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Stereodivergent assembly of δ -valerolactones with an azaarene-containing quaternary stereocenter enabled by Cu/Ru relay catalysis†

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Developing methodologies for the expedient construction of biologically important δ -valerolactones bearing a privileged azaarene moiety and a sterically congested all-carbon quaternary stereocenter is important and full of challenges. We present herein a novel multicatalytic strategy for the stereodivergent synthesis of highly functionalized chiral δ -valerolactones bearing 1,4-nonadjacent quaternary/tertiary stereocenters by orthogonally merging borrowing hydrogen and Michael addition between α -azaaryl acetates and allylic alcohols followed by lactonization in a one-pot manner. Enabled by Cu/Ru relay catalysis, this cascade protocol offers the advantages of atom/step economy, redox-neutrality, mild reaction conditions, and broad substrate tolerance. Scale-up experiments and synthetic transformations further demonstrated the potential for synthetic applications. Mechanistic experiments support the envisioned bimetallic relay catalytic mechanism, and the key role of Cs_2CO_3 in promoting lactonization was also revealed.

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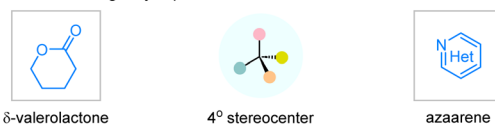
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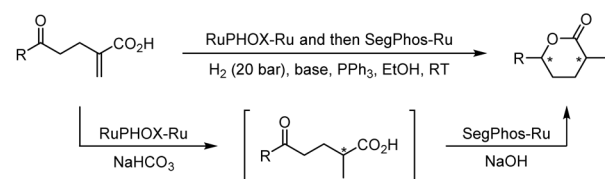
Introduction

The stereoselective incorporation of all-carbon quaternary stereocenters into privileged heterocyclic molecular architectures to enhance three-dimensional complex geometries represents a significant objective in organic and medicinal synthesis as increased saturation and complexity often lead to increased biological activity and benefit drug discovery.¹ Ubiquitous δ -valerolactones (Scheme 1a), especially in enantioenriched forms, are crucial subunits of numerous natural products² and various molecules of pharmaceutical interest that display a wide range of biological properties, including antibacterial,³ antiviral,⁴ anticancer,⁵ and cholesterol-lowering agents (HMGCR inhibitors).⁶ Two of the world's best-selling statin drugs, Lipitor and Zocor, contain a β -hydroxy- δ -valerolactone skeleton or its ring-opening δ -hydroxy carboxylate moiety.⁷ In addition, δ -valerolactones are also synthetically useful building blocks, such as the Prelog-Djerassi lactone, for the preparation of important bioactive compounds.⁸ Due to the

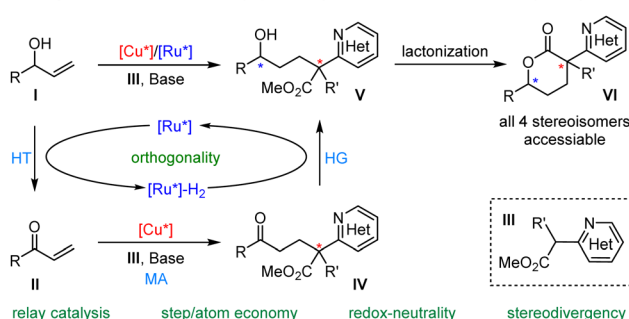
a) Ubiquitous and biologically important core structures



b) Previous work: Stereodivergent synthesis of all four stereoisomers of δ -valerolactones bearing two 1,4-nonadjacent tertiary stereocenters via Ru/Ru sequential AH



c) Design plan for stereodivergent access to all four stereoisomers of δ -valerolactones bearing azaarene and 1,4-tertiary-quaternary stereocenters via Cu/Ru relay catalysis



Scheme 1 Background information.

