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Communication

Z-Retentive Asymmetric Allylic Substitution Reactions of Aldimine Esters under Ru/Cu Dual Catalysis

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ABSTRACT: Ru/Cu dual catalysis has been applied for Z-retentive asymmetric allylic substitution reactions of aldimine esters. This reaction provides an enantioselective synthesis of chiral Z-olefins in high yields (up to 91% yield) with excellent enantioselectivity (up to 98% ee) under mild conditions. The previously unreacted trisubstituted allylic electrophiles under Ir catalytic system are found to be compatible, affording the stereoretentive products in either Z- or E-form. Both linear and branched allylic electrophiles are suitable substrates with excellent reaction outcomes. Notably, Ru and Cu complexes are added in one-pot and simplifies the manipulation of this protocol and self-sorting phenomena could be observed in this Ru/Cu dual catalytic system.

Transition-metal-catalyzed asymmetric allylic substitution reactions have evolved as a powerful method for the construction of carbon−carbon and carbon−heteroatom bonds.[1] The transition metals employed for asymmetric allylic substitution reactions mainly focused on Pd, Ir, and Rh. In this regard, asymmetric allylic substitution reactions enabled by ruthenium catalytic systems remain less explored despite of the cheapness and robustness of the Ru complexes.[2] The known Ru-catalyzed asymmetric allylic substitution reactions generally lead to branched-selective products, and utilization of prochiral nucleophiles in a linear-selective fashion has rarely been documented (Scheme 1a).

Recently, our group reported Z-retentive asymmetric allylic substitution reactions for the synthesis of Z-olefins bearing a quaternary stereocenter at the homoallylic position.[3] The reactions took advantage of dual catalytic systems such as Ir/Cu and Pd/Cu complexes by using prochiral nucleophiles.[4] Despite this progress, trisubstituted allylic electrophiles could not be tolerated due to their low reactivity and difficulty in stereoselective control.[5]

It is noteworthy that Z-olefins bearing a homoallylic stereogenic center are frequently embedded in diverse natural products and bioactive molecules, and have therefore attracted considerable interests.[6] In line with our interest in Z-retentive asymmetric allylic substitution reactions, we envisaged that the Ru/Cu dual catalytic system might be implemented in Z-retentive asymmetric allylic substitution reactions to provide a solution to the previous challenges such as the low reactivity of trisubstituted electrophiles. However, several challenges exist: (1) potential ligand exchange between dual catalytic systems; (2) the compatibility between the bulky trisubstituted electrophiles and two metal catalysts. Recently, we executed this design and developed a dual Ru/Cu catalytic system that was highly efficient for Z-retentive asymmetric allylic alkylation reactions of α-aldimine esters to construct chiral Z-trisubstituted olefins. This efficient catalytic system was found to be compatible with trisubstituted allylic electrophiles, and both Z- and E-forms could be tolerated in a retentive manner. Herein we report the details of this study.

