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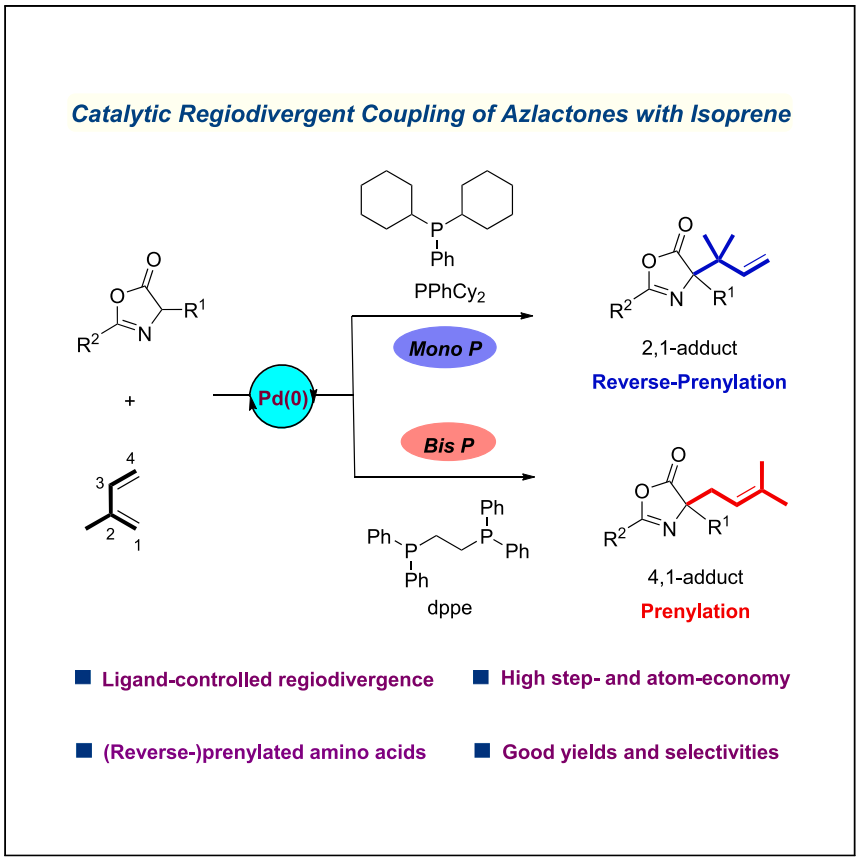

Allylation of azlactones is an efficient route to α-quaternary amino acids, but analogous prenylation reactions are less well explored. Zhang et al. report a ligand-controlled regiodivergent coupling of azlactones with isoprene enabling the rapid synthesis of prenylated and reverse-prenylated amino acids.

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Highlights

Regiodivergent coupling of azlactones and isoprene

Ligand-controlled regioselectivity

High step and atom economy

Prenylated and reverse-prenylated amino acids

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Ligand-controlled regiodivergence in Pd-catalyzed coupling of azlactones with isoprene

Wei-Nan Zhang,[1,2,5] Yan-Cheng Hu,[2,3,5] Yan Liu,[2,4] Xiao-Yu Wang,[2,4] Ying-Ying Zhao,[1,*] and Qing-An Chen[2,4,6,*]

SUMMARY

Transition-metal-catalyzed allylation of azlactones represents an elegant strategy for the synthesis of valuable α-quaternary amino acids. While much progress has been achieved, catalytic prenylation and reverse prenylation of azlactones have been less explored. Regiodivergent catalysis, aiming at attaining distinct regioisomers from the same starting materials through varying the catalyst, is an emerging strategy in synthetic chemistry. Herein, we present an atom-economical coupling of azlactones and isoprene with palladium catalysis in which ligand-controlled regiodivergence is achieved. With monophosphine $PPhCy_2$ as ligand, reverse-prenylated azlactones are produced, while the selectivity switches to prenylation when varying to bisphosphine ligand dppe. The regiodivergence relies on tuning the coordination environment and steric effects. Initial rate kinetic analysis suggests a change in the rate-determining step induced by the optimal ligand. Furthermore, this protocol provides an expedient entry point to access quaternary-prenylated and reverse-prenylated amino acids, which have potential in the incorporation of peptides.

INTRODUCTION

Prenyl and reverse-prenyl groups are important five-carbon isopentenyl skeletons that are widespread in numerous natural products.[1–5] These molecules often demonstrate promising biological activities compared to their non-prenylated analogs. In biosynthesis, the key intermediate π-prenyl carbocation is first formed from dimethylallyl pyrophosphate, and the subsequent prenyltranferase-controlled nucleophilic attack gives rise to regiodivergent selectivity (Figure 1A).[6–15] By emulating the intermediacy of π-prenyl species and enzyme-dependent regiodivergence in biological processes, the exploration of chemically catalytic regiodivergent prenylation and reverse prenylation has received much attention in recent years.[16–20] Most of the precedents employed activated dimethylallylic alcohols[21–27] and their derivatives such as carbonates,[28–32] acetates,[33–36] and organometals[18,37–39] as (reverse-)prenyl donors. However, the preinstallation and consequent release of the activating groups diminish the synthetic efficiency and atom economy.[40–43] Given that isoprene is an abundant five-carbon diene in industry, from the viewpoint of green chemistry, the development of regiodivergent prenylation and reverse prenylation with isoprene is highly appealing yet still remains in its infancy.[44–47]

Modified peptides not only open an avenue for understanding diverse biological phenomena but also provide opportunities for lead drug discovery.[48–51] α-Quaternary

