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Copper/ruthenium relay catalysis enables 1,6-double chiral inductions with stereodivergence†

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The dual catalysis strategy is an efficient and powerful tool to fulfill the stereodivergent synthesis of stereoisomeric products from the same set of starting materials. Great attention has been given to the construction of chiral compounds with two contiguous stereocenters. However, the synthesis of two remote noncontiguous stereocenters is more challenging and is less developed, despite the high demand for synthetic tactics. We herein developed an unprecedented example of the stereodivergent preparation of synthetically useful and biologically important chiral ζ-hydroxy amino ester derivatives containing remote 1,6-noncontiguous stereocenters and a unique β,γ-unsaturation moiety. This cascade dehydrogenation/1,6-Michael addition/hydrogenation protocol between readily-available ketoimine esters and racemic branched dienyl carbinols was rationally realized with bimetallic copper/ruthenium relay catalysis. The key features of the process were atom economy, step economy, and redox-neutrality. All four stereoisomers of chiral ζ-hydroxy amino ester derivatives were easily achieved by the orthogonal permutations of a chiral copper catalyst and chiral ruthenium catalyst. Importantly, a much more challenging stereodivergent synthesis of all eight stereoisomers of chiral peptide products containing three remote stereocenters was accomplished with excellent results through the cooperation of two chiral catalyst pairs and substrate enantiomers.

Introduction

Chiral organic molecules containing multiple stereocenters are frequently found in many natural products, pharmaceuticals, proteins, and biologically active molecules.[1,2] Due to the synthetic versatility and promising biological and pharmaceutical activities, they play an important role in modern synthetic chemistry, especially in medicinal chemistry. It is important and challenging to achieve the precise synthesis of each stereoisomer, which is significantly helpful in elucidating the relationship between molecular structure and biological activities, while facilitating the rapid pace of drug discovery.[3,4] Therefore, the development of an efficient and facile strategy for the straightforward generation of all possible enantiopure stereoisomers has attracted a great deal of interest.[5–11] The stereodivergent dual catalysis strategy, including synergistic catalysis[12–17] and relay catalysis,[18–23] is a powerful protocol that
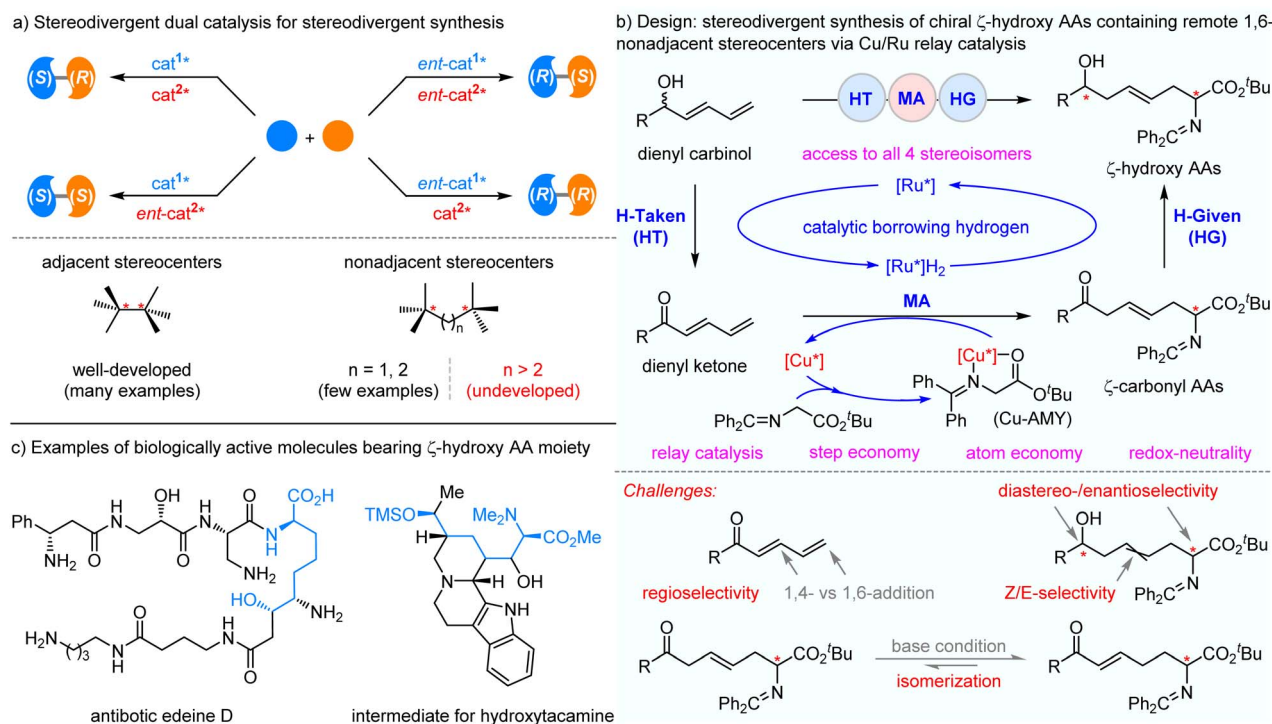
allows reliable synthesis of all stereoisomers from a common set of starting materials and conditions. This strategy can activate two substrates simultaneously or sequentially and control the formation of stereogenic centers independently during the reaction process by employing two distinct chiral catalysts. Owing to its great advantages, tremendous efforts have been devoted to the development of stereodivergent dual catalysis strategies in recent years. Despite significant achievements in stereodivergent reactions, the reported methodologies for stereodivergent synthesis mainly focus on the construction of 1,2-contiguous stereocenters with many elegant examples.[24–53] However, very limited research works disclose the synthesis of chiral molecules containing noncontiguous stereocenters. Successful examples of the synthesis of challenging 1,3-/1,4-nonadjacent stereocenters are sparse.[54–64] In sharp contrast, for the stereodivergent construction of remoter and much more arduous 1,6-nonadjacent stereocenters, it remains an unsolved and prominent synthetic challenge to achieve the full set of four stereoisomers with high yields and excellent stereoselectivities (Scheme 1a).