Scheme 1. Ru-Catalyzed Allylic Substitution Reactions

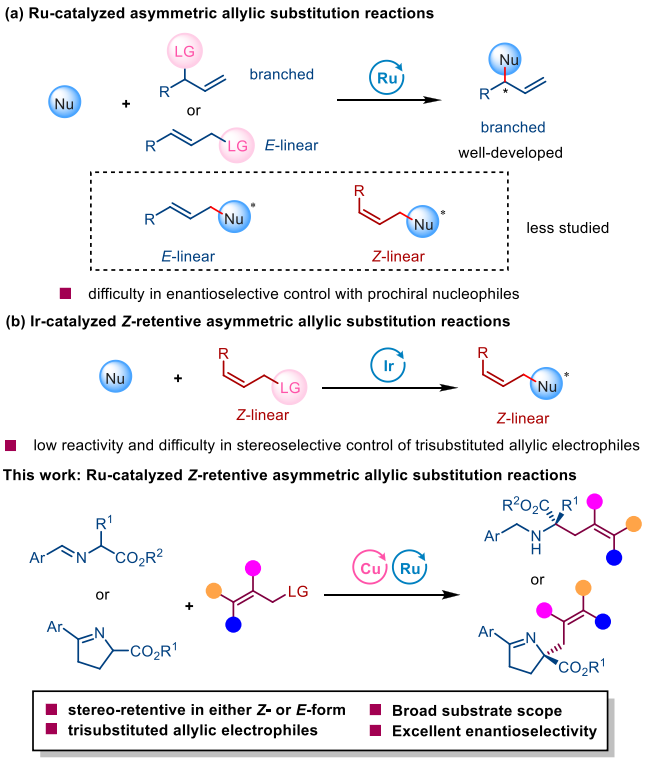

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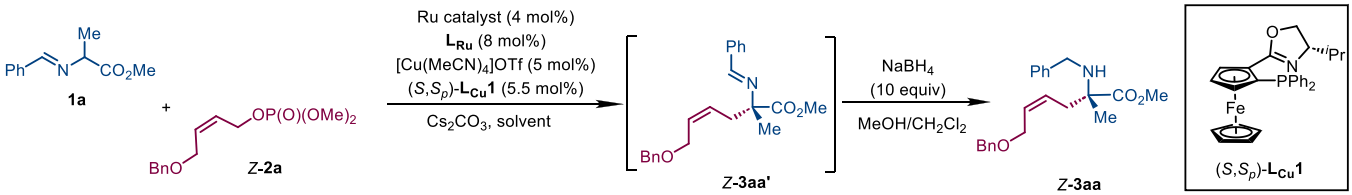
Table 1. Optimization of Reaction Conditions[a]



					Z-3aa′			Z-3aa
Entry	Ru catalyst	L_{Ru}	Solvent	T (°C)	L/B[b]	Z/E[b]	yield[b] (%)	ee[c] (%)
1	$[(p\text{-cymene})RuCl_2]_2$	PPh_3	CH_2Cl_2	50	78/22	>95/5	40	93
2	$[(p\text{-cymene})RuCl_2]_2$	PPh_3	THF	50	94/6	>95/5	40	88
3	$[(p\text{-cymene})RuCl_2]_2$	PPh_3	PhMe	50	91/9	>95/5	23	86
4	$[(p\text{-cymene})RuCl_2]_2$	PPh_3	MeCN	50	>95/5	>95/5	70	91
5	$[(p\text{-cymene})RuI_2]_2$	PPh_3	MeCN	50	>95/5	>95/5	74	84
6	$[Cp^*Ru(MeCN)_3]PF_6$	-	MeCN	50	94/6	86/14	41	86
7	$[(p\text{-cymene})RuCl_2]_2$	-	MeCN	50	93/7	>95/5	56	89
8	$[(p\text{-cymene})RuCl_2]_2$	PCy_3	MeCN	50	95/5	>95/5	62	80
9	$[(p\text{-cymene})RuCl_2]_2$	$P(2\text{-furyl})_3$	MeCN	50	>95/5	>95/5	80	93
10	$[(p\text{-cymene})RuCl_2]_2$	$P(2\text{-furyl})_3$	MeCN	25	>95/5	>95/5	75	94
11[e,f]	$[(p\text{-cymene})RuCl_2]_2$	$P(2\text{-furyl})_3$	MeCN	25	>95/5	>95/5	94	94
12[e,f,g]	$[(p\text{-cymene})RuCl_2]_2$	$P(2\text{-furyl})_3$	MeCN	25	>95/5	>95/5	94	94
13[e,f,g,h]	$[(p\text{-cymene})RuCl_2]_2$	$P(2\text{-furyl})_3$	MeCN	25	>95/5	>95/5	87[d]	94

[a]Reaction conditions: Step 1: **1a** (0.2 mmol), *Z*-**2a** (0.3 mmol), Ru catalyst (4 mol %), L_{Ru} (8 mol %), $[Cu(MeCN)_4]OTf$ (5 mol %), (S,S_p)-L_{Cu}**1** (5.5 mol %), and Cs_2CO_3 (1 equiv) in MeCN (2 mL) at 50 °C for 24 h. Step 2: Reaction residue of step 1, and $NaBH_4$ (10 equiv) in MeOH/CH_2Cl_2 (1:1, 4 mL) at room temperature. [b]L/B and *Z*/*E* ratios of **3aa′**, and the yield of *Z*-**3aa′** were determined by ^1H NMR analysis of the crude mixture prior to $NaBH_4$ reduction with mesitylene as an internal standard. [c]Determined by HPLC analysis. [d]Isolated yield of *Z*-**3aa**. [e]MeCN (1.5 mL). [f]Cs_2CO_3 (1.1 equiv). [g]*Z*-**2a** (0.24 mmol). [h]Preparation of a mixed complex solution in one-pot.