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pharmacological importance and synthetic utility of optically active δ -valerolactones bearing multiple stereocenters, there has been a growing interest in asymmetric preparation of such compounds in the last few decades. Various strategies have been developed to synthesize chiral δ -valerolactones;⁹ however, stoichiometric amounts of chiral auxiliaries and/or multiple-step sequences are generally required to achieve such chiral molecules as only one stereoisomer or its enantiomer.¹⁰ It is well-known that different stereoisomers of chiral molecules always exhibit different biological activities, which are closely related to their stereochemical configurations. Therefore, it is necessary to develop convenient and step-economical methods for the stereodivergent synthesis¹¹ of all stereoisomers of chiral δ -valerolactones bearing multiple stereocenters, which is conducive to elucidating the relationship between molecular configurations and biological activities and discovering new drugs.¹² Most recently, Zhang and co-workers developed a creative bimetallic Ru/Ru sequential catalysis for asymmetric hydrogenation of α -methylene δ -keto carboxylic acids, and achieved the only example of stereodivergent synthesis of chiral δ -valerolactones containing 1,4-non-adjacent tertiary/tertiary stereocenters¹³ (Scheme 1b). On the other hand, pyridine, as a privileged azaarene skeleton, is the most common nitrogen heterocycle among the 321 unique new small-molecule drugs approved by FDA (2013–2023).¹⁴ We envisioned that combining two biologically important δ -valerolactone and azaarene motifs into a single new three-dimensional molecule with saturation and complexity through a linchpin of all-carbon quaternary stereocenters would introduce some unprecedented benefits to enhance potency, selectivity, and other drug-like properties.¹⁵ To our knowledge, there is no efficient method that enables stereodivergent construction of δ -valerolactones with an azaarene group contained within a α -quaternary stereocenter in a convenient and step-economical manner.

Borrowing-hydrogen (BH) catalysis has emerged as a convenient and atom-economic relay catalytic protocol for preparing structurally important chiral molecules starting from easily available alcohols in recent years,¹⁵ and this process generally includes three steps: hydrogen borrowing, the reaction of the activated intermediate, and hydrogen returning. In continuation of our interest in stereodivergent synthesis¹⁶ and recent achievements in BH-involved bimetallic relay catalysis,^{17,18} we envisaged that orthogonally merging asymmetric borrowing-hydrogen catalysis and chiral Lewis acid catalysis with allylic alcohols and α -azaaryl acetates, to execute a one-pot dehydrogenation (HT)/Michael addition (MA)/hydrogenation (HG)/lactonization cascade process,¹⁹ could offer the opportunity to achieve stereodivergent synthesis of chiral δ -valerolactones with an azaarene-containing α -quaternary stereocenter and a tertiary stereocenter. As shown in Scheme 1c, the racemic branched allylic alcohol substrate **I** undergoes oxidative dehydrogenation with the aid of a chiral borrowing-hydrogen Ru-catalyst to form the active α,β -unsaturated ketone **II** and chiral Ru-hydride species, and the former reacts with the nucleophilic α -azaaryl acetate **III** ligated by chiral Cu-Lewis acid to give the corresponding Michael addition intermediate **IV**; the ensuing chiral Ru-hydride-enabled asymmetric reduction of the

carbonyl group followed by spontaneous δ -lactonization delivers enantioenriched α -azaaryl-containing δ -valerolactones **VI** bearing 1,4-nonadjacent tertiary and quaternary stereocenters in a stereodivergent manner. Although theoretically feasible, there are still some challenges in this design: (1) the potential coordination of the N-heteroarene group in the α -azaaryl acetate substrate may cause deactivation of the borrowing-hydrogen Ru-catalyst; (2) undesired background reactions in the Michael addition step, the annulation efficiency of lactonization, and the potential overreduction²⁰ of the resulting δ -valerolactones into 1,5-diols; (3) the feasibility of stereoselectivity control enabled by this Cu/Ru relay catalysis, since the sterically congested quaternary stereocenter formed in the preceding Michael addition step has potential impact on the asymmetric induction of the following reductive hydrogenation.