On the other hand, asymmetric borrowing-hydrogen catalysis[65–69] has emerged as an important and efficient relay catalytic approach to access structurally valuable chiral molecules from easily accessible alcohols in a rapid and atom-economical fashion.[70–72] Recently, with the strategy of relay catalysis, we successfully developed two methods of

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Scheme 1 (a) Stereodivergent dual catalysis, (b) our design: stereodivergent synthesis of 1,6-noncontiguous stereocenters, (c) examples of biologically active molecules bearing ζ-hydroxy amino ester derivatives.

stereodivergent construction of 1,4-nonadjacent stereocenters *via* merging asymmetric borrowing-hydrogen reaction with asymmetric Michael addition.[61,62] Considering the concerns of stereodivergent synthesis of privileged scaffolds with remote 1,6-nonadjacent stereocenters, we envisioned combining asymmetric borrowing-hydrogen catalysis and the azomethine ylides-involved Lewis acid catalysis[73–75] to achieve this challenging goal. As shown in Scheme 1b, the nucleophilic metallated Cu–azomethine ylide[73] (Cu–AMY) could be formed *in situ* by the coordination of glycine-derived diphenyl ketoimine ester with chiral copper(ı) Lewis acid under basic conditions. Meanwhile, the racemic branched dienyl carbinol substrate could be oxidatively dehydrogenated to generate an α,β,γ,δ-unsaturated ketone intermediate and chiral Ru–hydride (Ru–H) species, *via* the chiral borrowing-hydrogen Ru-catalyst. The ensuing asymmetric 1,6-Michael addition, followed by chiral Ru–hydride-promoted asymmetric reduction, would result in the stereodivergent synthesis of highly functionalized ζ-hydroxy amino ester derivative containing remote 1,6-nonadjacent stereocenters and β,γ-unsaturation. These are pervasive structural units, not only in a plethora of natural products and bioactive molecules, but also work as key synthetic intermediates (Scheme 1c).[76–78] The copper/ruthenium relay-catalyzed dehydrogenation/1,6-Michael addition/hydrogenation process, thus envisaged, has some challenges that must be overcome: (1) the competitive reactions among 1,6- *vs.* 1,4-addition lead to difficult control of regioselectivity (site selectivity). In most cases, the partial positive charge density is less at the δ-position than the β-position;[79–84] meanwhile the undesired Ru–H

reduction[85,86] of C=C double bonds in α,β,γ,δ-unsaturated ketone intermediate must be suppressed to improve the reaction efficiency; (2) the control of stereoselectivity, as the initial-formed stereocenter is formed at the remote 6-position of the chiral hydroxy center (five bonds between the two stereocenters) formed later; (3) the control over the *E/Z* geometry[87] of dienyl ketone-based asymmetric 1,6-addition reaction; (4) the potential base-promoted position isomerization of the β,γ-C=C double bond of Michael addition intermediate (chiral ketone) into the thermodynamically favored conjugated enone.[88]

Herein, we reported the stereodivergent synthesis of highly functionalized chiral ζ-hydroxy amino ester derivatives containing remote 1,6-nonadjacent stereocenters and a unique β,γ-unsaturation moiety through dehydrogenation/1,6-Michael addition/hydrogenation relay process between diphenyl ketimine ester/peptides and racemic branched dienyl carbinols enabled by bimetallic copper/ruthenium relay catalysis. This protocol takes advantage of orthogonal one-pot catalysis, omission of intermediate purification steps, full atom economy, redox-neutrality, and efficient access to all four stereoisomers with remote 1,6-nonadjacent stereocenters and predictable control of stereoselectivity.

Results and discussion

Optimization of reaction conditions

Initially, the design protocol was started with benzophenone-derived ketimine ester **1a** and racemic branched dienyl carbinol **2a** as the model substrates. This first step aimed to

investigate the feasibility of dehydrogenation/1,6-Michael addition/hydrogenation reaction promoted by the cooperative Cu/Ru bimetallic relay catalysis at 20 °C. To our delight, the expected product, highly functionalized ζ-hydroxy amino ester *trans*-3a, bearing 1,6-nonadjacent stereocenters and a β,γ-unsaturation moiety, was accessible in high yield with moderate diastereoselectivity and excellent enantioselectivity with the combined Cu(I)/L1[89] and [Ru]-1[90,91] as the catalysts and K$_3$PO$_4$ as the base (93% yield, 4 : 1 dr, >99% ee, Table 1, entry 1). To be noted, the cascade reaction developed here exhibited excellent *E*/*Z*-geometry selectivity, and (*E*)-3a formed as the sole product. No regio-isomer formed by 1,4-Michael addition was detected by crude ^{1}H NMR, suggesting that exclusive regioselectivity favored the less sterically hindered 1,6-Michael addition. Meanwhile, no side product with α,β-unsaturation was observed, indicating that the rate of base-promoted isomerization of the ketone intermediate was slower than that of 1,6-Michael addition. It was found that the subsequent solvent

screening did not deliver better results in 2-Me-THF, Et$_2$O and MTBE, but mess reaction systems were observed in 1,4-dioxane and toluene (Table 1, entries 2–6). A range of chiral ligands for copper complex were then examined, including the phosphoramidite ligand L2,[92] (*R*)-BINAP L3, and ferrocene-based P,N ligands (L4–L7) (Table 1, entries 7–12); ligand L7 provided the best results in 99% yield with >20 : 1 dr and >99% ee (see ESI† for details on more screening on chiral ligands, base and solvent). To our delight, when switching the borrowing-hydrogen catalyst [Ru]-1 to the enantiomeric complex *ent*-[Ru]-1 under otherwise identical conditions, the diastereomeric ζ-hydroxy amino ester *cis*-3a was separated in 96% yield with exclusive diastereoselectivity and excellent enantioselectivity (Table 1, entry 13). In addition, control experiments verified that both copper and ruthenium catalysts are indispensable for this asymmetric cascade process, and the desired product 3a could not be generated without either of the two chiral metal complexes (Table 1, entries 14 and 15).