Our study commenced with the evaluation of reaction conditions for α-aldimine ester **1a** and *Z*-allylic phosphate **2a** as the model substrates in the presence of $[(p\text{-cymene})RuCl_2]_2/PPh_3$ as the catalyst for allylic alkylation and $[Cu(MeCN)_4]OTf$/Phosferrox L_{Cu}**1** as the catalyst to activate aldimine ester, and Cs_2CO_3 as a base in CH_2Cl_2 at 50 °C (Table 1, entry 1). Pleasingly, *Z*-**3aa′** was obtained in 40% NMR yield with >95/5 *Z*/*E* albeit with moderate linear-to-branch ratio (L/B = 78/22), and 93% ee of *Z*-**3aa** was determined by HPLC analysis after $NaBH_4$ reduction. Notably, MeCN was found to be the optimal choice among the tested solvents (entry 2). Further examination of Cu sources, the Cu ligands (L_{Cu}) and other Ru catalysts gave less satisfactory results (entries 5−7, see the Supporting Information for details). According to the structure of a known Ru complex $[(p\text{-cymene})RuCl_2(PPh_3)]$,[7] we envisioned that the property of phosphine ligands (L_{Ru}) might influence the reaction efficiency. Further investigations revealed that $P(2\text{-furyl})_3$ could give better yield and enantioselectivity (entry 9, 80% NMR yield, 93% ee). Reducing the reaction temperature to 25 °C while increasing the concentration of the reaction and using 1 equiv of Cs_2CO_3 further improved the yield and enantioselectivity (entries 10−11). When 1.2 equiv of *Z*-allylic phosphate *Z*-**2a** was used, 94% NMR yield of *Z*-**3aa′** with 94% ee was obtained (entry 12). Notably, a one-pot protocol could be successfully applied for the preparation of the dual catalytic systems to simplify the manipulation process, which provided the target product *Z*-**3aa** in 87% yield and 94% ee with excellent L/B and *Z*/*E* ratios (>95/5 *Z*/*E*, > 95/5 L/B) after $NaBH_4$ reduction (entry 13).

With the optimized conditions in hand, we then explored the substrate scope of this reaction (Scheme 2). The target molecules *Z*-**3** were delivered with excellent L/B (>95/5) and *Z*/*E* (>95/5) ratios. First, we investigated the substituents on the aldimine ester. The reactions of substrates bearing either an ^{i}Pr or ^{t}Bu ester group proceeded smoothly over a prolonged reaction time, furnishing their corresponding products (*Z*-**3ba**−*Z*-**3ca**) in good yields with excellent enantioselectivity (79−86% yields, 94−96% ee). The α-aldimine methyl esters bearing various groups were also suitable substrates, giving *Z*-**3da**−*Z*-**3ha** in good to excellent yields and entioselectivity (75−91% yields, 77−92% ee). Notably, substrates containing an extra coordination site (methyl sulfide, *tert*-butyl ether, protected amine, ester and olefin) were well tolerated, affording corresponding products (*Z*-**3ia**−*Z*-**3ma**) in moderate to good yields with good to excellent enantioselectivity (70−90% yields, 80−94% ee). The α-aldimine esters bearing different groups on the phenyl ring underwent this transformation smoothly and afforded *Z*-**3na**−*Z*-**3oa** in 83% yield with 91−96% ee.

Subsequently, the scope of the allylic phosphates was explored (Scheme 2). *Z*-allylic phosphates bearing groups such as MOM ether (*Z*-**2b**), allylic ether (*Z*-**2c**), acetate (*Z*-**2d**), and silyl ether (*Z*-**2e**−*Z*-**2f**) reacted smoothly to afford *Z*-**3ab**−*Z*-**3af** in good yields (70−86%) with excellent enantioselectivity (92−95% ee). Furthermore, the reactions of *Z*-crotyl phosphate and its derivatives possessing linear alkyl, cyclohexyl, thioether, chloride or iodide group delivered *Z*-**3ag**−*Z*-**3ap** in 52−88% yields with 90−95% ee. To our delight, the substrate scope could be further expanded to *E*-allylic phosphate *E*-**2j**, delivering product *E*-**3aj** in 75% yield with 93% ee. The configuration of *Z*-**3ca** was determined as *S* by comparing the optical rotation with the reported results[3a] and was used as the basis of configuration assignment for other products. To confirm the scalability of the present method, a 5

