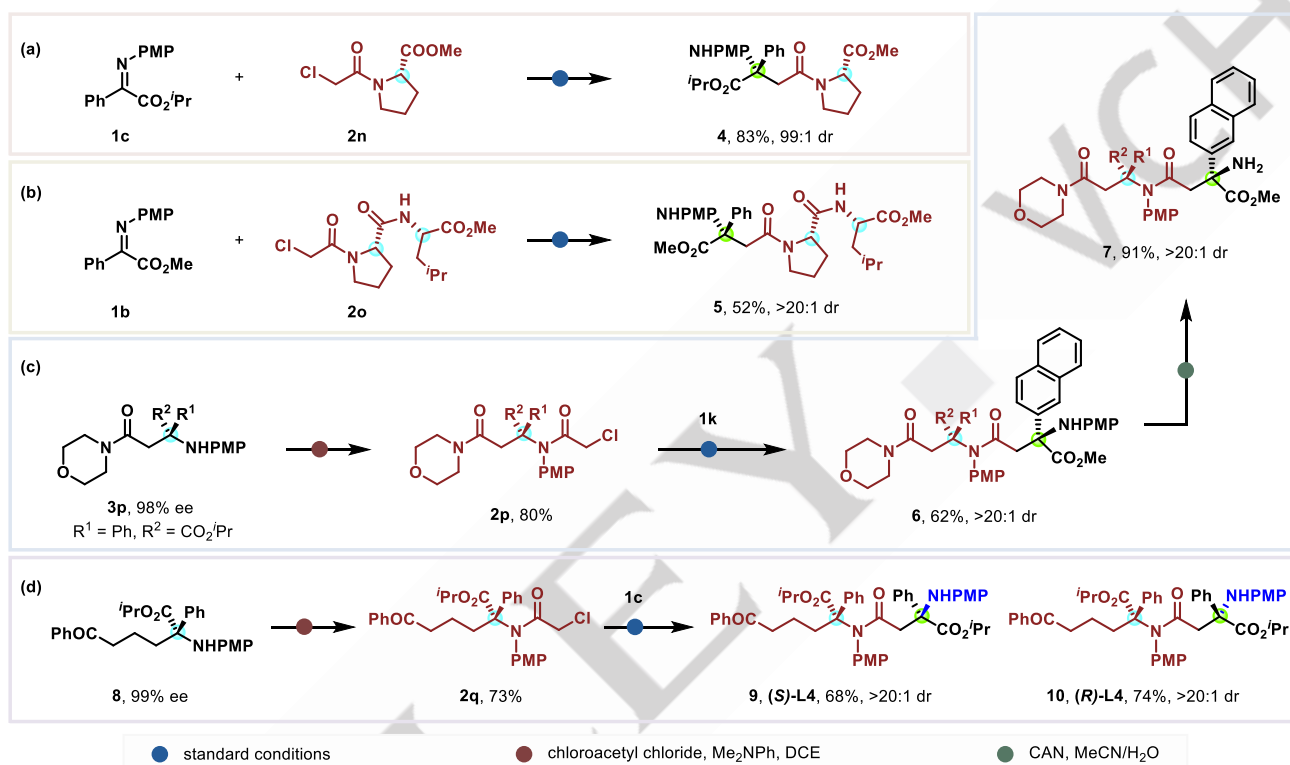

Scheme 3. Oligomerization of amino acid derivatives enabled by enantioselective reductive additions.

To further showcase the potential synthetic utility of this asymmetric reductive addition protocol, we performed the following derivatization (Scheme 4). First, the asymmetric reductive addition reaction of ketimine that was formed *in situ* by condensation of ketoester and aniline furnished the β-amino ester **3a** in 71% yield, while maintaining a high level of enantiopurity (98% ee) (Scheme 4a). A gram-scale reaction could successfully be conducted to provide product **3q** in a similarly high yield without any erosion of enantioselectivity, further demonstrating the practicality of this method for scalable synthesis (Scheme 4b). Treatment of **3t** with LiHMDS allowed the formation of β-lactam product **11** in 80% yield with 97% ee through intramolecular lactamization process (Scheme 4c).

To shed light on the mechanism of this transformation, we conducted the following preliminary mechanistic studies (Scheme 5). First, when α-bromo amide was utilized as an electrophile instead of α-chloro amide to participate in the asymmetric reductive addition reaction with ketimine **1a** under the standard conditions, the desired β-tertiary amino amide **3l** could only be obtained with very low yield and poor

enantioselectivity (13% yield, 21% ee) (Scheme 5a). Subsequently, we started to elucidate the potential roles of
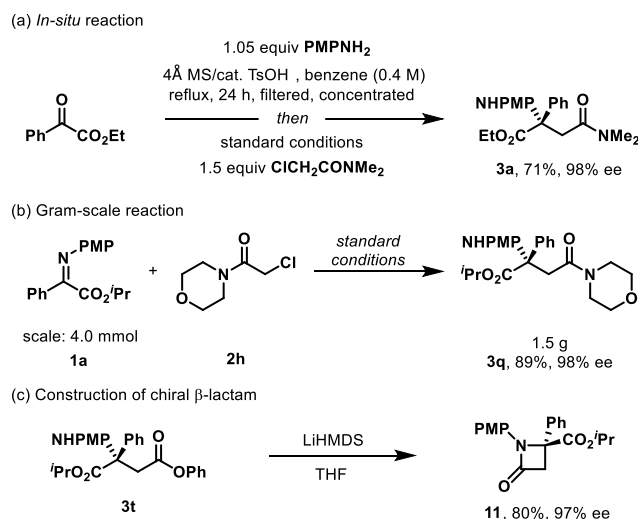

Scheme 4. Synthetic application.