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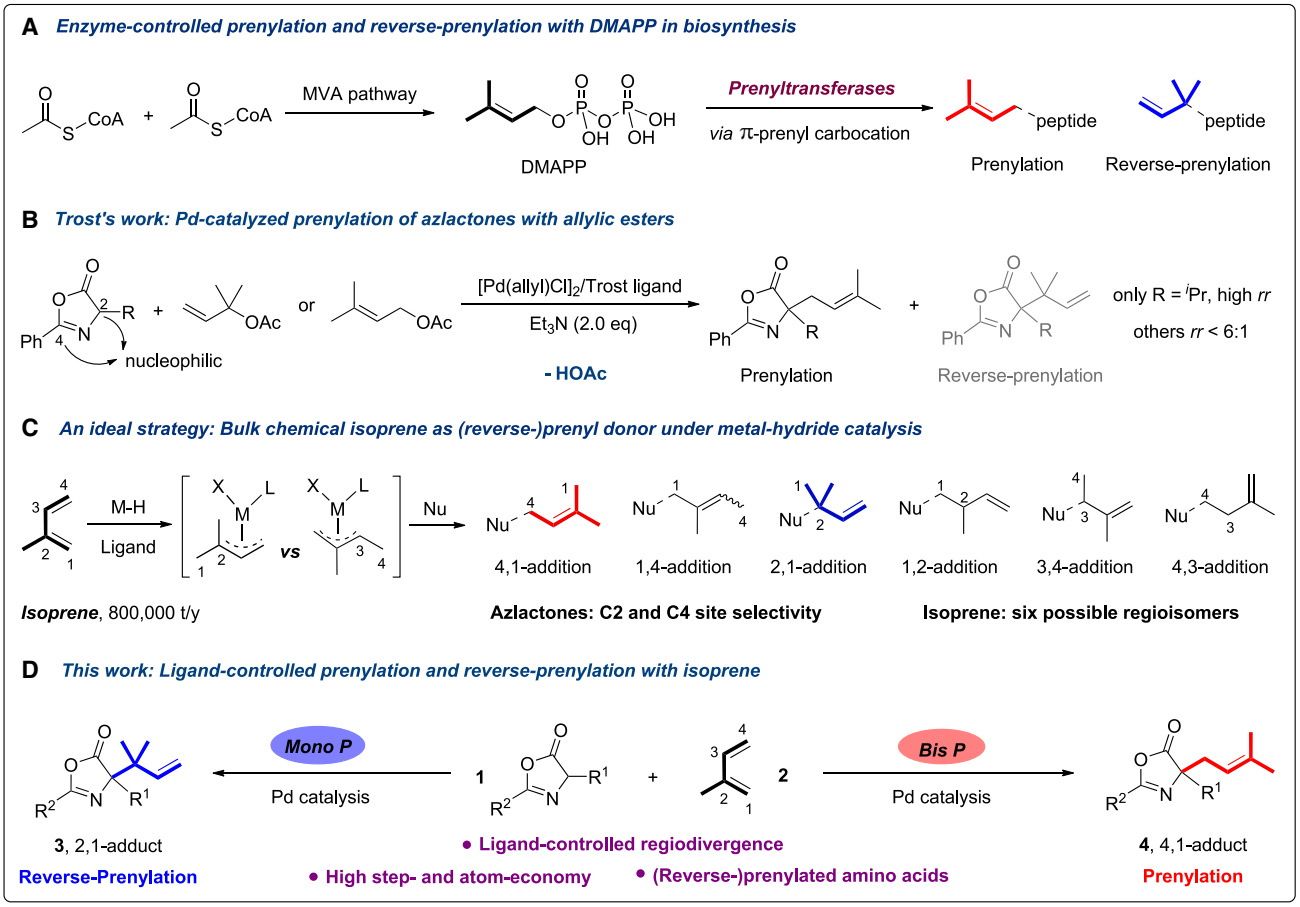

Figure 1. Pd-catalyzed prenylation and reverse prenylation of azlactones with isoprene

(A) Enzyme-controlled prenylation and reverse prenylation with dimethylallyl pyrophosphate (DMAPP) in biosynthesis.

(B) Pd-catalyzed prenylation of azlactones with allylic esters.

(C) Bulk chemical isoprene as (reverse-)prenyl donor under metal-hydride catalysis.

(D) This work: ligand-controlled prenylation and reverse prenylation with isoprene.

amino acids play an important role in the synthesis of modified peptides because the quaternary carbon center can restrict conformational flexibility and improve pharmacokinetic properties.[52–59] Thus, the rapid assembly of quaternary α-alkyl amino acids has been an active research area.[60–63] Azlactones can be regarded as "masked" amino acids in organic synthesis.[64,65] Transition-metal-catalyzed allylation of azlactones represents an elegant strategy for the synthesis of α-quaternary amino acids.[66–71] While some great progress has been achieved, catalytic prenylation and reverse prenylation of azlactones are less explored.[72] Considering prenyl and reverse-prenyl groups can increase the lipophilicity and binding affinity to biological membranes,[73–75] it is of great interest to introduce such unique motifs at α-carbon of amino acids, which can not only incorporate conformational constraints but also lead to a significant enhancement of biological activity.[76–81] In 1999, the group of Trost accomplished the first prenylation of azlactones with palladium catalysis, in which activated allylic acetates were employed as the precursors (Figure 1B).[82,83] Prompted by this work and our long-standing endeavor for developing functionalizations of isoprene,[45,46,84–90] we envisioned that with metal-hydride catalysis, isoprene can be transformed into π-prenylmetal species and subsequent nucleophilic attack by azlactones might deliver prenylated and reverse-prenylated products through