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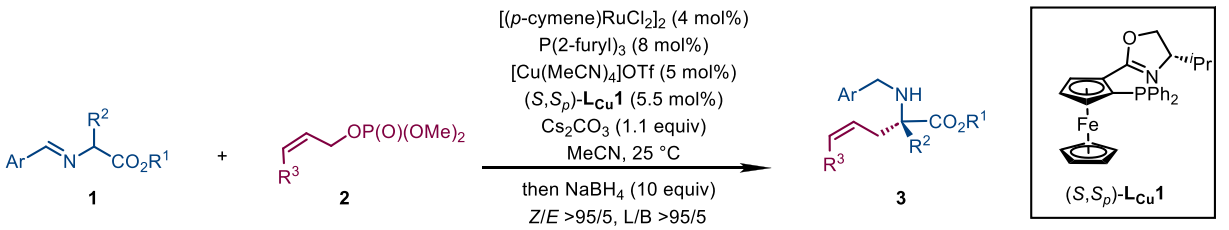
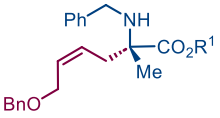
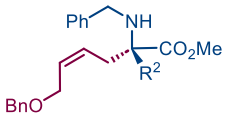
Scheme 2. Substrate Scope[a]

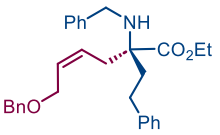




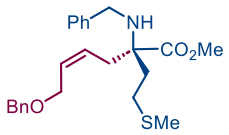
Z-3aa (R^1 = Me)
16 h, 87% yield, 94% ee
[Gram-scale reaction]
48 h, 1.45 g, 82% yield, 94% ee
Z-3ba (R^1 = ^{i}Pr)
36 h, 79% yield, 96% ee
Z-3ca (R^1 = ^{t}Bu)
48 h, 86% yield, 94% ee



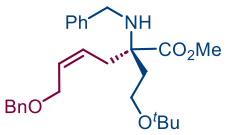
Z-3da (R^2 = ^{n}Pr) 16 h, 90% yield, 91% ee
Z-3ea (R^2 = ^{i}Bu) 36 h, 75% yield, 88% ee
Z-3fa (R^2 = cyclopropyl) 36 h, 80% yield, 92% ee
Z-3ga (R^2 = Bn) 24 h, 83% yield, 77% ee



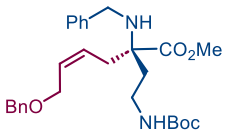
Z-3ha
24 h, 91% yield, 92% ee



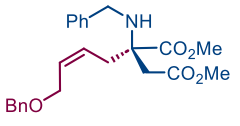
Z-3ia
24 h, 86% yield, 90% ee



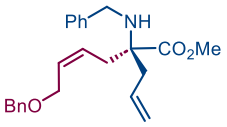
Z-3ja
24 h, 84% yield, 92% ee



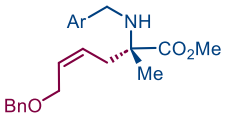
Z-3ka
36 h, 70% yield, 93% ee



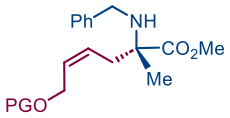
Z-3la
24 h, 80% yield, 80% ee



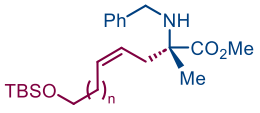
Z-3ma
20 h, 90% yield, 94% ee



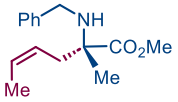
Z-3na (Ar = 4-MeOC$_6$H$_4$)
20 h, 83% yield, 96% ee
Z-3oa (Ar = 4-ClC$_6$H$_4$)
24 h, 83% yield, 91% ee



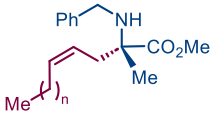
Z-3ab (PG = MOM) 24 h, 86% yield, 94% ee
Z-3ac (PG = allyl) 36 h, 73% yield, 95% ee
Z-3ad (PG = Ac) 16 h, 82% yield, 93% ee