Table 1 Optimization of reaction conditions[a]

Entry	Ligand for [Cu]	[Ru]	Solvent	Yield[b] (%)	dr[c] (*trans/cis*)	ee[c] (%)
1	L1	[Ru]-1	THF	93	4 : 1	>99
2	L1	[Ru]-1	1,4-Dioxane	Mess	NA	NA
3	L1	[Ru]-1	Toluene	Mess	NA	NA
4	L1	[Ru]-1	2-Me-THF	45	1 : 1	33
5	L1	[Ru]-1	Et$_2$O	64	1 : 1	91
6	L1	[Ru]-1	MTBE	83	2 : 1	96
7	L2	[Ru]-1	THF	60	1 : 1	—
8	L3	[Ru]-1	THF	59	1 : 1	—
9	L4	[Ru]-1	THF	72	13 : 1	99
10	L5	[Ru]-1	THF	99	1 : 3	96
11	L6	[Ru]-1	THF	99	6 : 1	99
12	L7	[Ru]-1	THF	99	>20 : 1	>99
13	L7	*ent*-[Ru]-1	THF	96	<1 : 20	>99
14	L7	—	THF	NA	NA	NA
15	—	[Ru]-1	THF	NA	NA	NA

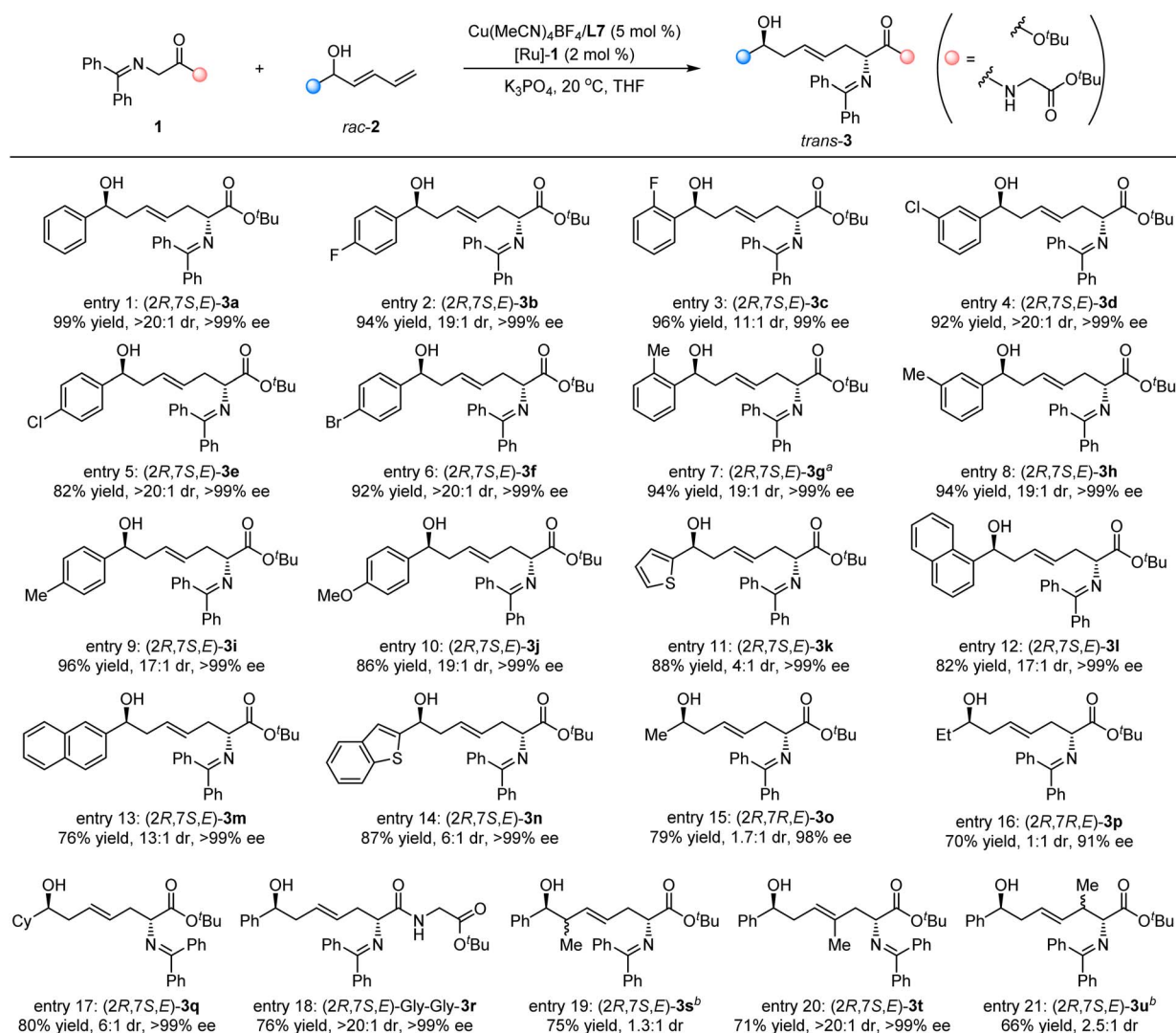[a] All reactions were carried out with 0.60 mmol 2a, 0.20 mmol 1a, 0.01 mmol [Cu], 0.011 mmol L7, 0.004 mmol [Ru]-1, and 0.20 mmol K$_3$PO$_4$ in 2 mL of solvent at 20 °C. The reaction was monitored by TLC. [b] Isolated yield for the diastereomeric mixture. [c] ee and dr were determined by HPLC analysis.

Substrate scope study

Having established optimal reaction conditions, we focused on the investigation of the substrate generality of this cooperative bimetallic Cu/Ru relay-catalyzed dehydrogenation/1,6-Michael addition/hydrogenation reaction. As summarized in Scheme 2, a variety of racemic dienyl carbinols **2** were examined to react with benzophenone-derived ketimine ester **1a** for the construction of densely functionalized chiral ζ-hydroxy amino esters. The racemic dienyl carbinols **2** bearing diverse substituted groups on the phenyl ring, such as electron-neutral (entry 1), electron-deficient (entries 2–6), and electron-donating (entries 7–10), at different positions served as compatible reaction partners and went through this cascade reaction efficiently to access the corresponding products, including *trans*-**3a**–**3j** bearing 1,6-nonadjacent stereocenters with excellent results (82–99% yields, 11 : 1 → 20 : 1 dr, exclusively >99% ee). In addition, the heteroaromatic ring-substituted dienyl

carbinols, **2k** and **2n**, also worked as viable reactants, affording the desired products, *trans*-**3k** and *trans*-**3n**, in high yields with moderate diastereoselectivities and >99% ee (Scheme 2, entries 11 and 14). Notably, 1-naphthyl and 2-naphthyl-substituted dienyl carbinols with steric hindrance were examined, and the corresponding products, *trans*-**3l** and *trans*-**3m**, could be obtained in good yields with acceptable diastereoselectivities and excellent enantioselectivities (82% yield, 17 : 1 dr, >99% ee and 76% yield, 13 : 1 dr, >99% ee; respectively). When racemic methyl (**2o**) or ethyl (**2p**)-substituted dienyl carbinol was examined, the cascade reaction proceeded smoothly to generate the corresponding product, *trans*-**3o** or *trans*-**3p**, in good yields with excellent enantioselectivity albeit with lower diastereoselectivity[93] (Scheme 2, entries 15 and 16). Remarkably, racemic cyclohexyl-substituted dienyl carbinol **2q** was compatible to give the desired product *trans*-**3q** in high yield with good diastereoselectivity and excellent enantioselectivity (80% yield,

Scheme 2 Substrate scope of the *trans*-selective dehydrogenation/1,6-Michael addition/hydrogenation reaction. All reactions were carried out with 0.60 mmol **2**, 0.20 mmol **1**, 0.01 mmol [Cu], 0.011 mmol **L7**, 0.004 mmol [Ru]-**1**, and 0.20 mmol K_3PO_4 in 2 mL of THF at 20 °C for 3–12 h. Isolated yield for the diastereomeric mixture. The dr and ee values were determined by HPLC analysis. [a] 40 °C for 12 h. [b] The ee values were not determined because the racemic samples could not be separated with all the chiral columns in the lab.

