Reflexive Chirality Transfer (RCT): Asymmetric 1,3-Dipolar Cycloaddition of α-Amino Acid Schiff Base with Non-Chiral Copper Catalyst

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ABSTRACT: Although optically pure α-amino acids are ubiquitous, their chirality is usually lost during the α-C–H deprotonation. Consequently, precious chiral catalysis has been necessary to synthesize optically active α-tetrasubstituted unnatural α-amino acid derivatives, even when starting with optically pure α-amino acids. However, here we report a catalytic asymmetric 1,3-dipolar cycloaddition that preserves the α-carbon chirality of α-amino acid derivatives. This process directly converts readily available optically active α-amino acid Schiff bases into optically active α-tetrasubstituted pyrrolidine derivatives without external chiral additives, despite the temporary loss of α-carbon chirality through the formation of planar 1,3-dipole intermediates. Mechanistic studies revealed that the α-carbon chirality of the α-amino acid Schiff base is transiently transferred to metal-centered chirality in enolates and subsequently restored as carbon-centered chirality of the products. This conceptually novel "Reflexive Chirality Transfer (RCT)" strategy offers a simple and cost-effective approach to optically active unnatural α-amino acid derivatives, addressing the current limitations of chiral pool synthesis.

1. INTRODUCTION

Optically pure α-amino acids are ubiquitous in nature and readily available from both commercial and natural sources. Thus, chiral α-amino acids and their derivatives are extensively utilized as valuable chiral synthons for the synthesis of natural products and biologically active substances, as well as in the preparation of chiral ligands and auxiliaries[1-4]. However, the use of α-amino acids as chiral pool has a severe limitation: the stereogenic α-carbon must remain intact because the chirality is easily lost during the formation of the corresponding carbanions or enolates. Consequently, the chirality at the α-carbon of α-amino acids is not transferred to α-functionalized products except for the specialized cases[5,6].

α-Amino acid Schiff bases (**I**)[7] are among the most commonly used precursors for synthesizing unnatural α-amino acid derivatives. However, the chirality at the α-carbon of **I** is also lost upon forming intermediates **II**, resulting in racemized products (*rac*-**III**) when reacting with electrophiles (E^+) (Figure 1a). Thus, for asymmetric α-position functionalization of **I**, an external chiral source is always necessary, even when starting with optically active α-amino acid Schiff bases (**I**). Significant efforts have been devoted to developing effective chiral catalysts, which now enable the synthesis of optically active unnatural α-amino acid derivatives **III*** (or *ent*-**III***) with excellent diastereo- and enantioselectivity (Figure 1b).[7,8] However, we envisioned that the chirality of optically pure α-amino acid Schiff bases **I** could be *transiently preserved as the metal-centered chirality of intermediates **II** even when using an achiral catalyst*. The reaction would yield the optically active product **III*** or *ent*-**III*** without requiring external chiral additives (Figure 1c). This approach leverages abundant proteogenic α-amino acids as a chiral pool, eliminating the need for precious chiral ligands.

Here, we report chiral ligand-free asymmetric 1,3-dipolar cycloaddition with optically active α-amino acid Schiff bases **1**, affording optically active pyrrolidine derivatives **3** in high enantioselectivity (Figure 1d). We discovered that a cationic copper(I) species with achiral phosphinooxazoline (PHOX) ligands facilitate the transformation. Mechanistic studies reveal that the chirality of the α-amino acid Schiff bases **1** is transiently retained as Cu(I)-centered chirality in the enolates (**II**) and subsequently restored as the carbon-centered chirality of the α-tetrasubstituted pyrrolidine derivatives **3**. This process involves dynamic and flexible chirality translocation, which is distinctly different from conventional catalytic asymmetric transformations. Thus, we term this novel phenomenon "Reflexive Chirality Transfer (RCT)", which would open up new avenues in asymmetric synthesis.