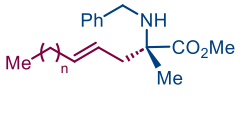
Z-3ae (n = 1)
24 h, 70% yield, 93% ee
Z-3af (n = 2)
24 h, 75% yield, 92% ee



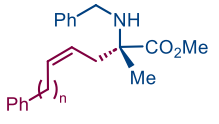
Z-3ag
20 h, 83% yield, 95% ee



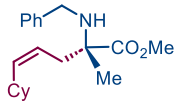
Z-3ah (n = 2)
36 h, 80% yield, 91% ee
Z-3ai (n = 5)
28 h, 73% yield, 91% ee



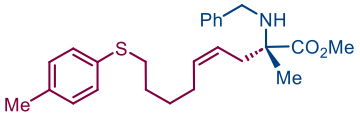
E-**3aj** (n = 5)
28 h, 75% yield, 93% ee
E/*Z* >95/5, L/B = 94/6



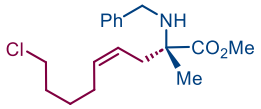
Z-3ak (n = 1)
36 h, 84% yield, 95% ee
Z-3al (n = 2)
28 h, 85% yield, 91% ee



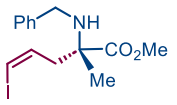
Z-3am
48 h, 88% yield, 90% ee



Z-3an
36 h, 62% yield, 91% ee



Z-3ao
36 h, 68% yield, 91% ee



Z-3ap
48 h, 52% yield, 95% ee[b]

[a]Reaction conditions: Step 1: Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), [(*p*-cymene)RuCl$_2$]$_2$ (4 mol %), P(2-furyl)$_3$ (8 mol %), [Cu(MeCN)$_4$]OTf (5 mol %), (S,S_p)-**L$_{Cu}$1** (5.5 mol %), Cs$_2$CO$_3$ (1.1 equiv) in MeCN (1.5 mL) at 25 °C. Step 2: Reaction residue of step 1, NaBH$_4$ (10 equiv) in CH$_2$Cl$_2$/MeOH (1:1, 4.0 mL) at room temperature. L/B and *Z*/*E* ratios were determined by ^{1}H NMR analysis of the crude mixtures of step 1. The ee values of **3** were determined by HPLC analysis. [b][Cu(MeCN)$_4$]OTf (10 mol %), (S,S_p)-**L$_{Cu}$1** (11 mol %).

mmol scale synthesis of *Z*-**3aa** was carried out under the standard conditions, and comparable results were obtained.

We then turned our attention to more challenging trisubstituted allylic electrophiles. While the reactions of the α-aldimine ester **1a** delivered the desired product in an unsatisfied enantioselectivity, the reactions of cyclic imino esters **4** with trisubstituted allylic phosphates formed the desired α-quaternary trisubstituted allylic 2*H*-pyrroles in high yields and enantioselectivity with good to excellent L/B and *Z*/*E* ratios under slightly modified conditions. A series of optimizing experiments (see the Supporting Information for details) showed that reactions with **L$_{Cu}$2** instead of **L$_{Cu}$1** furnished the desired *Z*-trisubstituted product *Z*-**6aa** in 81% yield and 93% ee with excellent L/B (>95/5) and *Z*/*E* (>95/5) ratios.

Then, the substrate scope for the asymmetric trisubstituted allylic substitution reactions of cyclic imino esters via a Ru/Cu dual catalysis was examined (Scheme 3 and Scheme 4). The

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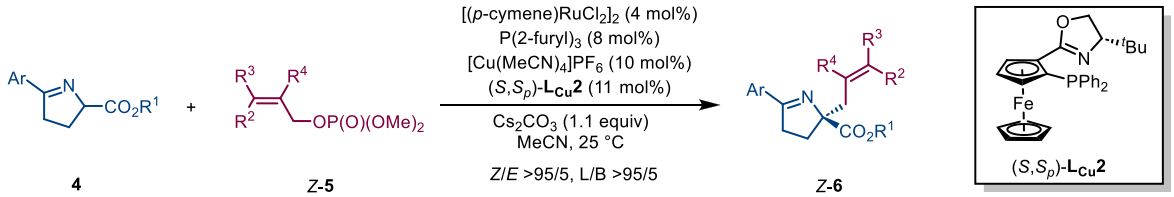
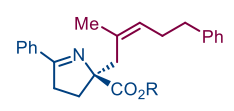
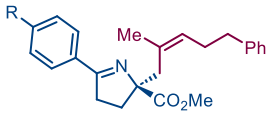
Scheme 3. Substrate Scope of *Z*-Trisubstituted Allylic Electrophiles[a,b]

