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Amino Acid Schiff Base Bearing Benzophenone Imine As a Platform for Highly Congested Unnatural α-Amino Acid Synthesis

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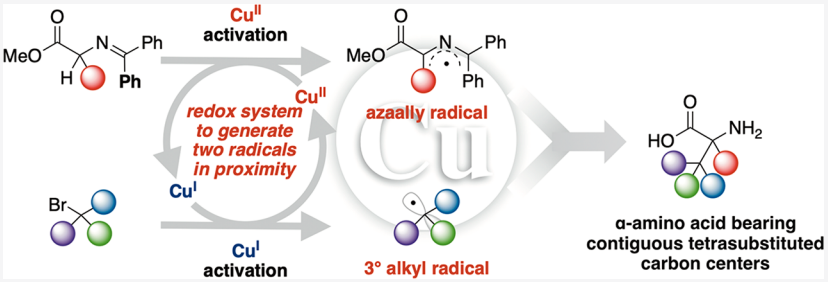


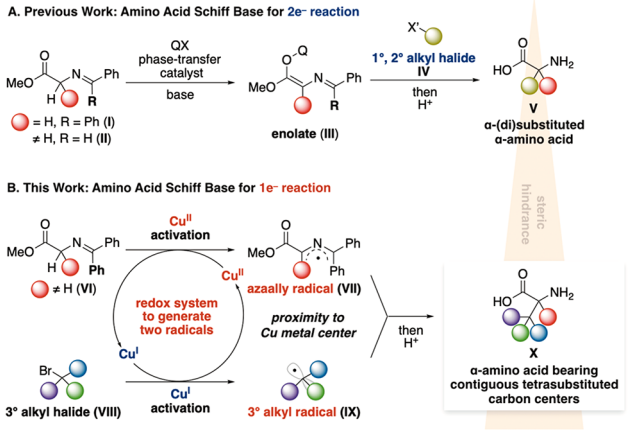
ABSTRACT: Unnatural α-amino acids are invaluable building blocks in synthetic organic chemistry and could upgrade the function of peptides. We developed a new mode for catalytic activation of amino acid Schiff bases, serving as a platform for highly congested unnatural α-amino acid synthesis. The redox active copper catalyst enabled efficient cross-coupling to construct contiguous tetrasubstituted carbon centers. The broad functional group compatibility highlights the mildness of the present catalysis. Notably, we achieved successive β-functionalization and oxidation of amino acid Schiff bases to afford dehydroalanine derivatives bearing tetrasubstituted carbon. A three-component cross-coupling reaction of an amino acid Schiff base, alkyl bromides, and styrene derivatives demonstrated the high utility of the present method. The diastereoselective reaction was also achieved using menthol derivatives as a chiral auxiliary, delivering enantiomerically enriched α-amino acid bearing α,β-continuous tetrasubstituted carbon. The synthesized highly congested unnatural α-amino acid could be derivatized and incorporated into peptide synthesis.

INTRODUCTION

Unnatural α-amino acids are invaluable building blocks in synthetic organic chemistry and could upgrade the function of peptides, which are widely used as pharmaceuticals and biological materials.[1] The establishment of an efficient method for synthesizing unnatural α-amino acids, for which artificial synthesis is essential, is one of the most urgent research topics. Of the unnatural α-amino acids, synthetic methods of α,α-disubstituted-α-amino acid (α-tetrasubstituted α-amino acids), which can control lipophilicity, conformation stability, and peptidase degradation, have been reported.[2] Meanwhile, synthetic methods of more hindered unnatural α-amino acid bearing α,β-continuous tetrasubstituted carbon, which have potential for upgrading these characteristics, is fairly rare because efficient and general methodologies to overcome extreme steric hindrance have not been established (Scheme 1A).[3]

Amino acid Schiff bases (**I**, **II**), which were developed by O'Donnell, are one of the most important starting materials for the synthesis of various natural and unnatural α-amino acids (Scheme 1).[4] For example, an enolate nucleophile **III** can be easily generated under phase-transfer catalytic conditions, allowing for subsequent coupling with alkyl halides **IV** via

Scheme 1. Amino Acid Schiff Bases for Unnatural α-Amino Acid Synthesis



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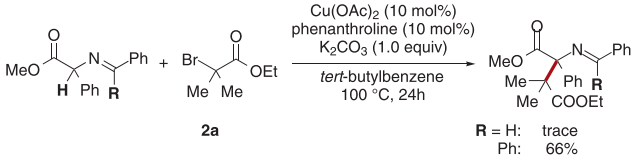
2e$^-$ (ionic) reactions (Scheme 1A).[5] This method can be applied to synthesize various α-mono- and disubstituted α-amino acids **V** from a glycinate Schiff base bearing benzophenone imine **I** or an amino acid Schiff base bearing aldimine **II**, respectively. The applicability of alkylating reagents, however, has been limited to primary and small secondary alkyl halides, and incorporation of highly congested tertiary alkyl groups has not been achieved due to the nature of the nucleophilic substitution reaction.