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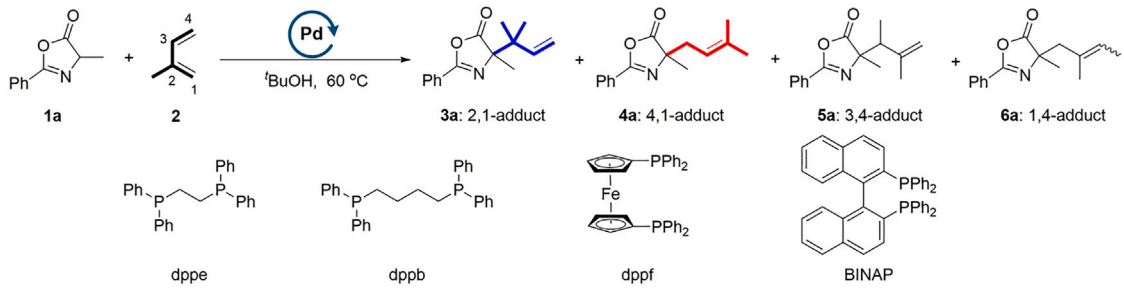
Table 1. Optimization for the palladium-catalyzed reverse-prenylation and prenylation of azlactone



Entry[a]	Pd complex	Ligand	3a (%)	4a (%)	5a (%)	6a (%)
1	Pd_2dba_3	P^tBu_3	–	–	–	–
2	Pd_2dba_3	PPh_3	30	40	2	10
3	Pd_2dba_3	$P(4\text{-}OMeC_6H_4)_3$	30	42	1	7
4	Pd_2dba_3	PCy_3	52	7	8	2
5	Pd_2dba_3	PPh_2Cy	53	23	2	16
6	Pd_2dba_3	PPh_2Me	13	58	1	11
7	Pd_2dba_3	$PPhCy_2$	66	3	4	5
8[b]	**Pd_2dba_3**	**$PPhCy_2$**	**77**	–	**2**	–
9	Pd_2dba_3	dppe	4	67	–	5
10	Pd_2dba_3	dppb	9	54	1	8
11	Pd_2dba_3	dppf	11	58	3	10
12	Pd_2dba_3	BINAP	19	54	3	8
13	$Pd(P^tBu_3)_2$	dppe	5	78	–	8
14[b]	$Pd(P^tBu_3)_2$	dppe	5	79	–	5
15[b,c]	**$Pd(P^tBu_3)_2$**	**dppe**	**4**	**82**	–	**3**

[a]Conditions: **1a** (0.10 mmol), **2** (0.30 mmol), Pd_2dba_3 (2.5 mol %) or $Pd(P^tBu_3)_2$ (5 mol %), mono P ligand (10 mol %) or bis P ligand (5 mol %), ^{t}BuOH (0.20 mL), 60°C, 24 h. The yields were determined by ^{1}H NMR of crude mixture using 1,3,5-trimethoxybenzene as internal standard.
[b]40°C.
[c]2,6-Difluorobenzoic acid (20 mol %) was used as additive.

modulating the catalysts. To implement this approach, we need to address the following challenges: (1) the keto-enol tautomerization of azlactones renders nucleophilicity of both C2 and C4 positions, which introduces site-selectivity challenges.[91,92] (2) Since four alkenyl carbons of isoprene are electronically unbiased, it is difficult to generate π-prenylmetal species selectively, and six possible regioisomers can be produced (Figure 1C). Herein, we realize a site- and regioselective coupling between azlactones and isoprene with palladium catalysis, and notably, phosphine ligand-controlled regiodivergence is established (Figure 1D). This protocol features high step and atom economy and allows for the convenient synthesis of quaternary α-prenyl and α-reverse-prenyl amino acids.

RESULTS AND DISCUSSION

Optimization

Initially, azlactone **1a** and isoprene **2** were selected as the model substrates to verify our hypothesis under palladium catalysis (Table 1; for details, see supplemental experimental procedures and Tables S1–S5). When using Pd_2dba_3 and bulky P^tBu_3 as the catalyst combo, the reaction did not take place in ^{t}BuOH at 60°C (entry 1). In contrast, the use of PPh_3 as ligand led to the formation of the desired reverse-prenylated and prenylated products (**3a**, **4a**), along with other two regioisomers (**5a**, **6a**) (entry 2). The electron-rich methoxyl-substituted phosphine ligand afforded a similar result (entry 3). In the presence of trialkyl phosphine ligand PCy_3, reverse prenylation turned out to be a dominant pathway (entry 4). A similar trend was

observed for PPh_2Cy, while the PPh_2Me ligand delivered adduct **4a** as a major product, which suggests that bulky cyclohexyl is crucial for the formation of reverse-prenylated product **3a** (entries 5 and 6). Thus, not surprisingly, $PPhCy_2$ could further enhance the efficiency of the reverse-prenylation process (entry 7). Gratifyingly, the target adduct **3a** was delivered in 77% yield with >20/1 regioselectivity when lowering the temperature to 40°C (entry 8). More importantly, the selectivity was diverted to prenylation when bisphosphine ligands were employed in the reaction. Ligand dppe exhibited the best performance in terms of regioselectivity, while other bidentate ligands such as dppb, dppf, and BINAP all provided inferior results (entries 9–12). Replacing precatalyst Pd_2dba_3 with bulky $Pd(P^tBu_3)_2$ gave rise to prenylated product **4a** in 78% yield with a decent regioselectivity (entry 13). A comparable result was attained when the reaction was conducted at 40°C (entry 14). The utilization of Brønsted acid 2,6-difluorobenzoic acid as additive led to a slight improvement in the yield and selectivity (entry 15). Moreover, the use of some chiral phosphine ligands was attempted to induce the chirality of both transformations (for details, please see Table S6). Chiral monophosphine ligand (2*R*,3*R*)-Me-BIDIME showed no catalytic performance. By comparison, bisphosphine ligands such as (*S*,*S*)-BDPP and (*R*)-BINAP could promote prenylation of azlactone, but no enantioselectivity was observed.