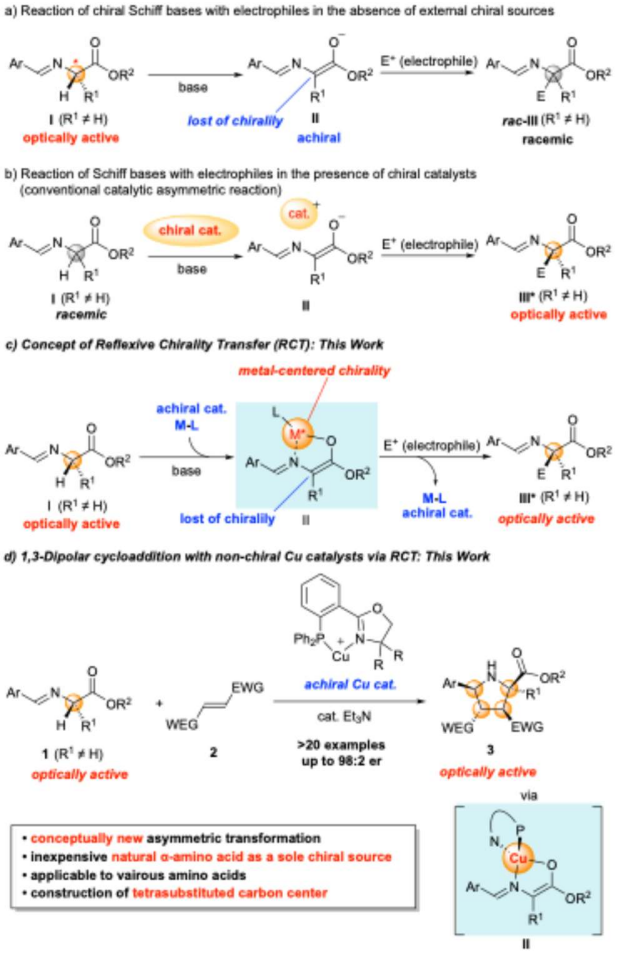


Figure 1. Reactions of chiral α-amino acid Schiff bases with electrophiles. a) Reaction of chiral Schiff bases with electrophiles in the absence of external chiral sources, giving racemic products. b) Reaction of chiral Schiff bases with electrophiles in the presence of chiral catalysts, giving optically active products (conventional catalytic asymmetric reaction). c) This work: A concept of reflexive chirality transfer (RCT). d) This work: Asymmetric 1,3-dipolar cycloaddition of α-amino acid Schiff base with non-chiral copper catalyst via reflexive chirality transfer (RCT) process.

2. RESULTS & DISCUSSION

2.1 Reaction Design. We focused on the potential for metal enolates to exhibit metal-centered chirality. Metal enolates generated from α-amino acid Schiff bases typically coordinate to a metal ion via the imine nitrogen and the carbonyl oxygen. Thus, the use of Lewis acid catalysts that consist of achiral but asymmetric bidentate ligands and metal ions that possess a tetrahedral coordination geometry would result in metal enolates with metal-centered chirality. The occurrence of such metal-centered chirality was reported in several asymmetric transformations of α-amino acid Schiff bases that use *chiral* bidentate ligands[9], however, little attention was paid to the metal-centered chirality of the enolates.

Our hypothesis is shown in Figure 2. First, the coordination of an optically active amino Schiff base (**I**) to an achiral metal complex (**IV**) results in the reversible formation of complexes **V** and **V'** with metal-centered chirality. Since **V** and **V'** have two chiral centers (i.e., α-position of Schiff base and metal-center), **V** and **V'** are *diastereomeric*. Thus, selective deprotonation from one diastereomer would be possible (e.g., This figure assumes that deprotonation occurs from **V**.), affording non-racemic, optically active enolates (*N*-metallo azomethine ylides) (**II**). Subsequent enantiofacial selective reaction of the optically enriched enolates (**II**) with electrophiles gives optically active products (**III**).

Optically active metal complexes with metal-centered chirality (chiral-at-metal complexes) have long attracted much attention for the use of asymmetric synthesis[10]. Very recently, various contributions have enabled the use of octahedral chiral-at-metal complexes as chiral catalysts[11]. However, the use of tetrahedral chiral-at-metal complexes as chiral catalyst is quite limited due to the lability of metal-centered chirality. For example, a racemization barrier of tetrahedral Cu(I) complex is about 16 kcal/mol at 27 ℃[12]. Thus, for the use tetrahedral chiral-at-metal complexes as chiral catalysts, a sophisticated design of the achiral ligands to stabilize the complex is needed[13]. In contrast, our strategy utilizes complexation-induced metal-centered chirality as a transient chirality information memory, taking advantage of the labile and reversible nature of metal-centered chirality.