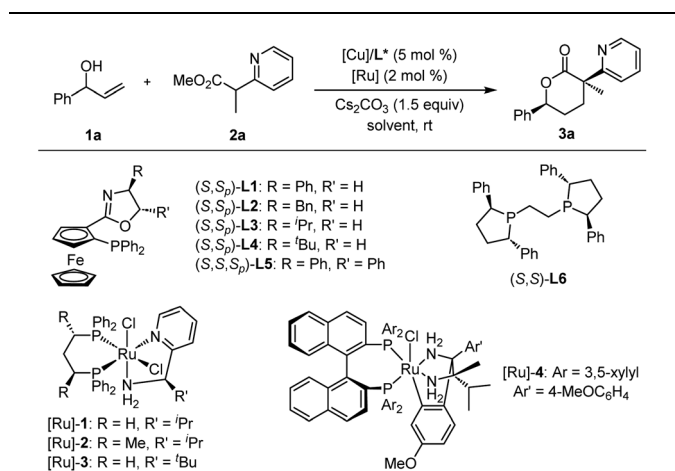
Herein, we uncover a concise methodology enabled by bimetallic copper/ruthenium relay catalysis, which orthogonally merges borrowing hydrogen and Michael addition followed by lactonization. This cascade process circumvents substrate pre-activation, intermediate isolation and purification to realize the stereodivergent and rapid synthesis of highly functionalized chiral δ -valerolactones with an azaarene-containing α -quaternary and a tertiary stereocenter in good yields with excellent stereoselectivity control. This protocol features step economy, redox-neutrality, high atom economy,²¹ and the precise synthesis of all four stereoisomers of otherwise inaccessible chiral δ -valerolactones with 1,4-nonadjacent stereocenters from the same set of readily available starting materials.

Results and discussion

Optimization of reaction conditions

To verify the feasibility of the designed protocol, we began to investigate the cooperative Cu/Ru bimetallic relay catalysis for the cascade dehydrogenation/1,4-Michael addition/hydrogenation/lactonization process between the model substrates phenyl allylic alcohol **1a** and methyl 2-(pyridin-2-yl)propanoate **2a**. To our delight, the expected δ -valerolactone product **3a** was obtained in good yield with high diastereoselectivity and excellent enantioselectivity using the Cu(I)/**L1** and [Ru]-**1** catalytic system with THF as the solvent and Cs₂CO₃ as the base (76% yield, 16 : 1 dr, >99% ee, Table 1, entry 1). A series of chiral ferrocene-based P,N-ligands (**L2**–**L5**) and the chiral diphosphine ligand (*S,S*)-Ph-BPE **L6** for the copper complex were then examined, and ligand **L5** derived from chiral 1,2-diphenyl amino alcohol provided the best results, giving an 80% yield with >20 : 1 dr and 99% ee (Table 1, entries 2–6). The evaluation of other chiral borrowing-hydrogen catalysts was continued, but no further improvement was achieved (Table 1, entries 7–9). With the combination of [Cu]/**L5** and [Ru]-**1** as catalysts, several bases, including inorganic bases K₃PO₄ and Na₂CO₃, as well as organic bases DBU and Et₃N, were then applied, and K₃PO₄ provided the desired product **3a** with similar results (Table 1, entry 10). Further solvent screening showed that 1,4-dioxane gave comparable results (Table 1, entries 14–16). Ester group variation in other α -methyl pyridinyl acetates, such as ethyl ester and *tert*-butyl ester, was also investigated; product **3a** could be