4

COMMUNICATION

α-chloroamide and α-bromoamide during the reaction (Scheme 5b). The α-chloro amide **2c** remained inactive and was recovered in 96% yield upon the sole treatment of zinc metal. In sharp contrast, when corresponding α-bromo amide **2r** was exposed to the above-mentioned condition, the debrominated product **12** (11% yield) and the enamine **13** (75% yield) through the cascade addition with MeCN and isomerization process were observed (Scheme 5b). Taken together, the above results indicated that the less reactive α-chloro amide served as a radical precursor to engage in this reductive addition reaction, while α-bromo amide **2r** was more reactive to generate the classic Reformatsky reagent, thus leading to much inferior outcomes in both reaction yield and enantioselectivity. Consequently, these findings serve to emphasize the differentiation between our reductive radical addition process and the classic Reformatsky addition sequences. Furthermore, we conducted experiments to probe the presence of radical species during the reaction. Employing allyl-substituted α-chloroamide **2s** as a starting material afforded adduct **14** (43% yield, 97% ee) and the cyclized adduct **15** (25% yield, 1:1 dr), which was still observed in excellent 99% ee

(Scheme 5c). When we used ethene-1,1-diyldibenzene as a radical scavenger, the desired product **3a** could also be successfully obtained, along with the formation of an α-amide radical-trapping mixture **16** and **17** in a combined 39% yield (Scheme 5d). The above-combined results implied that α-carbonyl radical species might be generated and subsequently involved in the stereoselective reductive addition process. Based on the abovementioned mechanism studies, a plausible mechanism is elucidated as shown in Scheme 5e. The reaction can be initiated by generation of Co(I) species **int A** through ligand exchange of LCo(II) with imine **1** in the presence of Zn. The **int A** then engages in SET process with α-chloro carbonyl electrophiles **2** to generate **int B** and α-carbonyl radical. Subsequently, the α-carbonyl radical could react with **int B**, followed by reduction process to generate **int D**. The Co(II) species **int E** is formed via addition to the C=N double bond of **int D**, finally to give rise to the enantioenriched product **3** and regenerated **int A** for the next cycle via protonation, ligand exchange and reduction process.
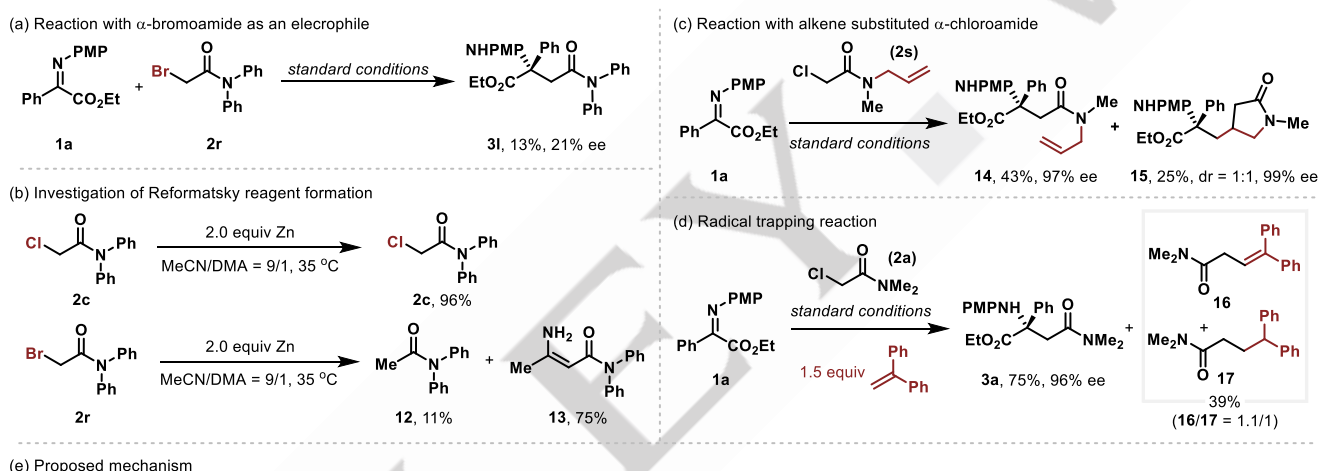
Scheme 5. Mechanistic studies.

In conclusion, we have developed a cobalt-catalyzed enantioselective reductive addition of ketimine with α-chloro carbonyl electrophile to construct the sterically hindered tetrasubstituted stereocenter. This reaction allows for the formation of β-tertiary amino acid derivatives with broad substrate scope and high enantioselectivity. Mechanism studies

ruled out the possibility of Reformatsky-type addition process and validated the formation of α-carbonyl radical species to participate in the stereoselective radical addition. The protocol exhibits potential applicability in the synthesis of the iterative α-amino acid units and oligopeptide, providing a convenient approach for late-stage modification of bioactive molecules.

COMMUNICATION

Systematic evaluation of other enantioselective radical addition reactions towards imines for the construction of valuable building blocks is currently underway.

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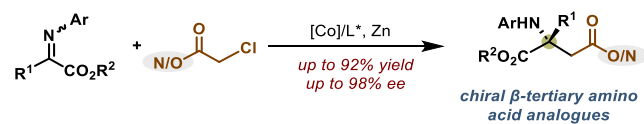
chiral β-tertiary amino acid analogues

Cobalt-catalyzed enantioselective reductive addition reaction of ketimine using α-chloro carbonyl electrophile has been developed to access diversified enantioenriched β-tertiary amino acid with excellent enantioselectivity and broad functional group tolerance. The synthetic utility of this protocol includes the efficient assembly of iterative amino acid units and oligopeptide.