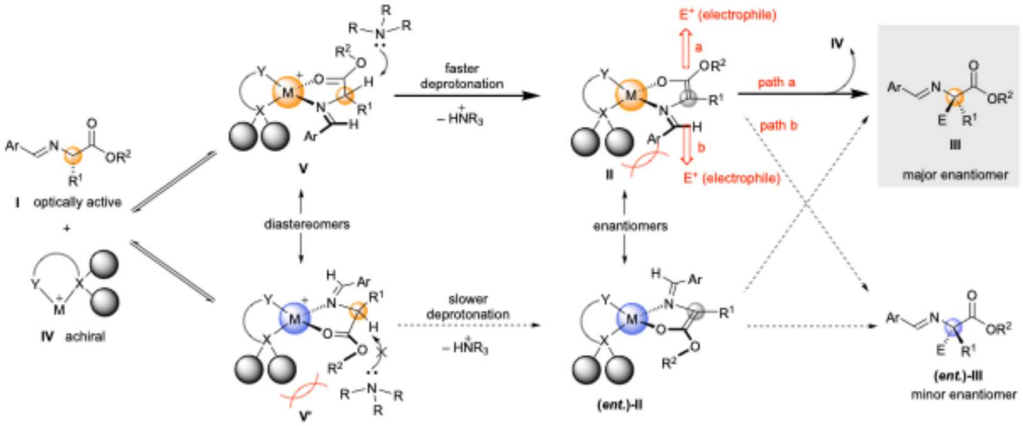
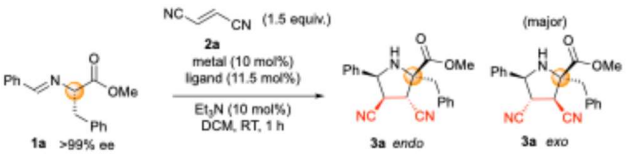


Figure 2. Hypothetical mechanistic framework of RCT.

2.2 Optimization of conditions. To assess the feasibility of the hypothesis shown in Figure 2, we selected Cu(I)-catalyzed 1,3-dipolar cycloaddition of α-amino acid Schiff bases as a model reaction because Cu(I) complexes typically exhibit tetrahedral coordination geometry[9,12]. Moreover, asymmetric 1,3-dipolar cycloaddition reactions are of great importance in synthetic

organic chemistry. These reactions utilize various 1,3-dipoles and alkenes to construct five-membered (hetero)cycles in a single step, generating up to four contiguous stereocenters in high regio- and stereo-control[14]. Given the prominence of pyrrolidine motifs in natural products[15], pharmaceuticals[16], and chiral organocatalysts[17], asymmetric 1,3-dipolar cycloaddition of α-amino acid Schiff bases with alkenes has been extensively studied over the past three decades by using expensive chiral ligands[18,19].

We initially screened a series of achiral bidentate N-P, N-N, and N-S ligands (**L1**–**L8**, Table 1, entries 1–8). In most cases, the reaction of α-amino acid Schiff base (*S*)-**1a** with fumaronitrile (**2a**) proceeded smoothly to give the *exo*-type product (**3a**) in almost racemic form. Notably, the phosphinooxazoline (PHOX) ligand **L8**, which has two methyl groups on the oxazoline moiety, gave the product **3a** with an enantiomer ratio (er) of 88:12, while the unsubstituted ligand **L7** produced almost racemic **3a**. These results highlighted the importance of the steric differences between the oxazoline and diphenylphosphine moieties. Further screening of PHOX ligands revealed that the ligand with two ethyl groups (**L9**) was the best choice for enantiomer ratios, affording **3a** with 95:5 er. The absolute configuration of **3a** was determined to be (2*R*,3*S*,4*S*,5*S*) by the chemical collection of the other cyclized product (*vide infra*). The reaction without the PHOX ligand gave racemic **3a**, indicating the significance of the PHOX ligand (**L9**) for preserving the chirality. Entries 13–16 suggest the importance of the cationic copper for the catalyst turnover. Other metals, Zn(II) and Ag(I), which are often used for the asymmetric 1,3-dipolar cycloaddition of α-amino acid Schiff bases, did not work well in this case (entries 17, 18). Finally, the reaction at 0 °C slightly improved the diastereo- and enantioselectivity (*endo*/*exo* = 9:91, 97:3 er).



entry	metal	ligand	conversion (%) [a]	endo/exo [b]	er of **3a** exo [c]
1	$Cu(MeCN)PF_6$	**L1**	>95	11/89	51:49
2	$Cu(MeCN)PF_6$	**L2**	>95	18/82	50:50
3	$Cu(MeCN)PF_6$	**L3**	70	8/92	50:50
4	$Cu(MeCN)PF_6$	**L4**	14	11/89	52:48
5	$Cu(MeCN)PF_6$	**L5**	36	14/86	54:46
6	$Cu(MeCN)PF_6$	**L6**	84	15/85	50:50
7	$Cu(MeCN)PF_6$	**L7**	85	14/86	49:51
8	$Cu(MeCN)PF_6$	**L8**	87	14/86	88:12
9	$Cu(MeCN)PF_6$	**L9**	89	10/90	95:5
10	$Cu(MeCN)PF_6$	**L10**	89	10/90	88:12
11	$Cu(MeCN)PF_6$	**L11**	85	15/85	59:41
12	$Cu(MeCN)PF_6$	none	78	13/87	51:49
13	$Cu(OTf)_2$	**L9**	58	13/87	88:12
14	CuOTf·toluene	**L9**	62	13/87	67:33
15	CuI	**L9**	<5	–	–
16	$Cu(MeCN)BF_4$	**L9**	89	10/90	95:5
17	$Zn(OTf)_2$	**L9**	7	24/76	–
18[d]	$AgSbF_6$	**L9**	42	20/80	55:45
19	$Cu(MeCN)PF_6$	**L9**	90 (86)[e]	9/91	97:3

[a] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b] Determied by ^{1}H NMR. [c] Determied by chiral HPLC. [d] The reaction was performed at 0 °C. [e]Isolated yield.