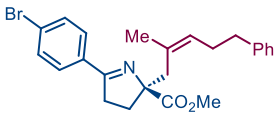




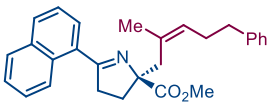
Z-**6aa** (R = Me) 48 h, 81% yield, 93% ee
Z-**6ba** (R = ^{t}Bu) 72 h, 80% yield, 98% ee



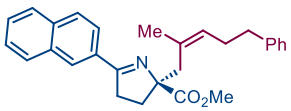
Z-**6ca** (R = OMe) 72 h, 76% yield, 95% ee
Z-**6da** (R = Me) 72 h, 72% yield, 91% ee
Z-**6ea** (R = F) 72 h, 74% yield, 95% ee
Z-**6fa** (R = Cl) 72 h, 77% yield, 92% ee



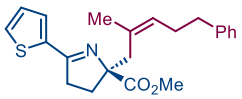
Z-**6ga**
96 h, 65% yield, 89% ee
Z/*E* = 92/8, L/B >95/5



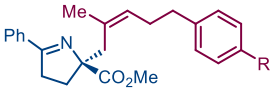
Z-**6ha**
72 h, 75% yield, 83% ee



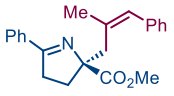
Z-**6ia**
72 h, 70% yield, 91% ee



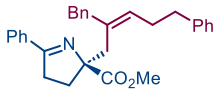
Z-**6ja**
72 h, 78% yield, 88% ee



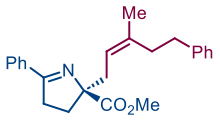
Z-**6ab** (R = OMe) 96 h, 70% yield, 88% ee
Z-**6ac** (R = Cl) 96 h, 85% yield, 95% ee
Z-**6ad** (R = Br) 96 h, 78% yield, 95% ee
Z-**6ae** (R = CF_3) 96 h, 56% yield, 92% ee
(*Z*/*E* = 88/12, L/B >95/5)



Z-**6af**
72 h, 50% yield, 87% ee[c]
L/B = 94/6



Z-**6ag**
72 h, 50% yield, 89% ee



Z-**6ah**
72 h, 58% yield, 94% ee[c]
L/B = 87/13

[a]Reaction conditions: **4** (0.20 mmol), *Z*-**5** (0.40 mmol), $[(p\text{-cymene})RuCl_2]_2$ (4 mol %), $P(2\text{-furyl})_3$ (8 mol %), $[Cu(MeCN)_4]PF_6$ (10 mol %), (S,S_p)-$\mathbf{L_{Cu}2}$ (11 mol %) and Cs_2CO_3 (1.1 equiv) in MeCN (0.5 mL) at 25 °C. [b]Determined by HPLC analysis. [c](S,S_p)-$\mathbf{L_{Cu}1}$ (11 mol %).

reaction of ^{t}Bu cyclic imino ester **4b** could undergo smoothly to afford *Z*-**6ba** in 80% yield with 98% ee. Various aryl-substituted cyclic imino esters were all tolerated well by reaction with **5aa**, giving the desired *Z*-trisubstituted allylic products *Z*-**6ca**−*Z*-**6ja** in good yields (65−78%) with excellent stereoselectivity (83−95% ee). Subsequently, a variety of *Z*-trisubstituted allylic phosphates were investigated. As detailed in Scheme 3, different substituents on the phenyl ring of allylic phosphate substrates *Z*-**6ab**−*Z*-**6ae** were tolerated well. The allylic phosphate *Z*-**5f** bearing a phenyl group on R^3 delivered *Z*-**6af** in 50% yield with 87% ee. When R^3 was a Bn group, the reaction was able to afford the corresponding product *Z*-**6ag** (50% yield, 89% ee). When the methyl group was moved to R^4 from R^3, product *Z*-**6ah** was synthesized in 58% yield with 94% ee, albeit with a slightly lower L/B ratio (87/13).