Substrate scope

With the optimized conditions in hand, the generality of this regiodivergent protocol was subsequently explored. For $Pd_2dba_3/PPhCy_2$-catalyzed reverse prenylation, a series of alkyl substituents including methyl-, ethyl-, propyl-, and iso-butyl in R^1 were well tolerated, providing products **3a–3d** in good yields with exclusive regioselectivity (Figure 2; see supplemental experimental procedures and supplemental information S4–S9). However, due to the steric hindrance, tert-butyl-substituted azlactone was an inapplicable substrate. The coupling of benzyl-derived azlactone with isoprene under the standard conditions gave adduct **3e** in 83% yield. Besides, methylthioethyl in R^1 was compatible with the transformation as well, resulting in the formation of the desired product **3f** in 77% yield. Notably, subjecting unsubstituted azlactone to the standard conditions furnished reverse-prenylated azlactone **3g** in 63% yield, and no disubstituted product was observed. This catalytic system could be further extended to reverse prenylation of the indolyl-derived substrate (**3h**). The scope with respect to the R^2 group was next examined. The electronic nature and positions of the substituents on the phenyl ring of R^2 exerted a minimal impact on the outcome. For instance, both electron-rich (**3i–3k**) and -deficient (**3l, 3n, 3o**) azlactones underwent reverse prenylation with high efficiencies. The regioselectivity for this process was confirmed by X-ray analysis of **3l** (CCDC 2240484; for details, see supplemental information S29), and 2-fluorophenyl-derived azlactone was converted to product **3m** in 73% yield. Moreover, 1-naphthyl and 2-furyl were suitable substituents as well, delivering their corresponding adducts **3p** and **3q** in 59% and 75% yields, respectively. The moderate yields in some cases were ascribed to the decomposition of prenylated and reverse-prenylated products during column chromatography. Surprisingly, with the aid of $Pd_2dba_3/PPhCy_2$, the coupling between 2,4-diphenyl azlactone and isoprene afforded C2-prenylated product **7r** in 86% yield with a high selectivity. Azlactone bearing a chloro group at the *ortho* position of phenyl R^1 yielded the desired product **7s** in 56% yield, albeit with a decreased regioselectivity. It is noteworthy that product **3a** cannot undergo the similar aza-Cope rearrangement pathway under standard conditions or at an elevated temperature. The unique aza-Cope rearrangement for the formation of products **7r** and **7s** might be ascribed to the inherent nature of the aromatic ring on R^1, as well as the steric repulsion between the large reverse-prenyl group and aryl R^1 of **3r** and **3s**.

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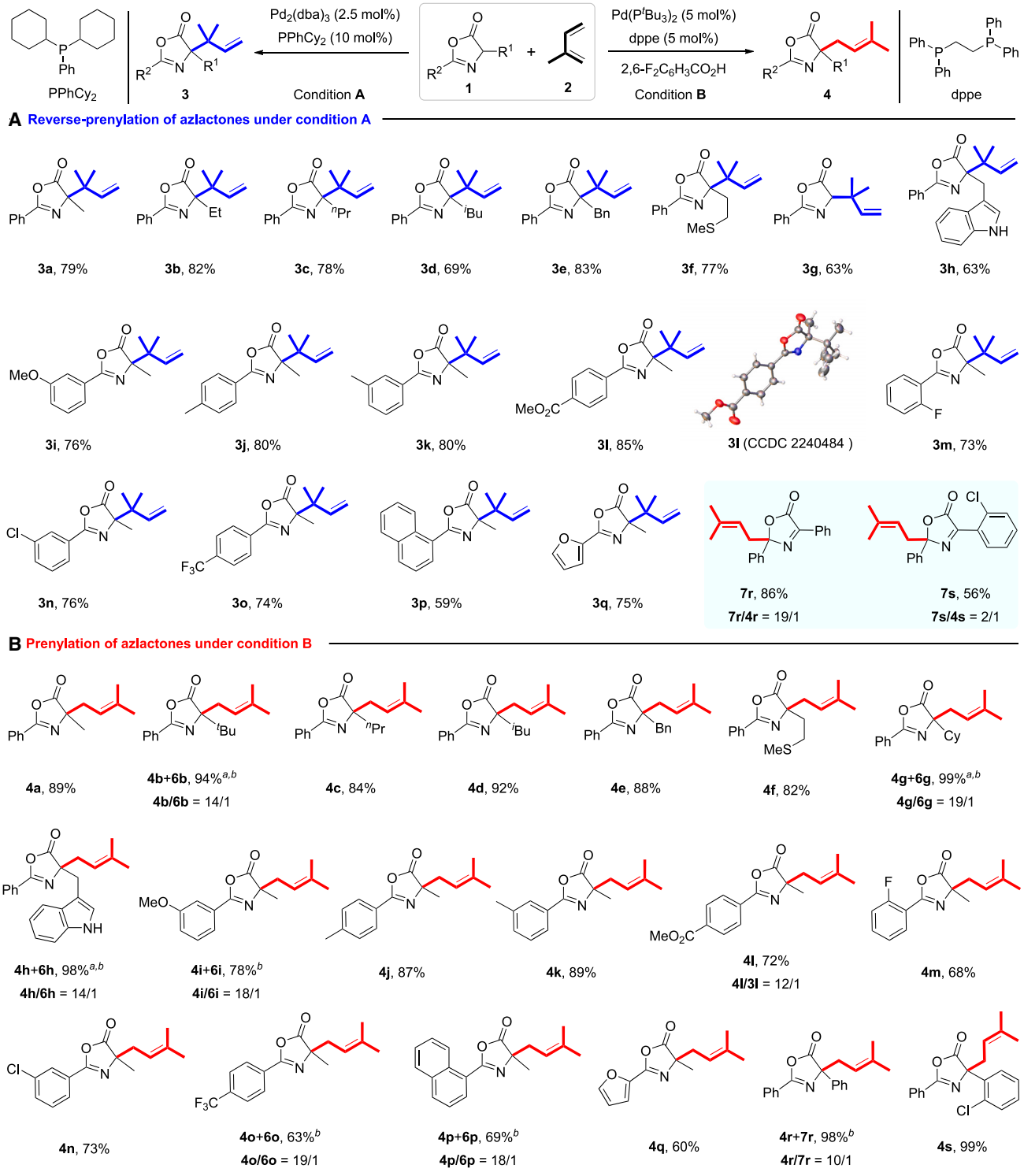