Table 1 Optimization of reaction conditions^a

Entry	[Ru]	L*	Solvent	Yield ^b (%)	dr ^c	ee ^d (%)
1	[Ru]-1	L1	THF	76	16 : 1	99
2	[Ru]-1	L2	THF	55	13 : 1	99
3	[Ru]-1	L3	THF	42	9 : 1	99
4	[Ru]-1	L4	THF	40	10 : 1	99
5	[Ru]-1	L5	THF	80	>20 : 1	99
6	[Ru]-1	L6	THF	52	4 : 1	97
7	[Ru]-2	L5	THF	74	>20 : 1	99
8	[Ru]-3	L5	THF	36	>20 : 1	99
9	[Ru]-4	L5	THF	30	5 : 1	99
10 ^e	[Ru]-1	L5	THF	72	19 : 1	99
11 ^f	[Ru]-1	L5	THF	NR	—	—
12 ^g	[Ru]-1	L5	THF	NR	—	—
13 ^h	[Ru]-1	L5	THF	NR	—	—
14	[Ru]-1	L5	Toluene	65	14 : 1	99
15	[Ru]-1	L5	1,4-Dioxane	78	>20 : 1	99
16	[Ru]-1	L5	DCM	76	16 : 1	99
17 ⁱ	[Ru]-1	L5	THF	75	18 : 1	99
18 ^j	[Ru]-1	L5	THF	70	3 : 1	95

^a All reactions were carried on with $[\text{Cu}]/\text{L}^*$ (5 mol %), $[\text{Ru}]$ (2 mol %), 0.6 mmol **1a**, 0.2 mmol **2a** and 0.3 mmol base in 2 mL of solvent for 24–36 h. $\text{Cu}(\text{I}) = \text{Cu}(\text{MeCN})_4\text{PF}_6$. ^b Yields refer to isolated yields after chromatography. ^c dr was determined by crude ^1H NMR analysis. ^d ee was determined by HPLC analysis. ^e K_3PO_4 was used as the base. ^f Na_2CO_3 was used as the base. ^g DBU was used as the base. ^h Et_3N was used as the base. ⁱ Ethyl 2-(pyridin-2-yl)propanoate was used instead of **2a**. ^j *tert*-Butyl 2-(pyridin-2-yl)propanoate was used instead of **2a**.

obtained with decreasing yield and stereoselectivity (Table 1, entries 17 and 18).

Substrate scope study

With the optimal reaction conditions in hand, we focused on the exploration of the substrate scope and generality of this Cu/Ru relay catalyzed cascade reaction. As summarized in Table 2, a variety of α -methyl azaaryl acetates **2** were employed to react with allylic alcohol **1a**. α -Methyl pyridinyl acetates bearing diverse substituents (F, Cl, Br, Ph, and MeO) at different positions on the pyridinyl ring are well tolerated in this transformation, giving the corresponding products **3b–3j** in good yields (62–73%) with high diastereoselectivity (7 : 1–14 : 1 dr)

and generally 99% ee (Table 2, entries 1–9). Other α -methyl azaaryl acetate nucleophiles with pyrazinyl or quinolinyl units were also investigated; the expected products **3k–3l** were generated with excellent reaction outcomes (57% yield, 11 : 1 dr, and 98% ee and 67% yield, >20 : 1 dr, and 99% ee; respectively, Table 2, entries 10 and 11). Moreover, a wide range of α -pyridinyl acetates bearing various alkyl substituted groups on the α -carbon, including aryl, cyclopropyl, alkenyl, and imide groups, were subjected to this transformation, giving the desired products **3m–3r** in good yields with a high level of stereoselective control (65–82% yields, 4 : 1–>20 : 1 dr, and 87–99% ee, Table 2, entries 12–17). Remarkably, the cyclic azaaryl acetate **2s** was well tolerated as the reaction partner, giving the desired product **3s** containing a unique α -spiro-quaternary stereocenter in good yield with excellent diastereo/enantioselectivity (78% yield, >20 : 1 dr, and 99% ee, Table 2, entry 18), which is an important scaffold in medicinal chemistry.²² Methyl 2-(pyridin-3-yl) and methyl 2-(pyridin-4-yl)propanoate were examined under the standard reaction conditions, and poor conversion was observed without formation of the desired products, demonstrating that the 2-(pyridin-2-yl) moiety in substrate **2** played a key role in enhancing the reactivity.