We thus focused on the use of an α-monosubstituted amino acid Schiff base bearing benzophenone imine **VI**, which is generally introduced to the glycinate. The Schiff base **VI** could generate an azaallyl radical species **VII** via a single electron transfer process,[6] in which the formed radical species would be further stabilized by a captodative effect (Scheme 1B).[7] We hypothesized that this radical species **VII** would be preferentially generated with the assistance of redox active Cu(II) catalyst (Cu^{II} activation: Cu^{II} to Cu^{I}). The formed radical species **VII** would couple with tertiary alkyl radical **IX** generated from tertiary alkyl bromide **VIII** and Cu(I) catalyst in proximity to the **VII** (Cu^{I} activation: Cu^{I} to Cu^{II}), affording extremely congested α-amino acid bearing contiguous tetrasubstituted carbon centers **X**.[8,9] Recently, Watson's group reported elegant copper catalyzed alkylation of nitroalkanes.[10] A wide variety of nitroalkanes and α-bromocarbonyl compounds could be used under mild conditions. Construction of contiguous tetrasubstituted carbon, however, is very limited. Here, we report that an α-amino acid Schiff base is a key platform for the synthesis of highly congested unnatural α-amino acids.

RESULTS AND DISCUSSION

We selected alkyl bromide **2a** as a cross-coupling partner to construct contiguous tetrasubstituted carbon centers.[11,12] Initially we compared the reactivity of a general amino acid-derived Schiff base bearing aldimine and one bearing benzophenone imine using a $Cu(OAc)_2$/phenanthroline complex (Scheme 2).[13] Although the aldimine substrate did not provide the desired product, benzophenone imine substrate **1a** provided the product in 66% yield.

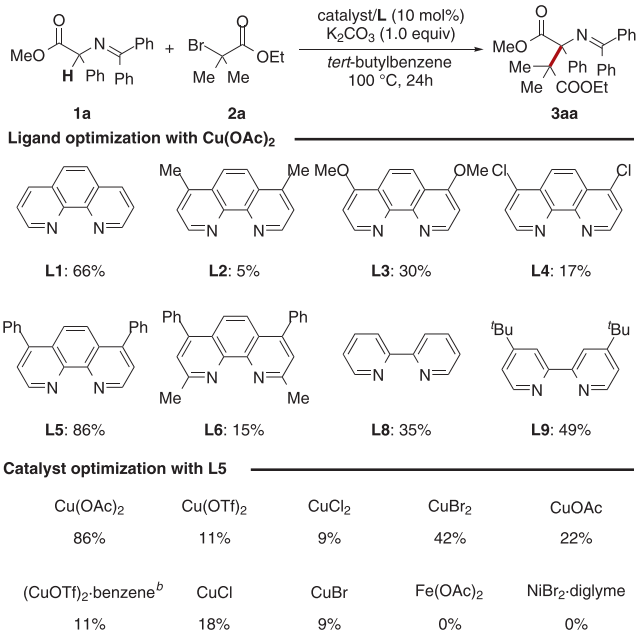
Scheme 2. Initial Trial Using Amino Acid Schiff Bases Bearing Aldimine and Benzophenone Imine



This initial trial prompted us to further optimize the reaction condition using benzophenone imine. As shown in Table 1, various bidentate ligands were evaluated. A survey of phenanthroline derivatives revealed that bathophenanthroline (**L5**) was the optimal ligand, affording product **3aa** in 86% yield. 2,2′-Bipyridyl ligands (**L8** and **L9**) provided product **3aa** in slightly lower yield than **L1**.

We then examined a series of copper salts. Both cationic Cu(II) triflate and Cu(II) halides were ineffective in the present reaction. In contrast, Cu(II) acetate, which can function as a Lewis acid/Brønsted base cooperative catalyst, was optimal, indicating that activation of **1a** would be achieved

Table 1. Optimization of the Reaction Conditions



[a]Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), K_2CO_3 (1.0 equiv), and *tert*-butylbenzene (0.5 mL). Yields were determined by ^{1}H NMR analysis. [b]5 mol % of the $(CuOTf)_2$·benzene complex was used.

by the internal basis of the Cu(II) acetate complex. Other Cu(I) catalysts afforded product **3aa** in low chemical yield. In addition, other redox active metals, iron and nickel, did not catalyze the reaction at all.