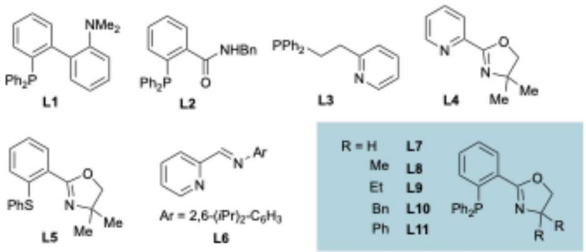
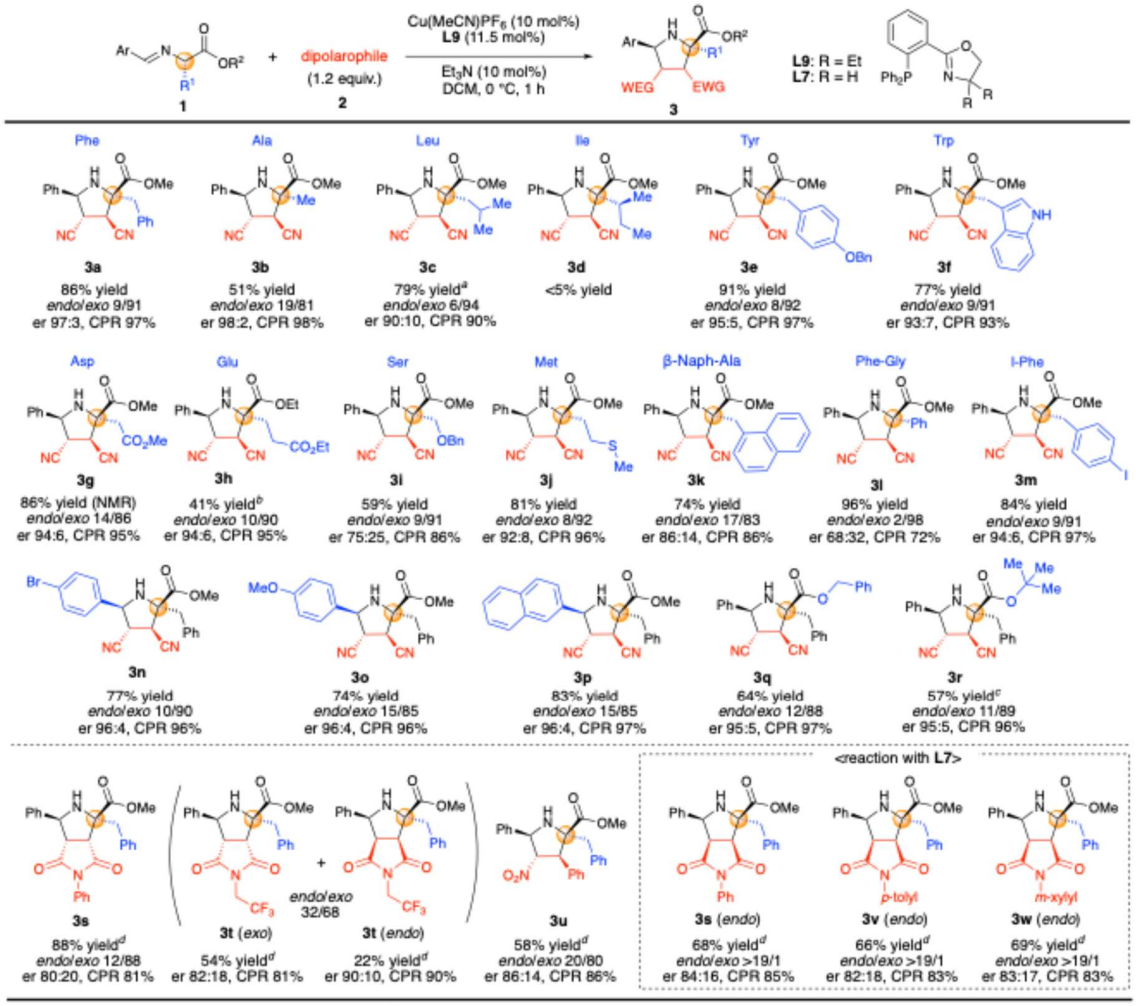


Table 1. Optimization of conditions.