Having investigated the substrate generality of α -azaaryl acetates, we turned our attention to the examination of this Cu/Ru relay catalysis with regard to allylic alcohols (Table 3). The racemic allylic alcohols **1** bearing different electron-deficient (F, Br, CF_3 , and CO_2Me) or electron-donating (Me and MeO) substituted groups on the phenyl ring underwent this cascade reaction smoothly, giving the corresponding δ -valerolactone products (**3t–3D**) in 55–73% yields with 6 : 1–19 : 1 dr and generally with 99% ee (Table 3, entries 1–11). It was found that the position of the substituted groups has a negligible effect on the reaction results. Encouraged by these promising results, sterically constrained 2-naphthyl and 1-naphthyl substituted allylic alcohols were also tested in this protocol as suitable reaction partners, providing the corresponding products **3E** and **3F** in good yields with excellent stereoselectivities (Table 3, entries 12 and 13). The allylic alcohols containing hetero-aromatic rings served as compatible substrates, generating the desired products **3G** and **3H** with satisfactory results (Table 3, entries 14 and 15). The challenging alkyl substituted allylic alcohols were further examined, and the expected product **3I** was obtained in good yield with acceptable diastereoselectivity and excellent enantioselectivity (Table 3, entry 16). The absolute configuration of product **3t** was unequivocally determined to be (3*R*,6*S*) by X-ray diffraction analysis (CCDC 2375149).²³

Stereodivergent synthesis

The stereodivergence of this cascade protocol was then demonstrated by the orthogonal permutation of the chiral copper catalysts and chiral ruthenium catalysts. As demonstrated in Scheme 2, when the reaction of α -methyl pyridinyl acetate **2a** was conducted with four different catalyst combinations, all four stereoisomers of (3*R*,6*S*)-, (3*R*,6*R*)-, (3*S*,6*S*)-, and (3*S*,6*R*)-**3a** could be readily obtained in good yields with high diastereoselectivities and excellent enantioselectivity,



Table 2 Substrate scope study of α -azaaryl acetates^a

Entry	Product	Yield (%)	dr	ee (%)
entry 1, 3b	3b	72	13:1	99
entry 2, 3c	3c	65	13:1	99
entry 3, 3d	3d	68	12:1	99
entry 4, 3e	3e	62	14:1	99
entry 5, 3f	3f	64	12:1	99
entry 6, 3g	3g	66	10:1	99
entry 7, 3h	3h	70	10:1	99
entry 8, 3i	3i	71	7:1	95
entry 9, 3j	3j	73	9:1	99
entry 10, 3k	3k	57	11:1	98
entry 11, 3l	3l	67	>20:1	99
entry 12, 3m	3m	82	10:1	98
entry 13, 3n	3n	75	9:1	99
entry 14, 3o	3o	72	11:1	99
entry 15, 3p	3p	65	4:1	87
entry 16, 3q	3q	82	>20:1	99
entry 17, 3r	3r	80	5:1	99
entry 18, 3s	3s	78	>20:1	99

^a All reactions were carried on with [Cu]/(*S,S*_p)-L5 (5 mol%), [Ru]-1 (2 mol%), 0.6 mmol **1a**, 0.2 mmol **2** and 0.3 mmol Cs₂CO₃ in 2 mL of THF for 36 h. Cu(I) = Cu(MeCN)₄PF₆. Yields refer to isolated yields after chromatography. dr was determined by crude ¹H NMR analysis. ee was determined by HPLC analysis.

Table 3 Substrate scope study of branched allylic alcohols^a

Entry	R	3	Yield ^b (%)	dr ^c	ee ^d (%)
1	4-FC ₆ H ₄	3t	65	18:1	99
2	4-BrC ₆ H ₄	3u	68	12:1	99
3	4-CF ₃ C ₆ H ₄	3v	55	7:1	99
4	4-CO ₂ MeC ₆ H ₄	3w	60	10:1	99
5	4-MeC ₆ H ₄	3x	73	14:1	99
6	4-OMeC ₆ H ₄	3y	67	11:1	99
7	3-MeC ₆ H ₄	3z	62	9:1	99
8	3-FC ₆ H ₄	3A	57	6:1	99
9	2-MeC ₆ H ₄	3B	61	19:1	99
10	2-FC ₆ H ₄	3C	64	14:1	99
11	3,5-Cl ₂ C ₆ H ₃	3D	66	9:1	99
12	2-Naphthyl	3E	81	18:1	99
13	1-Naphthyl	3F	71	16:1	99
14	3-Thienyl	3G	70	8:1	99
15	3-Furyl	3H	65	8:1	99
16	Cyclohexyl	3I	60	3:1	98