Having identified the optimal conditions, we evaluated the scope of the amino acid synthesis (Table 2). The present catalysis can be run on a gram scale and product **3aa** was isolated in 1.74 g (79% yield). It is noteworthy that bulky *tert*-butyl ester substrate could be applicable (**3aa′**). Various phenyl glycine derivatives were applicable, including electron-withdrawing and -donating substituents (Me, OMe, Cl, Ph) (**3ba**-**3ea**). The use of meta-substituted aryl groups (**3fa**, **3ga**) produced no detrimental effects. An acceptable yield was obtained when a highly hindered ortho-substituted phenyl substrate was used under the optimized reaction conditions (**3ha**). A naphthyl group was applicable to the present catalysis (**3ia**). Product **3ja** was isolated in 35% yield using an α-thienyl substrate. Azlactone was also converted to a α-amino acid derivative bearing contiguous tetrasubstituted carbon centers, although regioisomers were observed in a 4.2/1 ratio (**3ka**).[14]

We next performed the reaction using various alkyl bromides **2**. Cyclic scaffolds, cyclohexane, cyclopentane, and cyclobutane were incorporated into amino acid derivatives (**3aa**−**3ad**). The reaction of benzyl ester proceeded without any detrimental effects (**3ae**). The aniline functionality survived under the optimized conditions and product **3af** was isolated in 76% yield as a diastereomixture. Other functionalities, such as alkyl chloride, aryl iodide, and alkyl bromide, could be used under slightly modified reaction conditions (**3ag**, **3ah**, and **3aj**). The longer acyclic alkyl chain at the α-position of alkyl bromide **2** decreased the chemical yields due to steric hindrance (**3ah**−**3aj**). Although the chemical yield was moderate when using a protecting group-free primary hydroxy group (**3ak**), a tertiary hydroxy group provided the product in high yield (**3al**). Chemoselective α-alkylation of **1** was achieved in the presence

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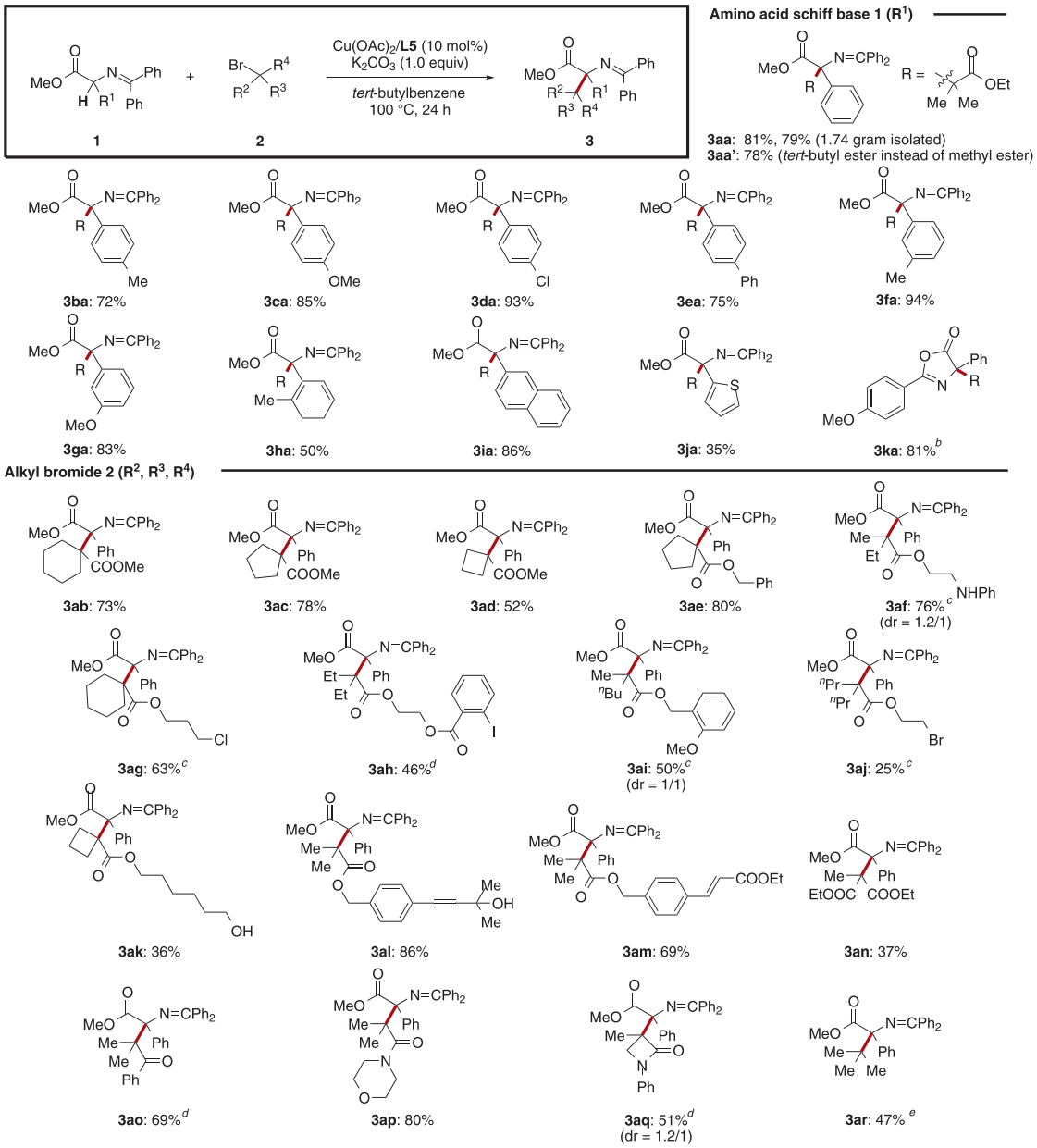
Table 2. Substrate Scope of α-Alkylation