6 : 1 dr, >99% ee, Scheme 2, entry 17). Encouraged by these promising results, we extended this bimetallic Cu/Ru catalyst system to the benzophenone-derived ketimine dipeptide; the Gly–Gly–peptide-containing substrate **1b** could be employed well in this relay catalytic system to deliver the desired product, *trans*-**3r**, in 76% yield with >20 : 1 dr and >99% ee (Scheme 2, entry 18). In addition, the influence of the substituted group on the position of the dienyl motif was also investigated. Although low diastereoselectivities were observed for the 1,6-adducts, **3s** and **3u**, the desired *trans*-**3t**-bearing methyl group on the γ-position could be obtained in 71% yield with >20 : 1 dr and >99% ee (Scheme 2, entries 19–21), and no 1,4-adducts were observed.

Considering the above success in the *trans*-selective synthesis of chiral ζ-hydroxy amino ester derivative bearing 1,6-nonadjacent stereocenters, we paid attention to the preparation of the diastereoisomers with *cis*-selectivity promoted by [Cu/**L7**]/*ent*-[Ru]-**1** catalytic system. A wide range of racemic dienyl carbinols **2** reacted with ketimine ester **1a** smoothly, giving the corresponding *cis*-selective products in good to high yields and excellent stereoselectivities. As summarized in Scheme 3, the electronic properties and positions of the substituted groups on the aryl ring of the dienyl carbinol substrates had a negligible impact on the reaction results. The corresponding products, *cis*-**3a**–**3j**, could be obtained in 75–97% yields with 11 : 1 → 20 : 1 dr and >99% ee (Scheme 3, entries 1–10). In addition, the naphthyl- or aromatic heterocyclic-substituted dienyl carbinols were observed to be suitable reaction partners to generate the desired products, *cis*-**3k**–**3n**, with excellent results (85–94% yields, 6 : 1–17 : 1 dr, 98% → 99% ee, Scheme 3, entries 11–14). The challenging alkyl substituted dienyl carbinols, **2o**–**2q**, also showed good reactivity, delivering the desired product, *cis*-**3o**–**3q**, in good yields with low to moderate diastereoselectivity and excellent enantioselectivity (Scheme 3, entries 15–17). To our delight, the ketimine amide **1b** bearing Gly–Gly–dipeptide also worked well to afford the expected product *cis*-**3r** in good yield with excellent stereoselectivity (Scheme 3, entry 18). In addition, the dienyl carbinols bearing methyl group on the different positions of the dienyl motif were also examined, and the 1,6-adducts, **3s**–**3u**, were obtained as the only regioisomers in good yields (Scheme 3, entries 19–21). Excellent diastereoselectivity and excellent enantioselectivity were observed for the *cis*-**3t**-bearing methyl group on the γ-position (Scheme 3, entry 20).

Having investigated the substrate generality of dienyl carbinols, we are interested in examining whether trienyl carbinols could be tolerated in the cooperative Cu/Ru bimetallic relay catalytic system to provide otherwise inaccessible θ-hydroxy amino ester derivative bearing more remote 1,8-nonadjacent stereocenters. As shown in Scheme 4, when (2*E*,4*E*)-1-phenylhepta-2,4,6-trien-1-ol **4a** was applied as the substrate, in combination with Cu(ɪ)/**L7**/[Ru]-**1** complexes as the relay catalyst, the corresponding *trans*-selective product, *trans*-**5a**, could be easily accessible in 94% yield with 16 : 1 dr and >99% ee. Trienyl carbinols containing electron-donating (Me, **4b**) or electron-deficient (F, **4c**)-substituted groups on the phenyl ring proceeded this asymmetric cascade dehydrogenation/1,8-Michael addition/hydrogenation reaction smoothly, and the