^a All reactions were carried out with [Cu]/(*S,S*_p)-L5 (5 mol%), [Ru]-1 (2 mol%), 0.6 mmol **1**, 0.2 mmol **2a** and 0.3 mmol Cs₂CO₃ in 2 mL of THF for 36 h. Cu(I) = Cu(MeCN)₄PF₆. ^b Yields refer to isolated yields after chromatography. ^c dr was determined by crude ¹H NMR analysis. ^d ee was determined by HPLC analysis.

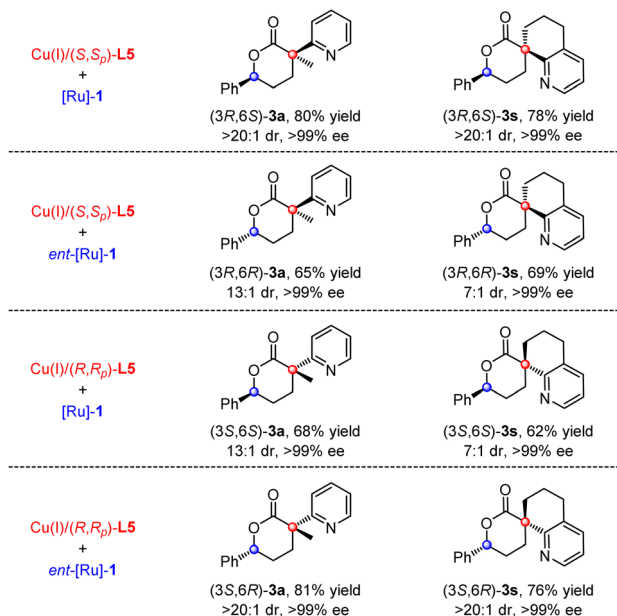
respectively. Likewise, the precise synthesis of all four stereoisomers of spiro heterocyclic **3s** could also be realized in good yields with decent diastereoselectivities and nearly perfect

enantioselectivity. These promising stereodivergence results provide strong evidence to support that each chiral catalyst in this bimetallic Cu/Ru relay catalytic system can independently control the stereochemistry of both the proceeding Michael addition and the subsequent reductive hydrogenation in this cascade protocol.

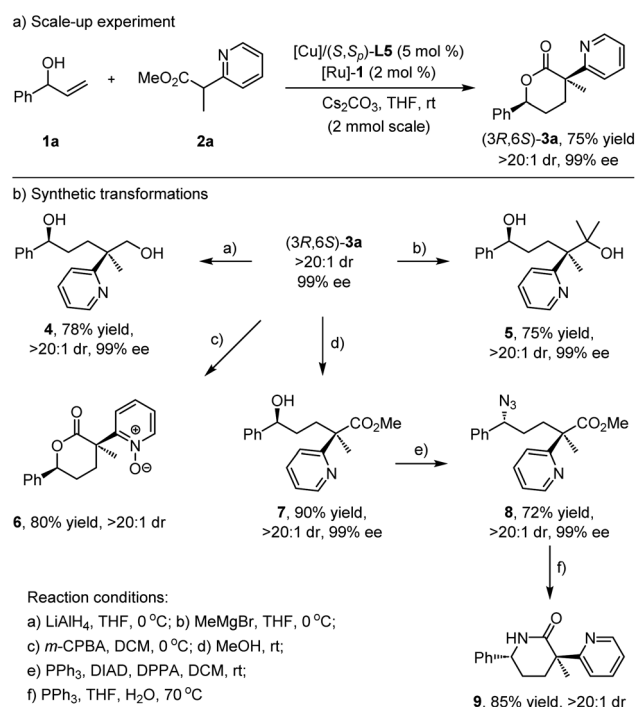
Scale-up experiments and synthetic application