Notably, this dual Ru/Cu catalytic system could not only be utilized for *Z*-retentive asymmetric allylic substitution reactions, but also for *E*-retentive reactions (Scheme 4). The cyclic imino esters **4** bearing various aryl-substituted groups were investigated, giving rise to *E*-**8aa**−*E*-**8ja** in yields of 68−91% with 89−98% ee. The allylic phosphate *E*-**7b** bearing a Bn group at the R^2 position could react smoothly, forging *E*-**8ab** with reasonable results (43% yield and 85% ee). The allyl phosphate *E*-**7c** derived from geraniol could be tolerated well in this transformation, giving *E*-**8ac** in 60% yield with 97% ee. The allylic phosphates **7d**−**7f** could be tolerated well, delivering **8ad**−**8af** 88−94% yields with 92−96% ee. Interestingly, the reaction with **7g** furnished reverse prenylation product **8ag**, displaying good yield and excellent enantioselectivity with high regio-retentive selectivity (80% yield, 98% ee, B/L > 95/5). The *S* configuration of **8ae** was determined by comparing the optical rotation with that reported in the literature[4i] and was used as the basis of configuration assignment for products **6** and **8**.

These Ru/Cu catalysts could be prepared in a one-pot protocol by directly mixing two metal catalysts and two ligands. For traditional dual catalytic systems, two distinct metal/ligand complexes need to be prepared in separate tubes and then combined together. The ^{31}P NMR results are presented in Scheme 5. In System B, when two metal catalysts (Ru and Cu) and two ligands ($\mathbf{L_{Ru}}$ and $\mathbf{L_{Cu}}$) were directly mixed in CD_3CN in one Schlenk tube, both signals of the Cu(I)-$\mathbf{L_{Cu}}$ complex and Ru(II)-$\mathbf{L_{Ru}}$ complex were observed and were found to be the same as those prepared in separated tubes and then combined together (System A). The self-sorting phenomena of two metal sources and two ligands could be observed. The control experiments further confirmed that the dynamic equilibrium of coordination and dissociation of the mixtures of metal/ligand complexes was driven strongly by the coordination of the Ru catalyst and phosphine ligand ($\mathbf{L_{Ru}}$), leading to the desired Cu(I)-$\mathbf{L_{Cu}}$ complex and Ru(II)-$\mathbf{L_{Ru}}$ complex (see the Supporting Information for more details).

In summary, a highly efficient dual Ru/Cu catalytic system was found to enable *Z*-retentive asymmetric allylic substitution reactions with a wide range of allylic electrophiles, including those previously unreacted trisubstituted ones. These reactions proceeded in moderate to excellent yields, with high regio- and enantioselectivities under mild reaction conditions, and displayed excellent functional group tolerance. The current

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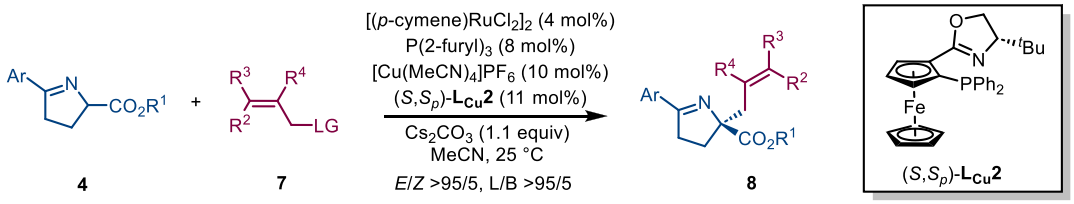
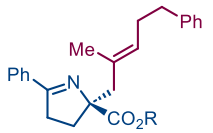
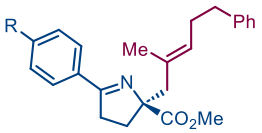
Scheme 4. Substrate Scope of the *E*-Trisubstituted and Other Allylic Electrophiles.[a,b]