desired products, *trans*-**5b** and *trans*-**5c**, were obtained in high yields with excellent diastereoselectivities and enantioselectivities (93% yield, >20 : 1 dr, >99% ee and 95% yield, 19 : 1 dr, >99% ee, respectively). It was found that ketimine amide **1b** bearing Gly–Gly–dipeptide could react with **4a** for the generation of the expected product, *trans*-**5d**, in 83% yield with >20 : 1 dr and >99% ee. To our delight, the *cis*-selective dehydrogenation/1,8-Michael addition/hydrogenation reaction was readily achieved, in combination with Cu(ɪ)/**L7**/*ent*-[Ru]-**1** catalytic system, and the corresponding products, *cis*-**5a**–**5d**, were obtained in high yields with high diastereoselectivities and excellent enantioselectivities.
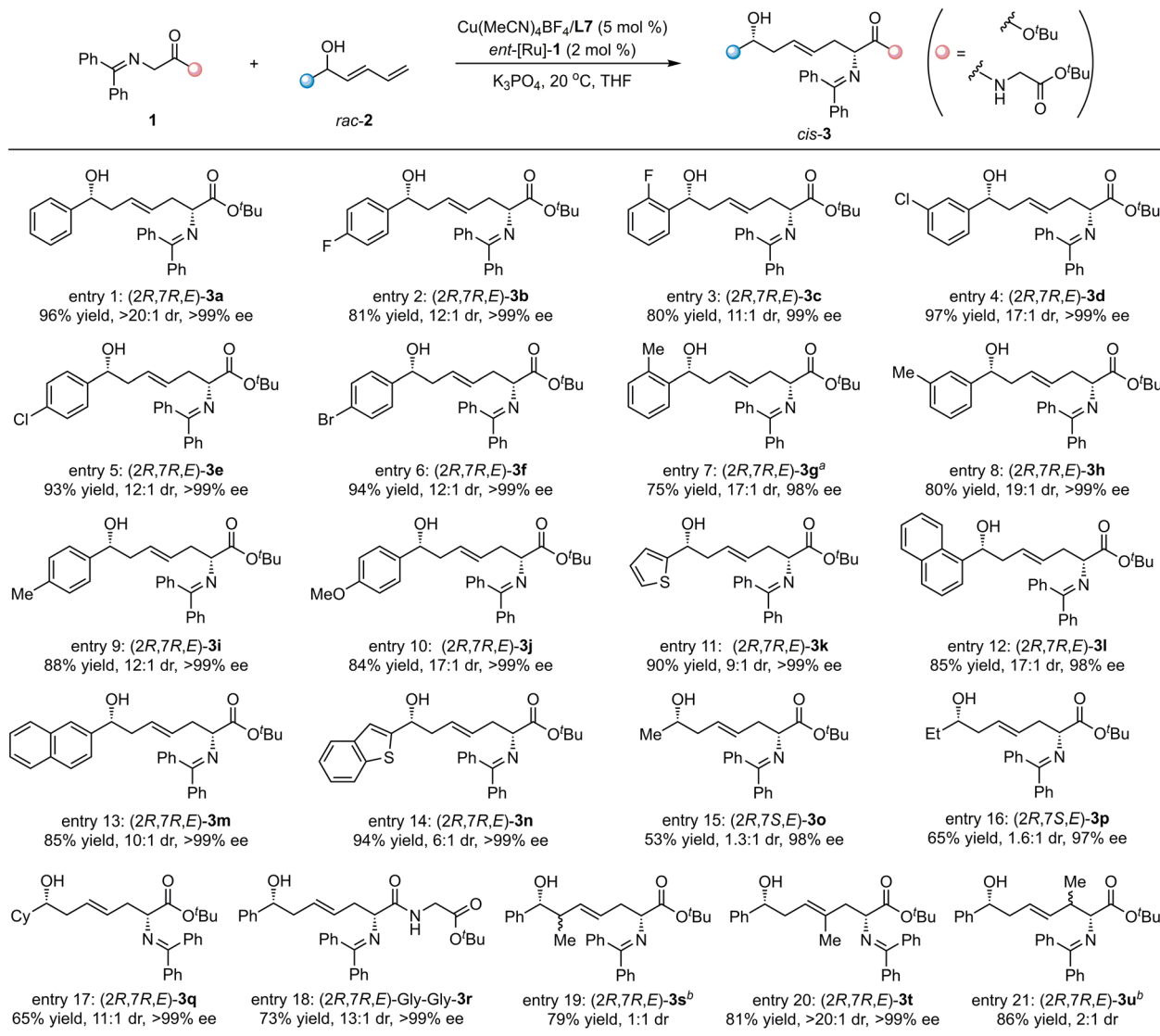
Stereodivergent synthesis

To demonstrate the stereodivergence of this protocol, the transformation between ketimine ester **1a** and racemic dienyl carbinol **2a** was first carried out by four distinct catalyst systems *via* the orthogonal permutation of two chiral copper catalysts and two ruthenium catalysts. As shown in Scheme 5, all four stereoisomers of product-(2*R*,7*S*,*E*)-**3a**, (2*R*,7*R*,*E*)-**3a**, (2*S*,7*S*,*E*)-**3a**, and (2*S*,7*R*,*E*)-**3a** in optically pure form (>99% ee) with exclusive diastereoselectivities (>20 : 1 dr) could be achieved readily in 96–99% yields. In addition, the ketimine amide **1b** bearing Gly–Gly–dipeptide and the trienyl carbinol **4a** were respectively examined as the reaction partners to further exhibit the stereodivergent synthesis; the corresponding products **3s** and **5a** with four stereoisomers in each case could be obtained in good to high yields with excellent stereoselectivities (70–99% yield, 13 : 1 → 20 : 1 dr, generally above 99% ee). These results offered profitable evidence to confirm that each chiral catalyst could independently control the asymmetric induction of each step in this cooperative bimetallic Cu/Ru relay-catalyzed cascade dehydrogenation/1,6 or 1,8-Michael addition/hydrogenation reaction.

To our knowledge, the stereodivergent synthesis of chiral molecules with remote and more than two stereocenters has not yet been reported. To further display the excellent robustness of this dual catalytic system, we applied a ketimine amide compound bearing Gly–D-Ala and Gly–L-Ala units, *i.e.*, **1c**, respectively, in this cascade transformation. We aimed to achieve the stereodivergent synthesis of chiral hydroxy amino acid derivatives with three stereocenters. As displayed in Scheme 6, we were able to prepare all eight stereoisomers of the desired product **3v** containing remote three stereocenters through the cooperation of chiral catalyst pair and substrate enantiomer in good yields with excellent stereoselectivities (45–60% yields, 20 : 1 → 20 : 1 dr). These reaction results demonstrated that the formation of these isomers was achieved well by the control chiral catalyst, but was not affected by the inherent chirality factors from the substrates.

Scale-up experiments and synthetic application

The highly functionalized chiral hydroxy amino ester derivative product renders this protocol a promising tool to access other useful optically active molecules through further synthetic elaborations. As depicted in Scheme 7a, the gram-scale