2.3 Scope of the reaction. The substrate scope of the Cu(I)-catalyzed enantioselective 1,3-dipolar cycloaddition via RCT is shown in Figure 3. The degree of preservation of the chirality from **1** to the products **3** is shown as the chirality preserved ratio ((percentage of the major enantiomer ratio of **3**~~1~~/percentage of the major enantiomer ratio of **1**) × 100~~3~~: CPR). Optically active α-amino acid Schiff bases derived from L-alanine and L-leucine ((*S*)-**1b** and (*S*)-**1c**) smoothly reacted with fumaronitrile (**2a**) to provide the corresponding cyclized products **3b** and **3c** with an excellent CPR. The reaction of (*S*)-**1d**, synthesized from (*S*)-isoleucine, did not gave the product in the conditions. This can be rationalized by the large allylic strain in the generated enolate. Tyrosine derivatives (*S*)-**1e** and tryptophane derivatives (*S*)-**1f** also gave the products **3e** and **3f** with maintenance of their chirality. Furthermore, various functional group-containing α-amino acid Schiff bases synthesized from L-aspartic acid, L-glutamic acid, L-serine, and L-methionine ((*S*)-**1g**–(*S*)-**1j**) **were** converted into the corresponding pyrrolidine derivatives

with good to excellent CPRs. Substrates from (*S*)-β-naphthylalanine, (*S*)-phenylglycine, and (*S*)-4-iodophenylalanine ((*S*)-**1k**–(*S*)-**1m**), which are unnatural but commercially available α-amino acids, were also applicable to the reaction, giving **3k**–**3m**. In the case with (*S*)-**1i** and (*S*)-**1l**, the CPRs were lower due to the concomitant epimerization. Changing aryl substituents on the imine moiety and ester groups had neglectable effects on the CPR and diastereoselectivity (**3n**–**3r**).

Dipolarophiles, including *N*-phenylmaleimide (**2s**), *N*-2,2,2-trifluoroethylmaleimide (**2t**), *N*-phenylmaleimide (**2u**), and β-nitrostylene (**2v**), smoothly coupled with (*S*)-**1a**, yielding the corresponding *exo*-type cyclized products (**3s**–**3u**) with good CPRs and diastereoselectivity. Notably, when **L7** was used for the reaction of (*S*)-**1a** with *N*-arylmaleimides (**2s**, **2w**, and **2x**), *endo*-type products (**3s**, **3w** and **3x**) were obtained with high diastereoselectivity and high CPRs[20]. These results indicate that chirality transfer from the α-carbon of (*S*)-**1** to the copper-centered chirality of the enolate occurs with high efficiency even with the unsubstituted PHOX ligand **L7**. The low CPR in the reactions of (*S*)-**1a** and **2a** with **L7** (Table 1, entry 8) would be due to the low facial selectivity of 1,3-cycloaddition with the chiral enolate, not the low optical purity of the metal-centered chirality in the enolate.



Isolated yield. The ratio of endo/exo was determined by ^{1}H NMR. Enantiomer ratio (er) was determined by HPLC using a chiral stationary phase. [a]The reaction time was 18 h. [b]The reaction time was 4 days. [c]The reaction time was 2 h. [d]The reaction was performed at room temperature.

Figure 3. Scope of the reaction.

We performed a gram-scale reaction (Figure 4). Optically pure α-amino acid Schiff base (*S*)-**1n** can be prepared from inexpensive L-phenylalanine methyl ester in a large scale. Subsequent copper-catalyzed 1,3-dipolar cycloaddition (*S*)-**1n** with **2a** followed by recrystallization provided optically pure (2*R*,3*S*,4*S*,5*S*)-**3n** in 1.12 g without external chiral ligand and column chromatography. The reaction highlights the practicality of the RCT strategy for synthesizing optically pure α-tetrasubstituted unnatural proline derivatives. The absolute configuration of **3n** was determined by single crystal X-ray analysis. The absolute configuration of **3a** was also determined as 2*R*,3*S*,4*S*,5*S* by debromination of **3n**. The absolute configuration of the other cyclized product **3** have not been determined (for ease to understand the relative configuration of the products, the stereochemistry of the other product **3** are described as extrapolated from the stereochemical outcome of **3a** and **3n**.)