To showcase the synthetic utility of this protocol, the scale-up experiment and synthetic elaborations were then performed. As depicted in Scheme 3a, the reaction between model substrates phenyl allylic alcohol **1a** and α -methyl pyridinyl acetate **2a** at a 2 mmol scale was carried out under standard conditions, and the chiral product (*3R,6S*)-**3a** was obtained in high yield with preserved diastereoselectivity and enantioselectivity (75% yield, >20:1 dr, and 99% ee). The lactone group in (*3R,6S*)-**3a** could be reduced by LiAlH₄ to afford chiral 1,5-diol **4** in 78% yield with >20:1 dr and 99% ee. Treatment of (*3R,6S*)-**3a** with the methyl Grignard reagent delivered another chiral 1,5-diol **5** in good yield without loss of stereoselectivity. The pyridinyl moiety in **3a** was easily oxidized by *m*-chloroperoxybenzoic acid (*m*-CPBA), affording pyridine-*N*-oxide **6** in 80% yield as a single stereoisomer. Alcoholysis of (*3R,6S*)-**3a** in methanol occurred smoothly at room temperature, and the corresponding ring-opening δ -hydroxyl α -methyl azaaryl acetate **7** could be readily isolated as a stable compound in 90% yield without any loss of diastereoselectivity and enantioselectivity. The Mitsunobu reaction of **7** provided enantioenriched azide derivative **8** in a highly stereospecific manner, and the subsequent cascade





Scheme 2 Stereodivergence demonstration.



Scheme 3 Scale-up experiment and synthetic elaborations.

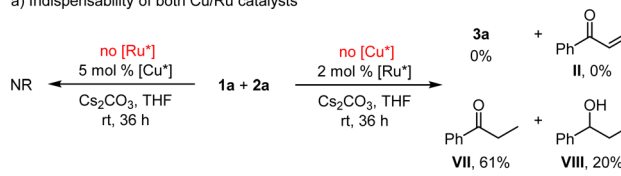
Staudinger reduction/lactamization delivered chiral δ -valerolactam²⁴ **9** in high yield (Scheme 3b).

Mechanistic studies

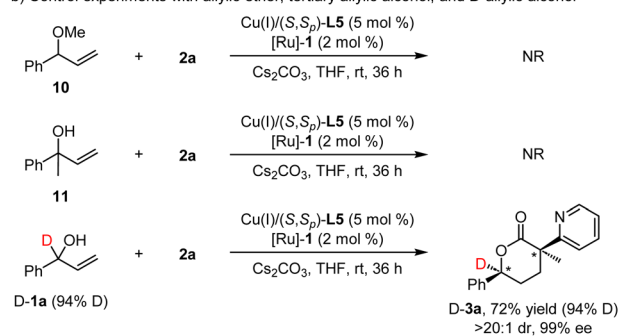
A series of control experiments were carried out to gain some mechanistic insights into this dual Cu/Ru relay catalysis. As displayed in Scheme 4a, no reaction occurred when the model

reaction was conducted in the absence of the chiral redox ruthenium catalyst. On the other hand, when the reaction was carried out without the chiral copper complex, the process became messy, and the redox process occurred on vinyl phenyl carbinol to afford a mixture of propiophenone **VII** and 1-phenyl-1-propanol **VIII**. These experimental results verified that these two chiral metal catalysts were indispensable in this cascade transformation. Control experiments with allyl methyl ether **10** and tertiary allylic alcohol **11** were conducted, and no conversion was observed under standard reaction conditions (Scheme 4b). Furthermore, the deuterium labeling experiment using allylic alcohol D-**1a** as the substrate was further performed under standard reaction conditions, and the target product D-**3a** containing 94% deuterium at the tertiary carbon stereocenter was observed. The similar deuterated ratio, with preserved diastereoselectivity and enantioselectivity control, supported