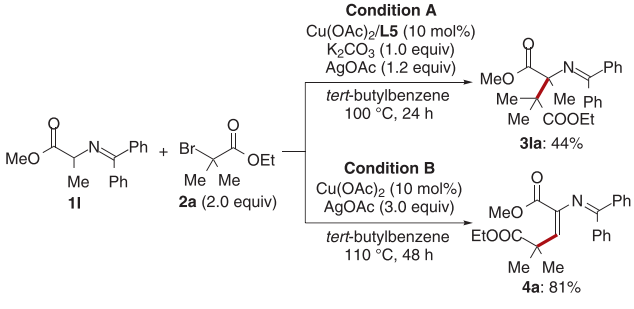


[a]Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), K_2CO_3 (1.0 equiv), and *tert*-butylbenzene (0.5 mL). Isolated yields were shown. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Regioisomer ratio of C4/C2 of azlactone = 4.2/1. [c]Reaction time was 72 h. [d]Reaction time was 48 h. [e]**1a** (0.1 mmol), **2r** (0.2 mmol), KO^{t}Bu (2.0 equiv), and DMA (1.0 mL).

of potentially reactive activated olefin (**3am**). Malonate-derived alkyl bromide provided product **3an** in 37% yield. Ketone and amide could be used instead of an ester of **2** (**3ao**, **3ap**). A 2-azetidinone scaffold bearing contiguous tetrasubstituted carbon could be constructed, affording product **3aq** in 51% yield as a diastereomixture. Remarkably, the unactivated alkyl halide, *tert*-butyl iodide, afforded the product **3ar** in 47% yield under slightly modified reaction conditions.

Alanine-derived Schiff base **1l** was applicable to the present catalysis and product **3la** was isolated in 44% yield under slightly modified reaction conditions (Scheme 3, condition A). The moderate yield was due to the competitive formation of β-alkyl dehydroalanine product **4a**.[15] Thus, we next focused on the synthesis of **4a** as the major product and found that simplified reaction conditions ($Cu(OAc)_2$/AgOAc) produced

Scheme 3. Chemoselective Cross-Coupling Using Alanine Schiff Base



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4a in 81% yield with an exclusive *E*-isomer formation (Scheme 3, condition B), demonstrating chemoselective synthesis of α-alkylation product **3** and β-alkylation product **4** by modifying the reaction conditions.[16]

The scope of α- and β-alkylations was next evaluated using aliphatic substituted amino acids (Table 3). A series of aliphatic substituted amino acids was used under the condition A, providing α-alkylation products (**3la**-**3oa**), although the chemical yields were moderate. Under condition B, we observed wide functional group tolerance similar to that shown in Table 2 (aniline, alkyl halides, aryl iodide, and hydroxy group). Various cyclic and acyclic alkyl chains were incorporated (**4a**−**4m**). Alkyl bromide bearing diester, ketone, amide, and 2-azetidinone could be used (**4n**−**4q**). For the β-alkylation, α-bromo nitroalkane provided product **4r** in 15% yield. It is noteworthy that tetrasubstituted olefins bearing a quaternary carbon, whose formation from the saturated starting material is particularly challenging, were constructed (**4s** and **4t**), highlighting that our strategy can also be used to construct sterically congested olefins.[17]

The efficiency of the present chemoselective catalysis was demonstrated by a three-component cross-coupling reaction (Scheme 4). Styrene was efficiently incorporated into the product and **6** was isolated in 71% yield as the exclusive regioisomer. Various alkyl bromides and styrene derivatives could be incorporated, demonstrating that the present method is highly useful for synthesizing a diverse set of unnatural α-amino acid derivatives bearing tetrasubstituted carbons at the α- and δ-positions. To the best of our knowledge, no catalytic difunctionalization of alkene by two different tetrasubstituted carbons have been reported.[18]