Figure 2. The substrate scope of reverse prenylation and prenylation of azlactone

Condition **A**: **1** (0.20 mmol), **2** (0.60 mmol), Pd_2dba_3 (2.5 mol %), $PPhCy_2$ (10 mol %), ^{t}BuOH (0.4 mL), 40°C, 24 h. Condition **B**: **1** (0.20 mmol), **2** (0.60 mmol), $Pd(P^tBu_3)_2$ (5 mol %), dppe (5 mol %), 2,6-$F_2C_6H_3CO_2H$ (20 mol %), ^{t}BuOH (0.4 mL), 40°C, 24 h. The regioselectivity ratio (*rr*) was determined by ^{1}H NMR analysis of crude mixture. Unless otherwise stated, *rr* was >20:1, and the isolated yield of single regioisomer is given.

[a]Without 2,6-$F_2C_6H_3CO_2H$, 48 h.

[b]Inseparable regioisomers.

When the catalyst was changed to Pd(P^tBu_3)$_2$/dppe and 2,6-difluorobenzoic acid, the selectivity was diverted to prenylation. Azlactones possessing a variety of alkyl substituents including methyl-, propyl-, and iso-butyl and benzyl- and methylthioethyl in R^1 were effectively coupled with isoprene, affording the target prenylated products in high yields (**4a**, **4c–4f**) (Figure 2; see supplemental experimental procedures and supplemental information S9–S13). The prenylation of sterically hindered tert-butyl-derived azlactone could proceed smoothly without acid additive, generating adduct **4b** with a good regioselectivity. These modified conditions were also amenable to cyclohexyl and indolyl substrates (**4g**, **4h**). Both electron-donating and -withdrawing substituents on the phenyl ring of R^2, regardless of their positions, were compatible with this process, and the desired prenylated products (**4i–4o**) were obtained in moderate to good yields (63%–86% yield). This prenylation operated equally well with 1-naphthyl and 2-furyl substituents in R^2 (**4p**, **4q**). Notably, with this catalytic system, 2,4-diphenyl azlactone was also implemented, yielding the expected C2-prenylated azlactone **4r** as a major product along with a small amount of C4-prenylated product **7r** (**4r**/**7r** = 10/1). When 2-chlorophenyl was engaged in R^2, C2 prenylation took place exclusively and furnished product **4s** in a nearly quantitative yield. Unfortunately, attempts for the synthesis of azlactones bearing Me and Et on R^2 failed.

Mechanistic study

To elucidate the mechanism of the process, initial rate kinetic experiments for the prenylation and reverse prenylation of azlactone **1a** with isoprene were performed. As shown in Figures 3A and 3B, the first-order dependence in both reactants (azlactone and isoprene) and palladium catalyst was observed for the reverse-prenylation reaction, indicating that these three species are present in the rate-determining transition structure. In comparison, the prenylation reaction exhibited first-order kinetics in azlactone and the palladium catalyst but zero-order dependence in isoprene, suggesting that the rate-determining step likely occurs prior to isoprene insertion into palladium hydride (see supplemental experimental procedures and Tables S6–S17). The interconversion experiments between products **3a** and **4a** revealed that the regiodivergence originates from the selective nucleophilic attack step instead of the isomerization process (Figure 3C; see supplemental experimental procedures and supplemental information S22 and S23). Besides, both reactions also took place readily in aprotic solvent acetonitrile, albeit with slightly decreased yields (Figure 3D; see supplemental experimental procedures and Table S5). The better result in ^{t}BuOH is likely attributed to the polar solvent accelerating the proton transfer between the keto and enol forms of azlactone[93] and the tert-butoxy group serving as a ligand to stabilize the palladium complexes. This result manifests that the active palladium-hydride species is formed from the oxidative addition of low-valent palladium catalyst and azlactone rather than tert-butanol. Furthermore, when the reactions were conducted in ^{t}BuOD, the deuterium content in products **3a** and **4a** was negligible, reaffirming that the hydride atom on the palladium center is derived from azlactone (Figure 3E; see supplemental experimental procedures and supplemental information S22).