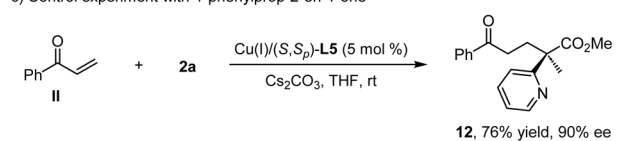
a) Indispensability of both Cu/Ru catalysts



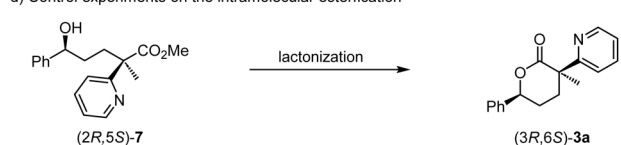
b) Control experiments with allylic ether, tertiary allylic alcohol, and D-allylic alcohol



c) Control experiment with 1-phenylprop-2-en-1-one



d) Control experiments on the intramolecular esterification



reaction conditions	yield (%)
THF, rt, 16 h	trace
Cs ₂ CO ₃ (1.5 eq.), THF, rt, 16 h	87
[Ru]-1 (2 mol %), THF, rt, 16 h	trace
[Ru]-1 (2 mol %), Cs ₂ CO ₃ (1.5 eq.), THF, rt, 16 h	89
Cu(MeCN) ₄ PF ₆ (5 mol %), THF, rt, 16 h	27
Cu(MeCN) ₄ PF ₆ (5 mol %), Cs ₂ CO ₃ (1.5 eq.), THF, rt, 16 h	93
Cu(MeCN) ₄ PF ₆ /(S,S _p)-L5 (5 mol %), THF, rt, 16 h	trace
Cu(MeCN) ₄ PF ₆ /(S,S _p)-L5 (5 mol %), Cs ₂ CO ₃ (1.5 eq.), THF, rt, 16 h	79

Scheme 4 Mechanistic investigation and control experiments.

the designed relay catalysis *via* orthogonally merging borrowing hydrogen and Michael addition. In addition, the Michael addition between 1-phenylprop-2-en-1-one **II** and α -methyl pyridinyl acetate **2a** was conducted in the presence of Cu/(*S,S*)-**L5**, and the corresponding adduct **12** could be obtained in 76% yield with 90% ee (Scheme 4c), which demonstrated that 1-phenylprop-2-en-1-one **II** was the active intermediate in this redox neutral process. As for the subsequent lactonization, which was supposed to occur spontaneously, the isolation of δ -hydroxyester **7** as a stable ring-opening molecule from δ -hydroxyester **3a** (*vide supra*) forced us to scrutinize this intramolecular transesterification. The control experimental results tabulated in Scheme 4d revealed that the base Cs₂CO₃ plays a key role in this lactonization, serving as an efficient promoter to convert the intermediacy of δ -hydroxyester to the final chiral δ -valerolactone.

Conclusions

In conclusion, we have successfully developed a novel multi-catalytic strategy for the expedient synthesis of biologically important chiral δ -valerolactones bearing 1,4-nonadjacent stereocenters with key features such as atom/step economy and redox-neutrality. The current method relies on orthogonally merging hydrogen borrowing and Michael addition reactions between α -azaaryl acetates and allylic alcohols, enabled by Cu/Ru-relay catalysis, followed by base-promoted lactonization in a one-pot manner, while tolerating a broad substrate scope with the highly functionalized δ -valerolactones being modularly assembled in good to high yields with excellent stereoselective control. The cascade protocol provides a conceptually novel pathway for the stereodivergent synthesis of all four stereoisomers of otherwise inaccessible δ -valerolactones bearing a unique azaarene-containing α -quaternary and a tertiary stereocenter. Considering the prominence of δ -valerolactones, all-carbon quaternary stereocenters, and pyridine moieties in medicinal chemistry, we anticipate that this stereodivergent cascade protocol will be useful for the preparation of the related complex molecules.

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. K. T., Z. J., X. L. L., L. H., H. F. L., P. K. Y., and X. C. performed the research. C. J. W., X. Q. D. and K. T. 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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