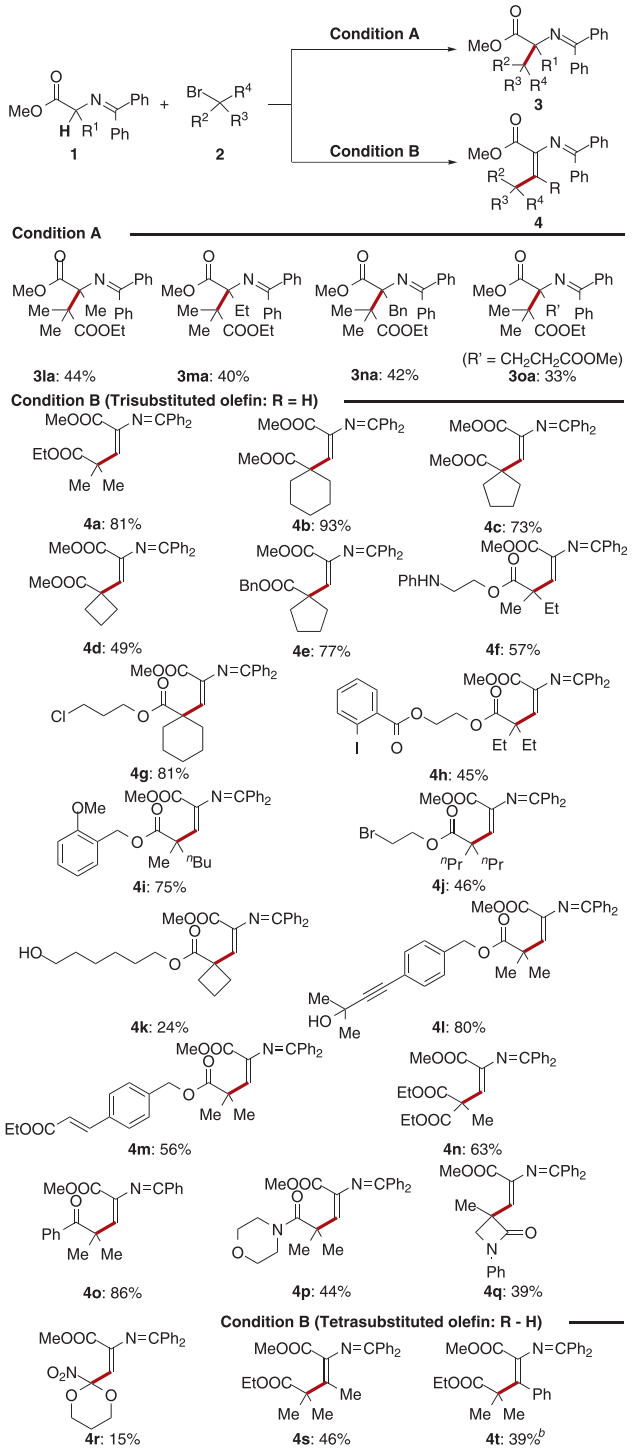
Finally, we focused on the synthesis of enantioenriched α-amino acid bearing α,β-continuous tetrasubstituted carbon. Although catalytic enantioselective variant using chiral ligand was found to be difficult at this stage, modified (−)-menthol derivatives as chiral auxiliary turned out to be effective to synthesis chiral products (Scheme 5).[19] A survey of (−)-menthol derivatives revealed that 1-naphthyl substituted menthol derivative **1δ** afforded the product in high yield with high diastereoselectivity under slightly modified reaction conditions. Noteworthy is that the product **3δa** could be easily purified by conventional column choreography to afford enantiomerically pure compounds. The substrate scope of diastereoselective reaction was described in Scheme 6. Several cyclic motifs could be incorporated at β-position with high diastereoselectivities (**3δb**-**3δe**). Both ketone and amide derived-alkyl bromides also exhibited high diastereoselectivities.

Selective deprotection of product **3aa** was achieved under mildly acidic conditions, affording amino ester **7** in 86% yield (Scheme 7a). Treatment with HCl under heated conditions delivered the protecting group-free amino acid **8** in 89% yield (Scheme 7b). The amide bond formation of **7** proceeded to afford the dipeptide **9** in high yield using Fmoc-Gly-Cl (Scheme 7c).[20] Hydrogenation and deprotection of **4a** proceeded simultaneously using palladium on carbon under hydrogen atmosphere, delivering γ-tetrasubstituted amino ester **10** (Scheme 7d).