On the basis of these observations and our previous work on metal-hydride-catalyzed transformations of isoprene,[13,45,85,87,88] a plausible mechanism for the regiodivergent selectivity was proposed (Figure 4). Azlactone is first transformed into its enol form **B** via an equilibrium process. Subsequent oxidative addition between Pd(0) species **A** and enol **B** gives rise to Pd(II)-H intermediate **C** or **F**. Initial rate kinetic analysis reveals that the formation of Pd complex **F** is rate determining for the prenylation reaction. Then, isoprene undergoes migratory insertion into Pd(II)-H to

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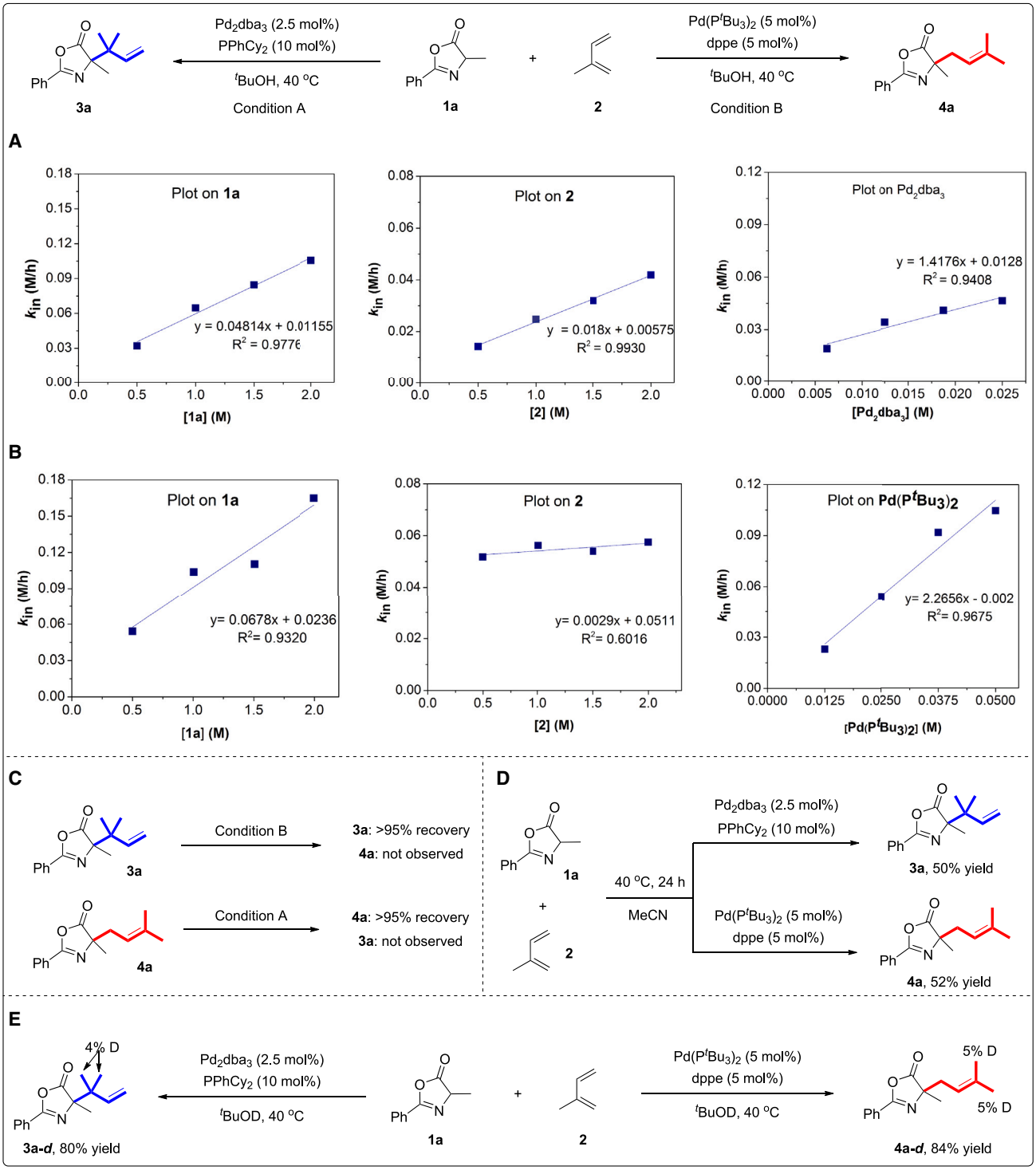

Figure 3. Mechanistic studies

(A) Kinetic studies on Pd-catalyzed reverse prenylation of azlactones for the formation of **3a**.

(B) Kinetic studies on Pd-catalyzed prenylation of azlactones for the formation of **4a**.

(C) Control experiments on the interconversion between **3a** and **4a**.

(D) MeCN as solvent.

(E) Deuterium-labeling study.