Scheme 3 The substrate scope of the *cis*–selective dehydrogenation/1,6–Michael addition/hydrogenation reaction. All reactions were carried out with 0.60 mmol **2**, 0.20 mmol **1**, 0.01 mmol [Cu], 0.011 mmol **L7**, 0.004 mmol *ent*-[Ru]-**1**, and 0.20 mmol K_3PO_4 in 2 mL of THF at 20 °C for 3–12 h. Isolated yield for the diastereomeric mixture. The dr and ee values were determined by HPLC analysis. [a] 40 °C for 12 h. [b] The ee values were not determined because the racemic samples could not be separated with all the chiral columns in the lab.
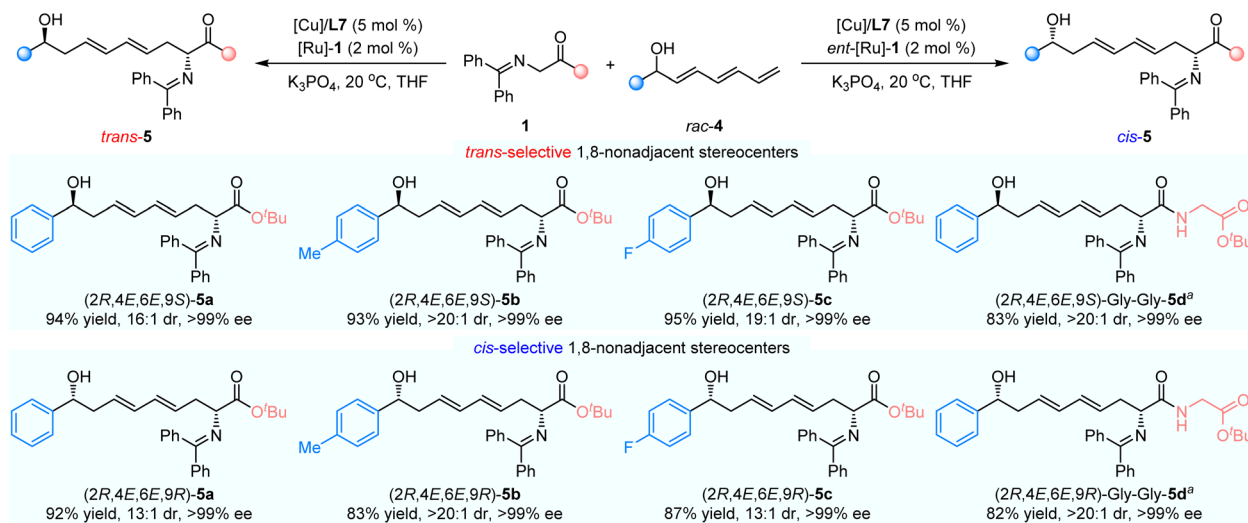
reactions between ketimine ester **1a** and racemic dienyl carbinol **2a** were carried out in the presence of a [Cu(ɪ)/**L7**]/[Ru]-**1** or [Cu(ɪ)/**L7**]/*ent*-[Ru]-**1** catalytic system to examine the synthetic practicability; *trans*-product (2*R*,7*S*,*E*)-**3a** and *cis*-product (2*R*,7*R*,*E*)-**3a** were respectively obtained in high yields and maintained stereoselectivities even under reduced catalyst loading. Product **6** containing a 1,2,3-triazole unit could be efficiently constructed in good yield without loss of stereo-selectivities through the Mitsunobu reaction followed by Cu-catalyzed click reaction with phenylacetylene (Scheme 7b). The sequential Mitsunobu reaction/Staudinger reduction of (2*R*,7*S*,*E*)-**3a** could finally furnish a high yield of enantio-enriched ζ-amino derivative **7** in 76% yield and diaster-eoselectivity. Acidic hydrolysis of **7** delivered the chiral 1,6-diamine **8** in high yield. The direct hydrogenation of (2*R*,7*S*,*E*)-**3a** promoted by Pd/C could furnish chiral α-amino ζ-alcohol

derivative **9** in 80% yield with >20 : 1 dr. In addition, treatment of (2*R*,7*S*,*E*)-**3a** with 15% citric acid, followed by amino protec-tion with *p*-toluenesulfonyl chloride (TsCl), delivered the chiral compound, *trans*-**10**, in 78% overall yield with >20 : 1 dr. In addition, I_2-enabled *endo-trig* cyclization of (2*R*,7*S*,*E*)-**3a** provided polysubstituted tetrahydrofurans, **11** and **11′**, in 45% and 27% yield, respectively. The absolute configuration of (2*R*,7*S*,*E*)-*trans*-**10** and its diastereoisomer, (2*R*,7*R*,*E*)-*cis*-**10**, were unambiguously determined by X-ray diffraction analysis[94] (CCDC 2328948 and 2328949), and those of *trans*- and *cis*-products (**3** and **5**) were deduced based on these results.