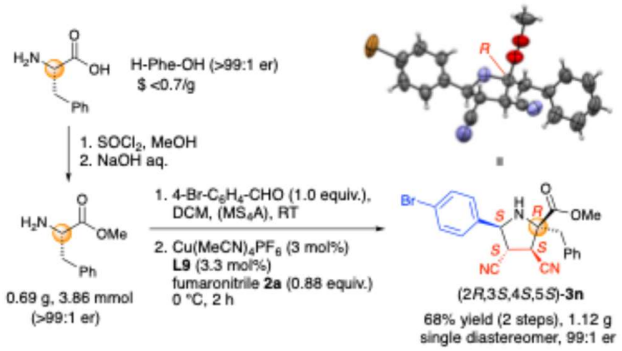
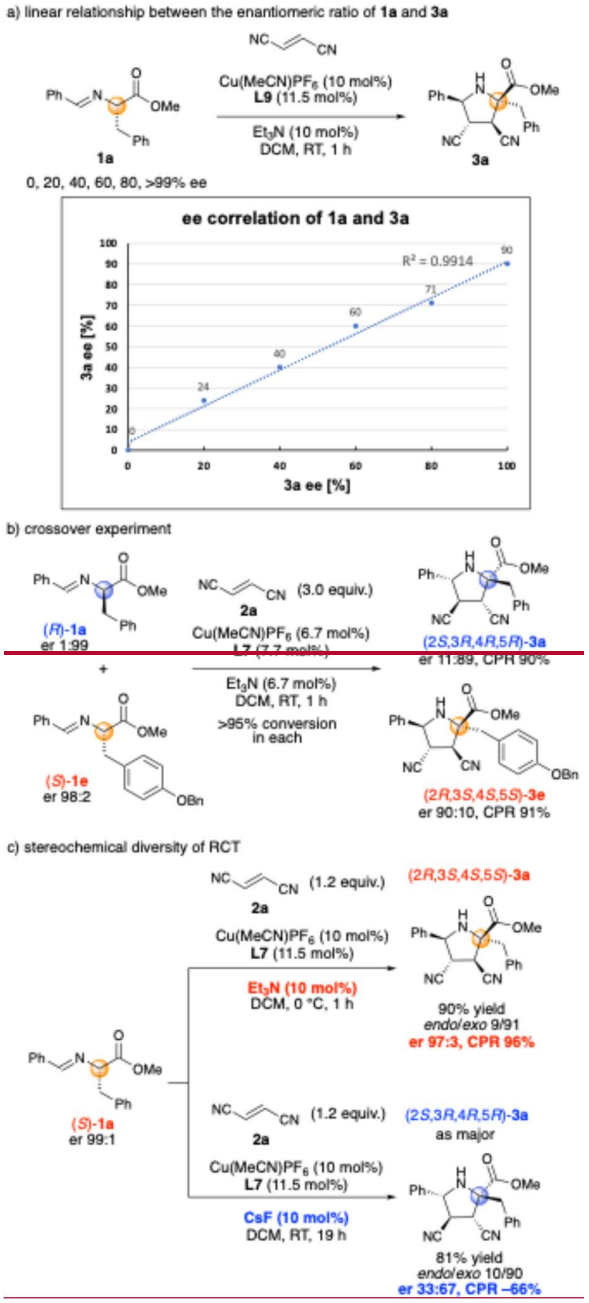


Figure 4. Chromatography- and chiral ligand-free gram-scale synthesis of α-tetrasubstituted pyrrolidine **3n.**

2.4 Mechanistic studies. The results of several mechanistic studies are shown in Figure 5. A linear relationship between the enantiomeric ratio of **1a** and **3a** was observed (Figure 5a)[21,0]. A crossover experiment using equimolar (*R*)-**1a** and (*S*)-**1e** gave (2*S*,3*R*,4*R*,5*R*)-**3a** with 89:11 er and (2*R*,3*S*,4*S*,5*S*)-**3e** with 90:10 er, respectively (Figure 5b). These results indicate that chirality transfer from **1** to **3** occurs in a unimolecular fashion with the assistant of the PHOX ligand. It is unlikely that the optically active α-amino acid Schiff base **1** or the product **3** acts as a chiral ligand of the enolates to induce the enantioselectivity in the 1,3-cycloaddition. Considering the absolute configuration of the products **3a** and **3n**, both deprotonation and 1,3-cycloaddition should occur on the same face, resulting in total retention of the configuration (where retention means that the α-C–H bond of the starting **1a** is replaced by the newly formed C–C bond without changing the spatial arrangement). With these mechanistic insights, we conducted computational studies to rationalize the observed enantioselectivity (Figure 5c, 5d). While the calculated $\Delta\Delta G^{\ddagger}$ values are slightly smaller than those expected from the observed enantiomer ratio, DFT calculations indicated that both deprotonation and 1,3-dipolar cycloaddition preferentially occur on the diphenylphosphine side rather than the oxazoline side. Based on the DFT calculations, the oxazoline moiety seems more of a steric barrier in the reaction probably. This is probably because the substituents on the oxazoline ring stick into the reacting site to be a steric hindrance against approaching reagents, triethylamine and dipolarophiles. The proposed stereochemical pathway, illustrated in Figure 5e, aligns with our initial hypothesis (Figure 2a)~~DFT calculations suggested that both deprotonation and 1,3-cycloaddition take place on the diphenylphosphine side, rather than the oxazoline side (for details, see Supplemental Information). The results of the mechanistic studies align with our initial hypothesis (Figure 2a)~~. Overall,~~:~~ t~~T~~he chirality of the α-amino acid Schiff bases (**I**) is transiently retained as Cu(I)-centered chirality in the enolates (**II**), which is then transferred back to carbon-centered chirality of the α-tetrasubstituted pyrrolidine derivatives (**III**) (*i.e.*, RCT process). ~~Finally, we also observed enantio-divergency of the reaction (Figure 5c): The use of CsF instead of triethylamine in the reaction of (*S*)-**1a** and **2a** with **L9** afforded (2*S*,3*R*,4*R*,5*R*)-**3a** in 33:67 er. The observed stereochemical divergency strongly suggested that the chirality at the α carbon of (*S*)-**1** is once lost and flexibly transferred as copper-centered chirality of the enolates. Although there is room for improvement in the enantiomer ratio, *both enantiomers of* **3a** *can be obtained from the identical substate (S)-***1a** *just by changing the bases*.~~