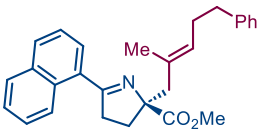




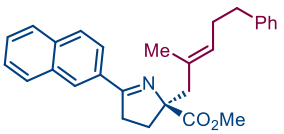
E-**8aa** (R = Me)
36 h, 91% yield, 94% ee
E-**8ba** (R = ^{t}Bu)
48 h, 82% yield, 98% ee



E-**8ca** (R = OMe) 72 h, 87% yield, 98% ee
E-**8da** (R = Me) 72 h, 80% yield, 97% ee
E-**8ea** (R = F) 48 h, 80% yield, 96% ee
E-**8fa** (R = Cl) 48 h, 75% yield, 96% ee
E-**8ga** (R = Br) 72 h, 68% yield, 90% ee

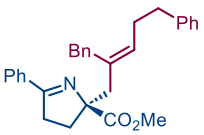


E-**8ha**
48 h, 79% yield, 89% ee

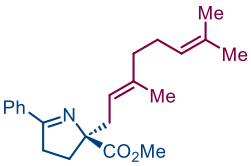


E-**8ia**
48 h, 85% yield, 94% ee

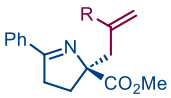
E-**8ja**
48 h, 88% yield, 94% ee



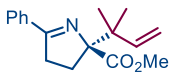
E-**8ab**
60 h, 43% yield, 85% ee
L/B = 93/7



E-**8ac**
72 h, 60% yield, 97% ee[c]

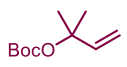


8ad (R = Ph)
72 h, 94% yield, 92% ee
8ae (R = Me)
48 h, 88% yield, 96% ee[d]
8af (R = Cl)
48 h, 90% yield, 95% ee[d]



8ag
72 h, 80% yield, 98% ee[e]
B/L >95/5

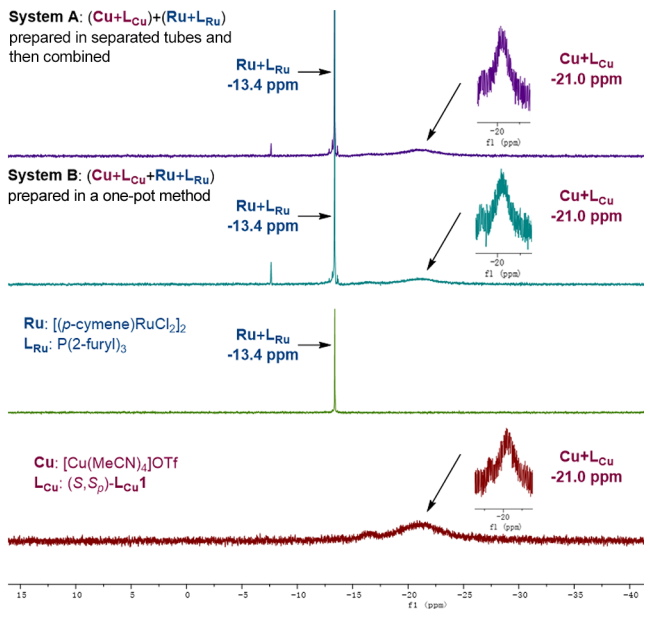
from



7g

[a]Reaction conditions: **4** (0.20 mmol), **7** (0.40 mmol, LG = OP(O)(OMe)$_2$), [(*p*-cymene)RuCl$_2$]$_2$ (4 mol %), P(2-furyl)$_3$ (8 mol %), [Cu(MeCN)$_4$]PF$_6$ (10 mol %), (*S*,*S*$_p$)-**L**$_{Cu}$**2** (11 mol %) and Cs$_2$CO$_3$ (1.1 equiv) in MeCN (0.5 mL) at 25 °C. [b]Determined by HPLC analysis. [c](*S*,*S*$_p$)-**L**$_{Cu}$**1** (11 mol %). [d]**7** (0.40 mmol, LG = OP(O)(OEt)$_2$). [e]**7g**: (0.40 mmol).

Scheme 5. ^{31}P NMR Experiments



method provides an efficient route for the synthesis of *Z*-disubstituted and stereochemically well-defined trisubstituted olefin molecules in their highly enantioenriched forms. Further studies on the reaction mechanism are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c13548.

Experimental details and characterization data for all new compounds (PDF)

NMR spectra for all compounds (ZIP)

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Notes

The authors declare no competing financial interest.

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