Kinetic resolution studies

As racemic dienyl carbinol **2a** was employed in this cascade dehydrogenation/1,6-Michael addition/hydrogenation reaction,
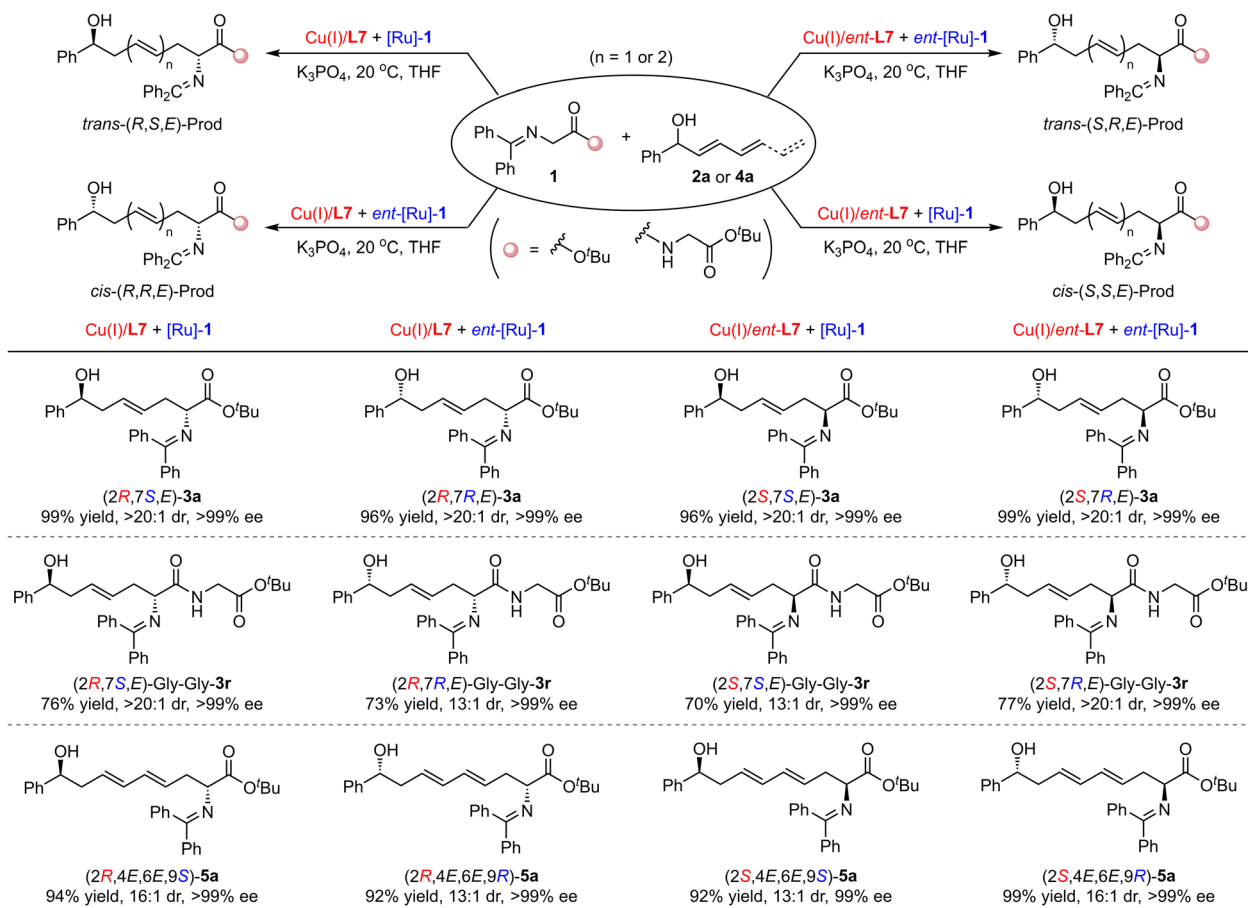
Scheme 4 Cu/Ru-relay catalysis for the construction of *cis*- and *trans*-α-AAs and small peptides bearing 1,8-nonadjacent stereocenters with trienyl carbinols. All reactions were carried out with 0.60 mmol **4**, 0.20 mmol **1**, 0.01 mmol [Cu], 0.011 mmol **L7**, 0.004 mmol [Ru]-**1** or *ent*-[Ru]-**1**, and 0.20 mmol K₃PO₄ in 2 mL of THF at 20 °C for 3–9 h. Isolated yield. The dr and ee values were determined by HPLC analysis. ^{a} 40 °C for 12 h.
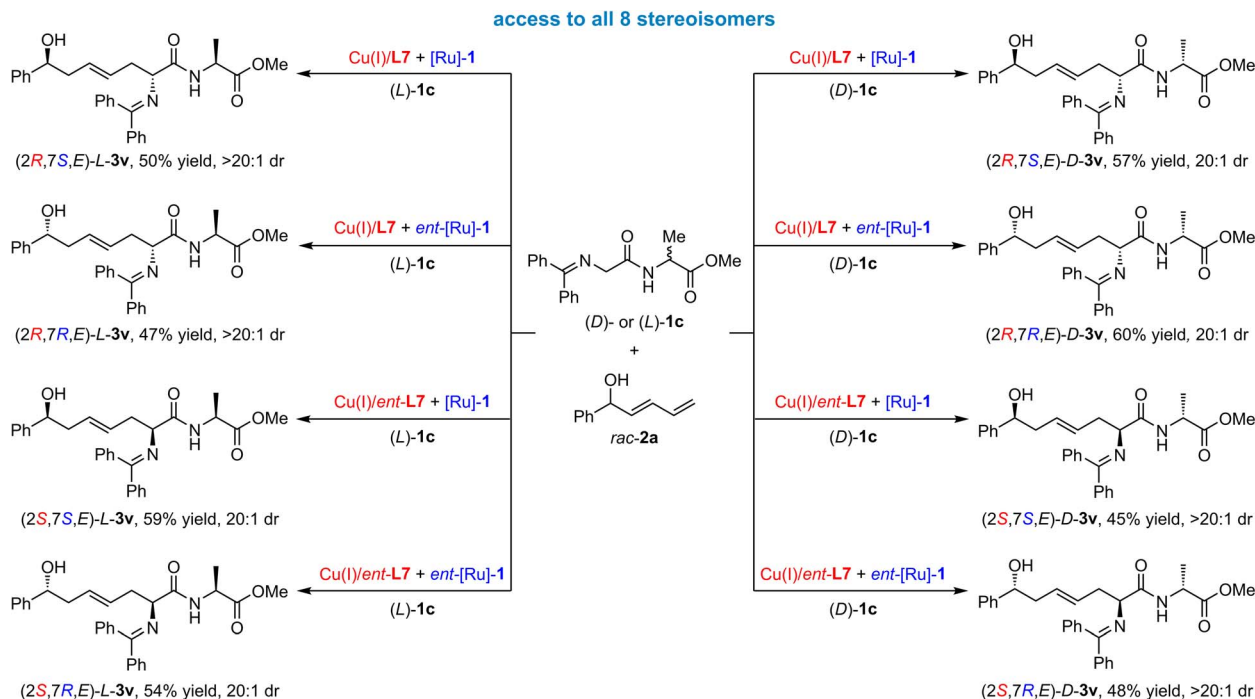
we wondered whether kinetic resolution or dynamic kinetic resolution process was involved in this relay catalytic system. A series of control experiments were carried out to investigate this aspect. As displayed in Scheme 8, the reaction with 0.38 mmol of racemic dienyl carbinol **2a** and 0.2 mmol of ketimine ester **1a** was carried out under standard reaction conditions; product