~~Figure 5. Mechanistic studies. a) Liner relationship between the enantiomeric ratio of 1a and 3a. b) Crossover experiment. c) Stereochemical diversity of RCT process.~~

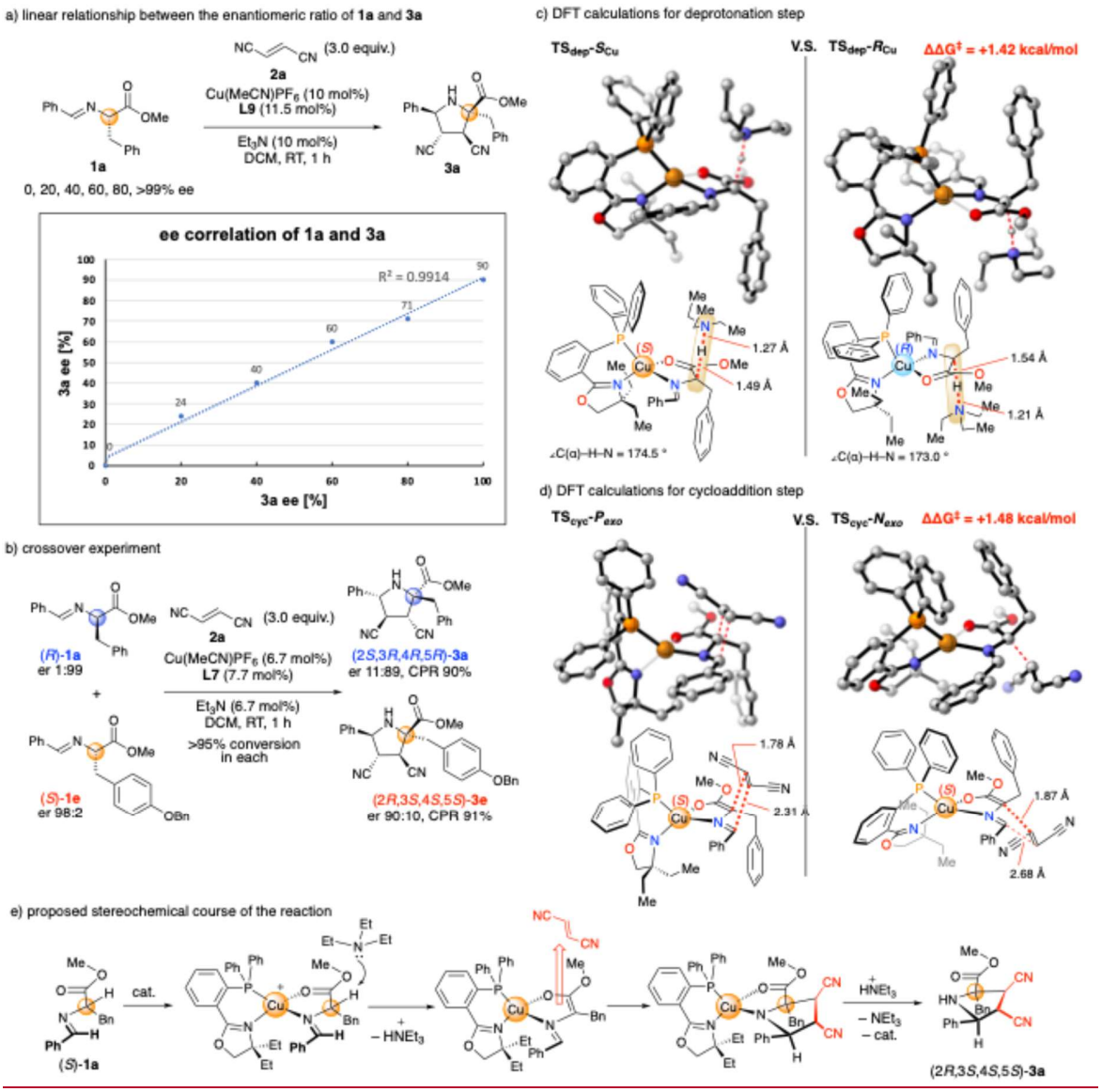


Figure 5. Mechanistic studies. a) Liner relationship between the enantiomeric ratio of **1a** and **3a**. b) Crossover experiment. c) DFT calculations for the deprotonation step~~Stereochemical diversity of RCT process~~. d) DFT calculations for the cycloaddition step. e) Proposed stereochemical course of the reaction.

Finally, we also observed enantio-divergency of the reaction (Figure 6): The use of CsF instead of triethylamine in the reaction of (*S*)-**1a** and **2a** with **L9** afforded (2*S*,3*R*,4*R*,5*R*)-**3a** in 33:67 er. The observed stereochemical divergency strongly suggested that the chirality at the α carbon of (*S*)-**1** is once lost and flexibly transferred as copper-centered chirality of the enolates. Although there is room for improvement in the enantiomer ratio, *both enantiomers of **3a** can be obtained from the identical substate (S)-**1a** just by changing the bases*.

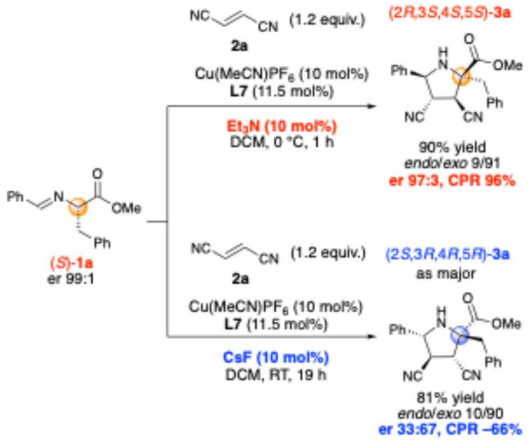


Figure 6. Stereochemical diversity of the reaction.

3. CONCLUSION~~SUMMARY~~

We have developed a conceptually novel asymmetric synthesis, termed "Reflexive Chirality Transfer (RCT)". The reaction allows direct access to optically active α-tetrasubstituted pyrrolidine derivatives from readily available optically pure α-amino acids, without any aid of external chiral additives. The RCT process does not fall into any category of current asymmetric organic reactions, overcoming long-standing challenges in asymmetric synthesis. This work also highlights the overlooked utility of the complexation-induced metal-centered chirality as a transient chiral memory. We hope this