As control experiments, each component was omitted from the standard reaction conditions (Scheme 8). No product was observed in the absence of copper salt (entry 2). Low chemical yield was also observed without ligand (entry 3). The addition of base was essential for high yield (entry 4). Trace amount of product **3aa** was observed at room temperature, presumably due to the relatively low acidity of α-proton of **1** (pK_a in DMSO 21.2).[21]

We further performed mechanistic studies (Scheme 9). In the absence of alkyl bromide **2a**, treatment of Schiff base **2l**

Table 3. Substrate Scope of Chemoselective Alkylation[a]



[a]Condition A: **1** (0.1 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), **L5** (10 mol %), K_2CO_3 (1.0 equiv), AgOAc (1.2 equiv), and *tert*-butylbenzene (0.5 mL). 100 °C, 24 h. Condition B: **1** (0.1 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), AgOAc (3.0 equiv), and *tert*-butylbenzene (0.5 mL). 110 °C, 48 h. Isolated yields were shown. [b]Reaction temperature was 130 °C.

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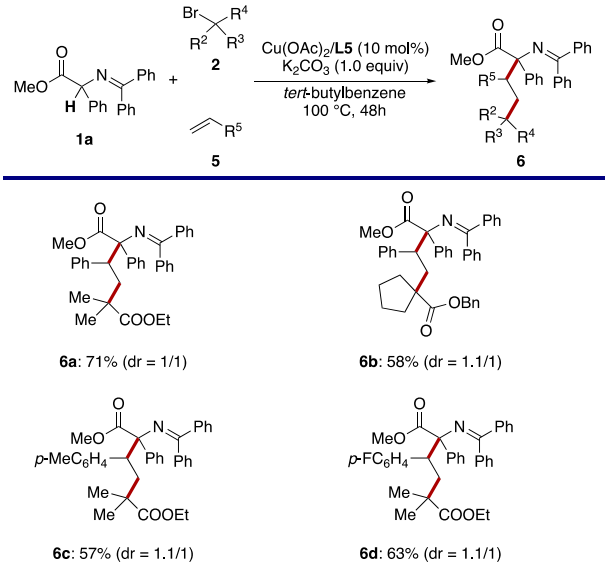
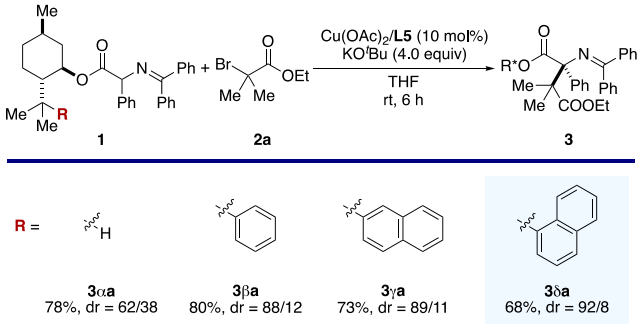
Scheme 4. Three-Components Cross-Coupling



[a]Conditions: **1** (0.1 mmol), **2** (0.12 mmol), **5** (0.20 mmol), K_2CO_3 (1.0 equiv), and *tert*-butylbenzene (0.5 mL). Isolated yields were shown

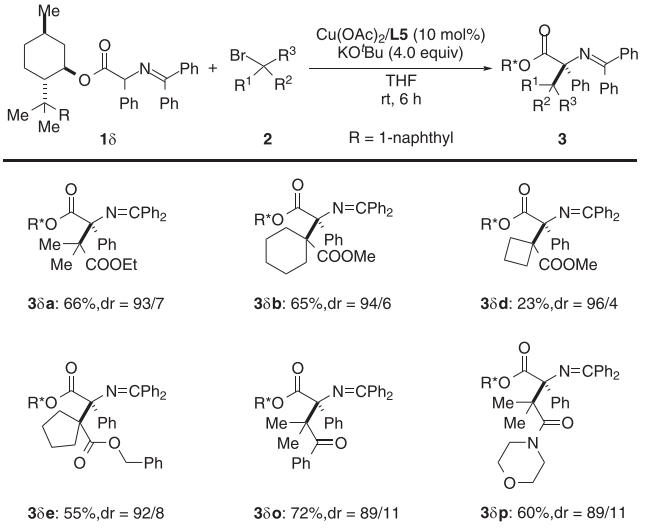
Scheme 5. Diastereoselective Reaction Using Chiral Auxiliary



[a]Conditions: **1** (0.1 mmol), **2** (0.4 mmol), $Cu(OAc)_2$ (10 mol %), **L5** (10 mol %), KO^tBu (4.0 equiv), and THF (1.0 mL), room temperature, 6 h.