Scheme 5 Representative examples of stereodivergent synthesis to access all four stereoisomers.
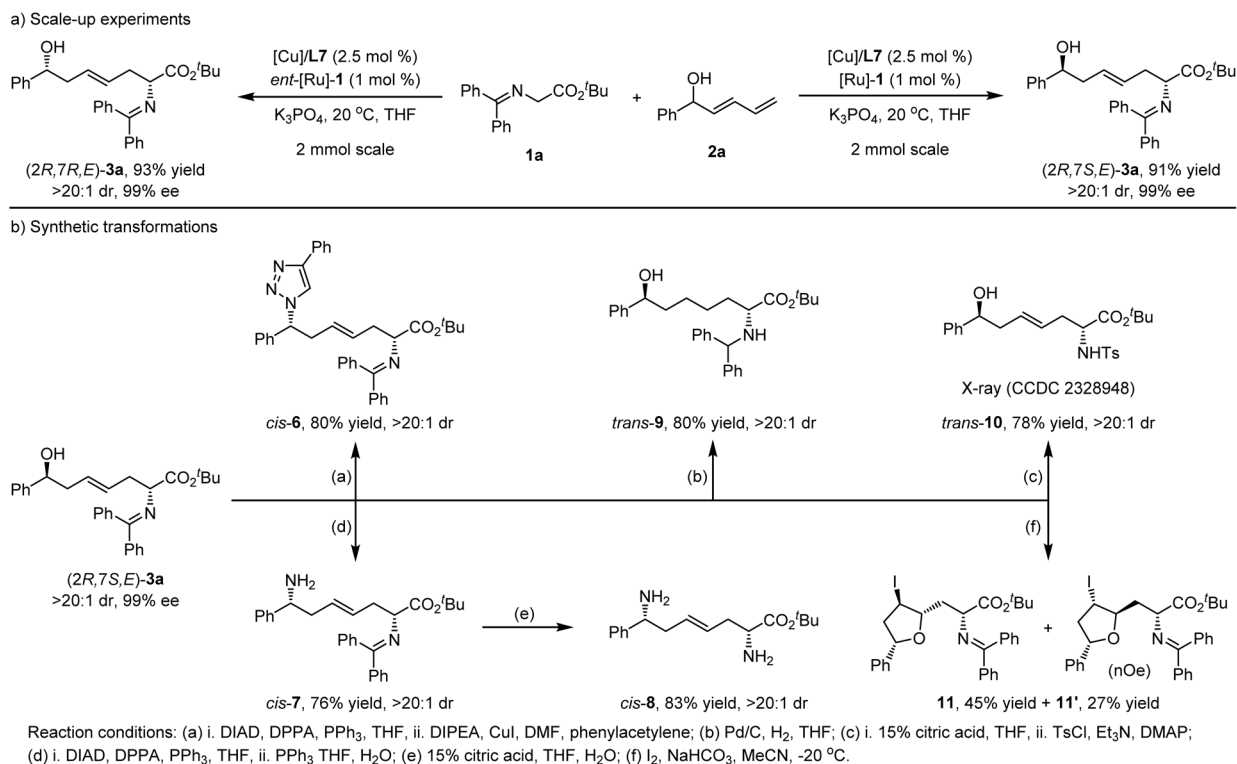
access to all 8 stereoisomers

Scheme 6 Stereodivergent synthesis of peptide products with three stereocenters to access all eight stereoisomers.

(2R,7S,E)-**3a** was obtained in 90% yield (based on **1a**) with >20 : 1 dr and 99% ee, and the remaining (R)-**2a** was recovered in 31% yield (based on racemic **2a**) with 93% ee. Meanwhile, the reaction with 0.2 mmol o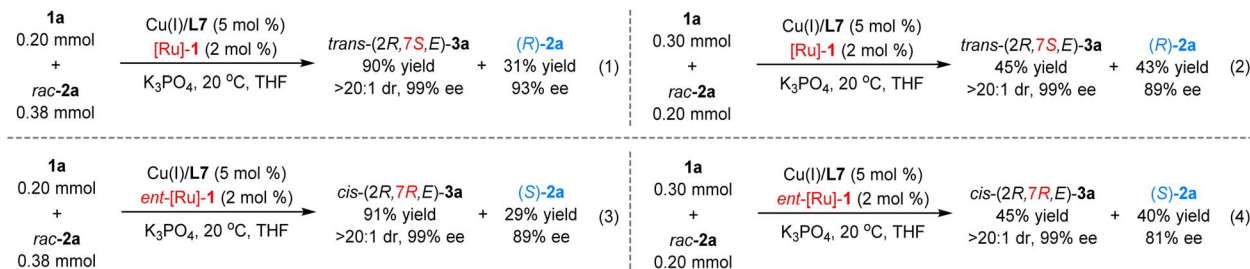f racemic dienyl carbinol **2a** and 0.3 mmol of ketimine ester **1a** led to only 45% yield of the product, (2R,7S,E)-**3a**, with excellent stereoselectivity, along with 43% yield of unreacted (R)-**2a** with 89% ee. Similar results were observed when [Cu/**L7**] and ent-[Ru]-**1** complexes were used as

Reaction conditions: (a) i. DIAD, DPPA, PPh$_3$, THF, ii. DIPEA, CuI, DMF, phenylacetylene; (b) Pd/C, H$_2$, THF; (c) i. 15% citric acid, THF, ii. TsCl, Et$_3$N, DMAP; (d) i. DIAD, DPPA, PPh$_3$, THF, ii. PPh$_3$ THF, H$_2$O; (e) 15% citric acid, THF, H$_2$O; (f) I$_2$, NaHCO$_3$, MeCN, -20 °C.

Scheme 7 (a) Scale-up experiments and (b) synthetic elaborations.

Scheme 8 Kinetic resolution studies.

the cooperative catalysts. These experimental results demonstrate that racemic dienyl carbinol **2a** should go through a kinetic resolution in this relay catalysis protocol.

Conclusions

In summary, we have successfully developed the first example of the stereodivergent synthesis of synthetically useful and biologically important chiral molecules containing remote 1,6-nonadjacent stereocenters. The dual Cu/Ru-relay catalysis enabled cascade dehydrogenation/1,6-Michael addition/hydrogenation protocol between ketimine esters and racemic dienyl carbinols, providing an efficient approach to synthesizing a wide range of chiral ζ-hydroxy amino ester derivatives with remote 1,6-nonadjacent stereocenters and a unique β,γ-unsaturation in good to high yields with excellent diastereoselectivities and enantioselectivities. The stereodivergent syntheses of all four stereoisomers of chiral ζ-hydroxy amino ester derivatives could be readily achieved by the orthogonal permutations of a chiral copper catalyst and a chiral ruthenium catalyst. Moreover, the more challenging synthesis among all eight stereoisomers of the desired dipeptide products containing three remote stereocenters was readily accomplished with excellent results through the current cascade relay catalytic system by the cooperation of two chiral catalyst pairs and substrate enantiomers. The synthetic utility of this protocol was demonstrated by a scale-up reaction and further synthetic transformations. Based on the results of the control experiment, the kinetic resolution of racemic dienyl carbinols was involved in this Cu/Ru-relay catalyzed cascade reaction. This current cascade borrowing hydrogen/Michael addition protocol may provide a general avenue for the stereodivergent synthesis of chiral amino acid derivatives bearing remote 1,6-nonadjacent stereocenters with the key features of atom economy, step economy, and redox-neutrality.

Data availability

All experimental procedures, characterisation data, mechanistic investigations, NMR spectra, and HPLC spectra can be found in the ESI.†

Author contributions

C. J. W. conceptualized the project. C. J. W. and X. Q. D. supervised the investigation. H. R. Y., X. C., X. C., and Z. F. W.

performed the research. C. J. W. and X. Q. D. co-wrote the paper. All authors analyzed the data, discussed the results, and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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94 Deposition numbers 2328948 (for (2R,7S,E)-*trans*-**10**), and 2328949 (for (2R,7R,E)-*cis*-**10**) contain the supplementary crystallographic data for this paper.