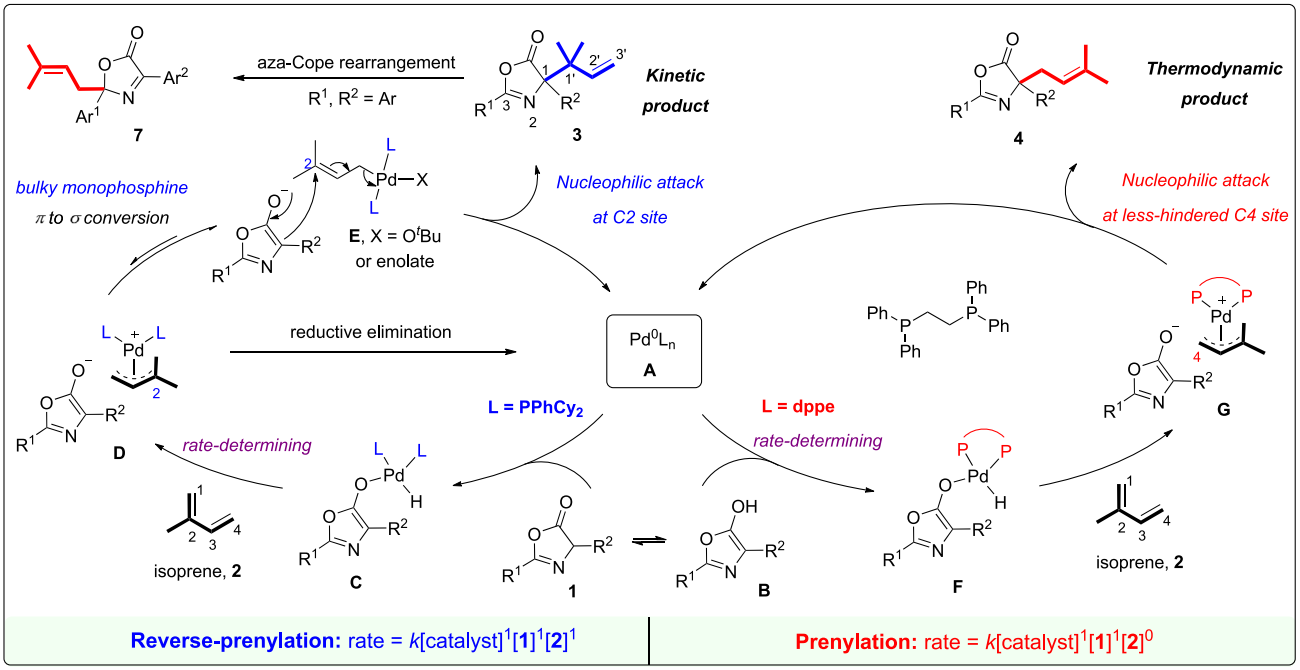

Figure 4. Proposed mechanism

The formation of Pd complex **F** is proposed to be rate determining for prenylation, while for reverse prenylation, formation of intermediate **D** is proposed to be rate determining.

generate the cationic π-prenyl-Pd species **D** or **G**. For the reverse-prenylation reaction, the first-order dependence in both reactants and palladium catalyst supports that the formation of intermediate **D** is rate determining. From Table 1, we can see that the bidentate ligands mainly afforded thermodynamic linear product **4a**, while kinetic branched product **3a** turned out to be predominant with bulky cyclohexyl-derived monophosphine ligands. This ligand-controlled regiodivergence can be explained by the involvement of π- and σ-type palladium complexes. Bulky monophosphine ligand $PPhCy_2$ in complex **D** prefers to shift the equilibrium to σ-prenyl-Pd species **E**. A final S_N2'-like nucleophilic attack by enolate at the more-substituted C2 site delivers reverse-prenylated product **3**. It should be noted that 3,3′-reductive elimination of intermediate **D** is another possibility accounting for the reverse-prenylation pathway.[94] In comparison, the rigid bidentate ligand dppe facilitates a nucleophilic attack at the less-hindered C4 site of π-prenyl-Pd complex **G** to provide thermodynamically stable prenylated product **4**. It should be noted that when aryl groups were involved in R^1 and R^2, congested reverse-prenylated azlactone **3** favorably proceeds through aza-Cope rearrangement to provide C2-prenylated product **7**. We conducted the reactions at low temperature to isolate the reverse-prenylated intermediate. Unfortunately, this attempt failed, and prenylated product **7** was still dominantly obtained. Despite this, according to the catalytic allylation of azlactone disclosed by Breit's group,[91] they successfully isolated the intermediates, which could further undergo aza-Cope rearrangement to afford the target product. Based on this precedent, the formation of product **7** in our work is believed to proceed through a domino reverse-prenylation and aza-Cope rearrangement pathway.

Synthetic transformations

Considering azlactones are versatile precursors of amino acids, we also attempted the synthesis of reverse-prenylated and prenylated amino acids via a one-pot