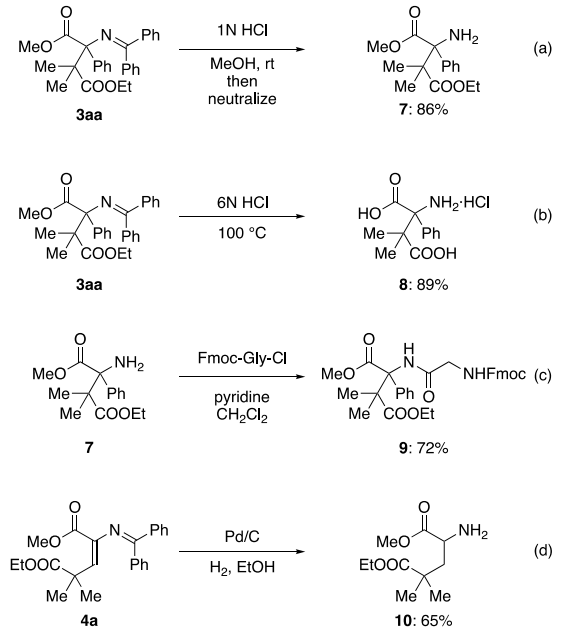
with a stoichiometric amount of Cu(I) complex did not provide the homocoupling dimer **11**. In contrast, homocoupling dimer **11** was observed in 32% yield using a Cu(II) complex, indicating that radical species would be generated with a Cu(II) complex (Scheme 9a).[22−24] Homocoupling dimer **11** was not observed without **L5** in the presence of $Cu(OAc)_2$. When amino acid Schiff base **2a** was treated with TEMPO under stoichiometric conditions, TEMPO adduct **12** was detected (Scheme 9b). Furthermore, when α-cyclopropyl substrate **13** was used under the optimized conditions, we detected ring-opened products **14** along with double alkylated product **15**, which also supported the generation of radical species (Scheme 9c). While alkyl bromide **2a** was not coupled with TEMPO under Cu(II) complex in the absence of an amino acid Schiff base, a Cu(I) complex provided TEMPO adduct **16** in 43% yield (Scheme 9d). These results indicated that a Cu(I) complex could activate alkyl bromide **2** to afford radical species. The addition of **L5** was also essential for activating **2a**.

Scheme 6. Diastereoselective Reaction Using Chiral Auxiliary[a]



[a]Conditions: **1** (0.3 mmol), **2** (1.2 mmol), $Cu(OAc)_2$ (10 mol %), **L5** (10 mol %), KO^tBu (4.0 equiv), and THF (3.0 mL), room temperature, 6 h. Isolated yields were shown.

Scheme 7. Transformation of the Products



On the basis of a series of control experiments, we present a proposed catalytic cycle in Figure 1A. Deprotonative activation of amino acid Schiff base **II** would be achieved by Cu(II) acetate **I**, which functions as a Lewis acid/Brønsted base cooperative catalyst, generating enolate intermediate **III**.[25,26] The resonance persistent azaally radical species **IV** would have large contribution to further cross-coupling reaction, which was supported by the homocoupling dimer **V** formation and a series of control experiments (Scheme 9a-c). The concomitantly generated Cu(I) acetate **VI** would activate alkyl bromide **VII**, providing tertiary alkyl radical species **VIII** with the generation of Cu(II) species **IX**. Finally, the cross-coupling of two different tertiary radicals, **IV** and **VIII** generated in proximity to the copper catalyst would deliver