report will open new avenues in chiral pool synthesis, offering a simple yet efficient route to optically active molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization of compounds and computational details (PDF) Crystallographic data for the structure reported in this article have been deposited at the Cambridge Crystallographic Data Centre under deposition number CCDC 2402021.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We would like to express our sincere gratitude to Prof. Paul A. Wender for discussing this research with us before submitting the paper and for helping us to name this phenomenon as Reflexive Chirality Transfer. The NMR analysis of all new organic compounds was performed using ECZ400, ESX400, ECS400 or ECZ500R NMR installed at the Faculty of Pharmaceutical Sciences, Hokkaido University. The HRMS analysis of all new organic compounds was performed using Thermo Scientific Exactive mass spectrometers for ESI-MS or JMS-T2000 GC for EI-MS. These instruments are registered in the Open Facility system managed by the Global Facility Center, Creative Research Institution, Hokkaido University. This work was financially supported by Grant-in-Aid for Young Scientists (JP22K15240 for K.M.) and Grant-in-Aids for Scientific Research (B) (23H02596 and 23K27287 for Y.S) from the Japan Society for the Promotion of Science. K. M. acknowledges financial support from The Asahi Glass Foundation.

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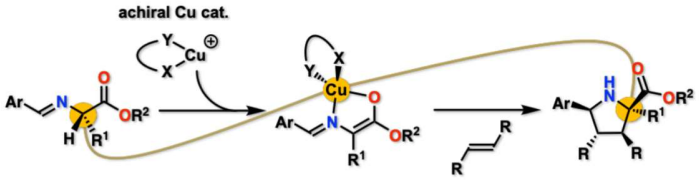
"Reflexive Chirality Transfer" process enables
1,3-dipolar cycloaddition with preserved α-carbon chirality



- conceptually new dynamic chirality transfer
- construction of tetrasubstituted carbon (up to 98:2 er)
- applicable to various amino acids

no need for chiral catalysts,
now use abundant optically pure amino acids