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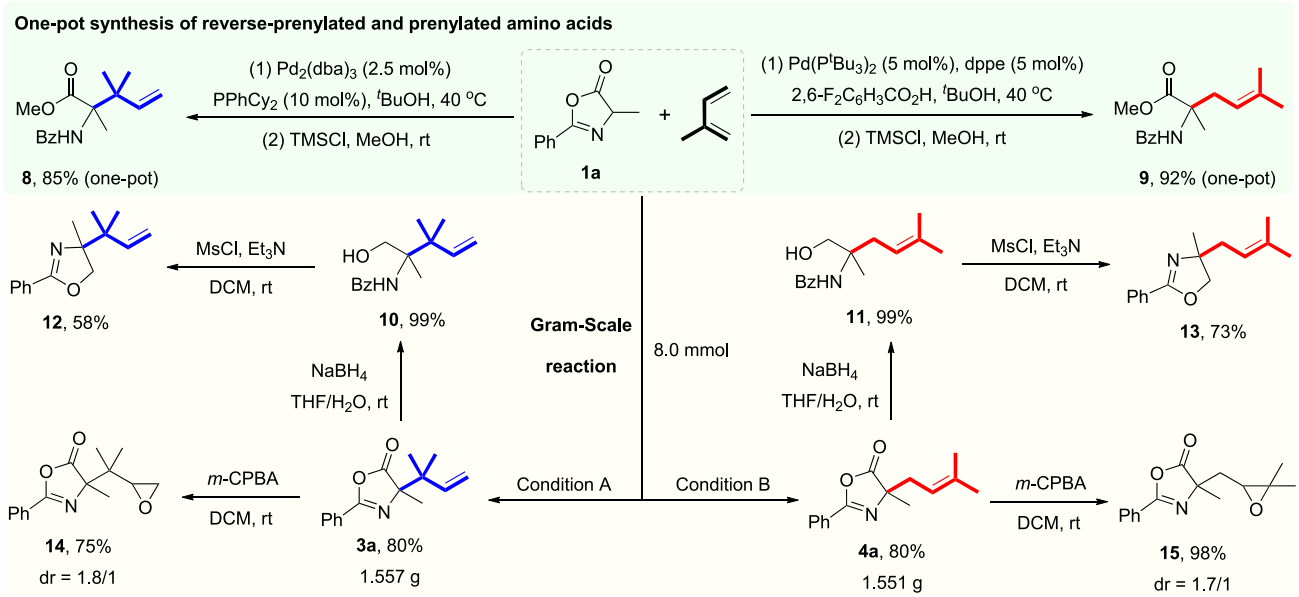

Figure 5. Scale-up experiment and synthetic transformations

The present methodology provides access to valuable products including prenylated and reverse-prenylated amino acid derivatives.

fashion (Figure 5, top; see supplemental experimental procedures and supplemental information S23 and S24). After the completion of reverse-prenylation and prenylation reactions, subsequent introduction of TMSCl and MeOH could easily produce quaternary α-reverse-prenyl amino ester **8** and α-prenyl amino ester **9** in 85% and 92% yields, respectively. To demonstrate the practical application of this regiodivergent protocol, gram-scale experiments and synthetic transformations were carried out (Figure 5, bottom; see supplemental experimental procedures and supplemental information S23). Both reactions could be easily scaled up to 8.0 mmol, providing products **3a** and **4a** both in 80% yields with excellent regioselectivities. Further treatment of **3a** and **4a** with $NaBH_4$ resulted in the formation of β-amino alcohols **10** and **11** in nearly quantitative yields. Notably, with the assistance of methanesulfonyl chloride and triethylamine, products **10** and **11** underwent intramolecular cyclization smoothly to afford useful oxazolines **12** and **13** in 59% and 73% yields, respectively (see supplemental experimental procedures and supplemental information S24–S26). Additionally, in the presence of *m*-chloroperoxybenzoic acid, products **3a** and **4a** could be transformed into their corresponding epoxides, **14** and **15**, in high efficiencies (see supplemental experimental procedures and supplemental information S27).

In summary, a ligand-controlled regiodivergence in palladium-catalyzed coupling between azlactones and isoprene has been developed. With the aid of monophosphine ligand $PPhCy_2$, reverse prenylation took place with high selectivity, while the utilization of bisphosphine ligand dppe diverted the pathway to prenylation. The rate-determining step of both processes was illustrated by initial rate kinetic analysis. The regiochemical outcome probably depends on the steric hindrance effect and the coordination geometry of the used phosphine ligand. Salient features of this method include high atom economy, switchable selectivity from the same reactants, broad substrate scope, easy scalability, and diverse synthetic applications. More importantly, this regiodivergent protocol allows rapid synthesis of quaternary-prenylated and reverse-prenylated amino acids, which are important to the

fields of biochemistry and medicinal chemistry. Further development of an asymmetric variant with this catalytic system is underway in our laboratory.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Qing-An Chen (qachen@dicp.ac.cn).

Materials availability

Unique and stable reagents generated in this study will be made available upon request, but we might require a payment and/or a completed materials transfer agreement if there is potential for commercial application.

Data and code availability

The authors declare that data supporting the findings of this study are available within the article and the supplemental information. All other data are available from the lead contact upon reasonable request.

Characterization and purification

Commercially available reagents were used without further purification. Other solvents were treated prior to use according to the standard methods. Unless otherwise stated, all reactions were conducted under inert atmosphere using standard Schlenk techniques or in a nitrogen-filled glovebox. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ on 400 or 700 MHz instruments with tetramethylsilane as the internal standard. Flash column chromatography was performed on silica gel (200–300 mesh). All reactions were monitored by thin-layer chromatography, NMR, or gas chromatography with flame-ionization detection analysis. High-resolution mass spectrometry data were obtained with a Micromass HPLC-Q-TOF [quadrupole time of flight] mass spectrometer (electrospray ionization) or an Agilent 6540 Accurate-MS spectrometer (Q-TOF).

Description of methods and characterization

Further experimental descriptions, general information, details of the reagents, and all syntheses and characterizations are provided in the supplemental experimental procedures.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrp.2024.101908.

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AUTHOR CONTRIBUTIONS

Q.-A.C. conceived and supervised the project. Q.-A.C., W.-N.Z., and Y.-C.H. designed the experiments. W.-N.Z., Y.-C.H., Y.L., X.-Y.W., and Y.-Y.Z. performed the experiments and analyzed the data. All authors discussed the results and commented on the manuscript.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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