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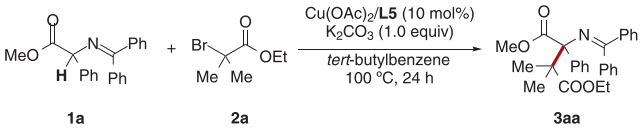
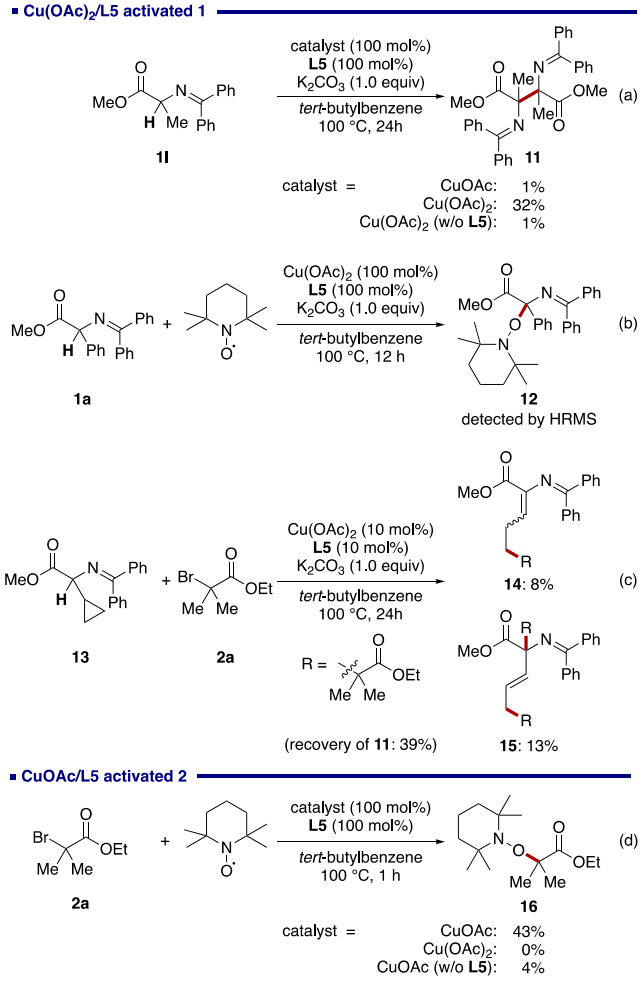
Scheme 8. Control Experiments[a]



entry	variation from standard conditions	yield (%)
1	none	86
2	w/o $Cu(OAc)_2$	n.d.
3	w/o **L5**	18
4	w/o K_2CO_3	8
5	at room temperature	3

[a]Conditions: **1** (0.1 mmol), **2** (0.2 mmol) K_2CO_3 (1.0 equiv), and *tert*-butylbenzene (0.5 mL). Yields were determined by ^1H NMR analysis using 2-methoxynaphthalene as an internal standard.

Scheme 9. Mechanistic Studies Using CuOAc and $Cu(OAc)_2$



the product **X**. The salt metathesis reaction of **IX** with KOAc would regenerate Cu(II) acetate **I**. The alternative mechanism involved Cu(III)/Cu(I) pathway, in which the reductive elimination of intermediate **XIII** occurs, cannot be ruled out (Figure 1B).

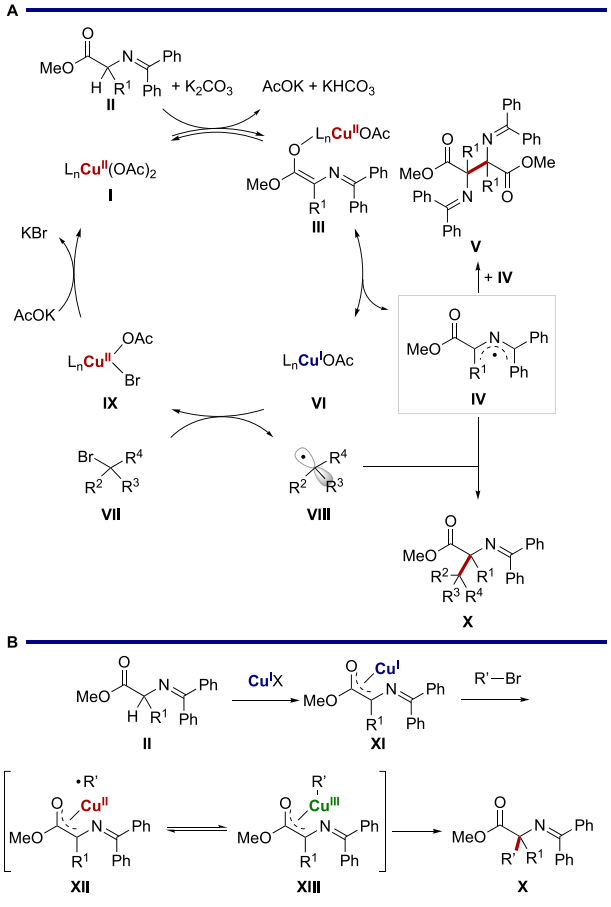


Figure 1. Postulated catalytic cycle.

In conclusion, we developed a new mode for catalytic activation of an amino acid Schiff base. The redox active copper catalyst enabled efficient cross-coupling, leading to hitherto-inaccessible highly congested unnatural α-amino acid derivatives. The broad functional group compatibility highlights the mildness of the present method. Noteworthy is that modifying the reaction conditions enabled β-alkylation followed by oxidation, affording dehydroalanine derivatives bearing tetrasubstituted carbon. Enantiomerically enrich α-amino acid synthesis could be also achieved using chiral auxiliary. The synthesized highly congested unnatural α-amino acid could be coupled with amino acid to afford the dipeptide. Studies to further examine the utility of a platform derived from an α-amino acid Schiff base for other reactions are in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c02707.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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