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Enantioselective Synthesis of Multisubstituted Spirocyclopentane Oxindoles Enabled by Pd/Chiral Rh(III) Complex Synergistic Catalysis

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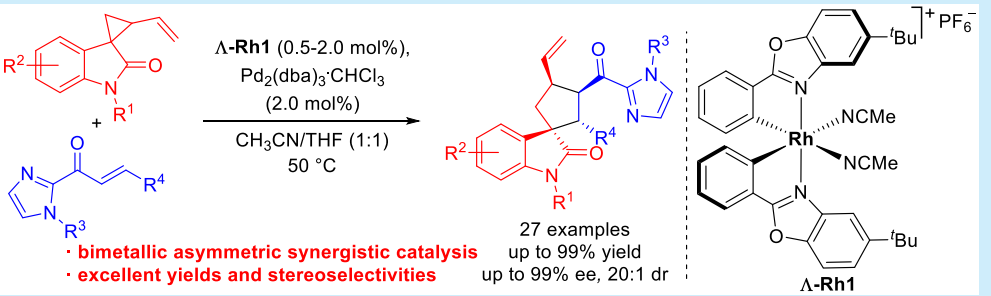

ABSTRACT: An asymmetric [3 + 2]-cycloaddition reaction of α,β-unsaturated 2-acyl imidazoles with spirovinylcyclopropanyl-2-oxindoles catalyzed synergistically by an achiral palladium(0) catalyst and a chiral-at-metal rhodium(III) complex has been developed. A series of biologically important 3-spirocyclopentane-2-oxindoles with four contiguous stereocenters were synthesized in high yields (up to 99%) with excellent stereoselectivities (up to 99% ee, 20:1 dr).

Spirocyclic oxindoles play an important role as a fascinating framework in many natural products and biologically active molecules.[1] Particularly, natural alkaloids bearing 3-spirocyclopentane-2-oxindole scaffold exhibit a broad range of biological and pharmacological activities (e.g., notoamides, paraherquamides, citrinalins, and cyclopiamines, Figure 1).[2]

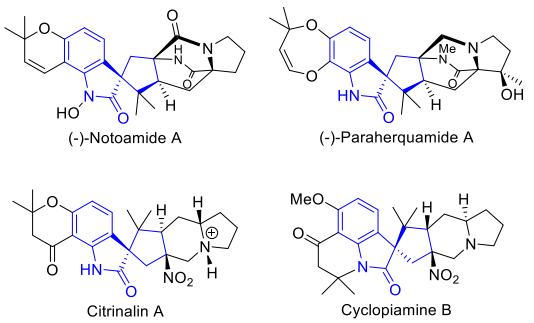

Figure 1. Representative examples of natural alkaloids containing the 3-spirocyclopentane-2-oxindole scaffold.

Attracted by the complex structure and potential application of chiral spirocyclopentane oxindole, significant attention has been paid to their catalytic asymmetric synthesis in the past few decades.[3] However, the construction of quaternary carbon stereocenters remains a challenging task in organic synthesis.[4] In addition, the construction of spiro systems often requires overcoming ring strain for functionalization and is accompanied by the generation of multiple stereocenters; thus, the control of diastereoselectivity during the bond formation is also a daunting challenge.[5] Therefore, the development of novel efficient asymmetric synthetic methods for the direct construction of the spirocyclic oxindole skeleton is in high demond, as new catalysts and synthetic strategies are desirable.

In the past few years, several elegant protocols that allow facile access to spirocyclopentane oxindoles via either transition metal catalyzed or organocatalytic [3 + 2]-cycloaddition reactions have been developed.[6] On the basis of the extraordinary performance of vinylcyclopropanes (VCPs) in construction of multicyclic and spirocyclic derivatives,[7,8] the ring-opening [3 + 2]-annulation of 2-oxindole derived spirovinylcyclopropanes (SVCPs) for the formation of racemic spirocyclic oxindoles has been realized with the aid of $Pd(OAc)_2$.[9] However, efficient methods for the catalytic asymmetric construction of 3-spirocyclopentane-2-oxindole scaffold by using chiral Lewis acid catalyst have rarely been disclosed. Inspired by these encouraging advances, and our previous work in developing chiral-at-metal rhodium(III) complexes[10] for highly enantioselective organic synthesis,[11] especially the asymmetric [3 + 2]-cycloaddition between 1,3-dipoles and chiral Lewis acid activated dipolarophiles,[11e,g] the

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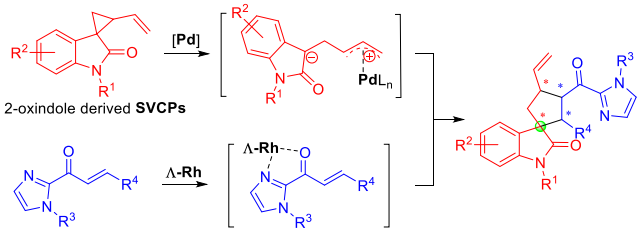
exploitation of a new asymmetric dual-catalytic system with the combination of an achiral Pd catalyst and a chiral Rh(III) complex is quite attractive to achieve the direct catalytic enantioselective synthesis of 3-spirocyclopentane-2-oxindole derivatives and allow for the facile construction of a wide range of spirocyclic scaffolds starting from VCPs.

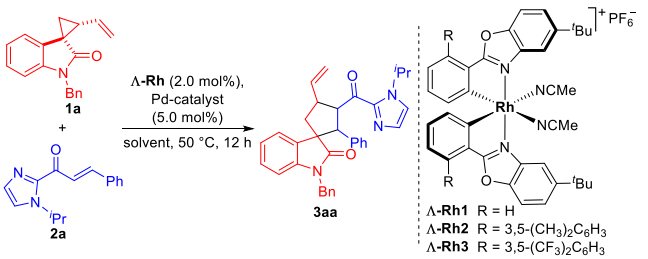
It would be logical to expect that bimetallic catalytic system can promote unprecedented new protocols that are not accessible conveniently via a single catalytic system. So far, much progress has been made in tandem bimetallic catalysis.[12] However, fewer examples of enantioselective synergistic bimetallic catalysis have been reported.[13] Recently, our group has developed a bimetallic gold(I)/chiral Rh(III) complex relay catalysis for asymmetric cascade reaction of keto esters with alkynyl alcohols and amides.[12g] Thus, we envisioned that spirocyclopentane skeletons could be constructed through enantioselective synergistic bimetallic catalyzed [3 + 2]-cycloaddition reaction between modified SVCPs as dipoles in the presence of Pd and dipolarophiles mediated by chiral Rh(III) complex (Scheme 1). Herein we report the successful implementation of this idea to provide 3-spirocyclopentane-2-oxindole derivatives in high yields with excellent enantiopurities.

Scheme 1. Asymmetric Construction of Spirocyclopentane Oxindole Scaffolds via Bimetallic Catalytic [3 + 2]-Cycloaddition



To evaluate the viability of this designed approach to the chiral 3-spirocyclopentane-2-oxindoles, a model reaction of Bn-protected SVCP-oxindole **1a**[9a] and *α,β*-unsaturated 2-acyl imidazole **2a** has been investigated in the presence of 5.0 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 2.0 mol % of **Λ-Rh1**[14] in THF at 50 °C. The desired cycloaddition reaction proceeded smoothly, delivering spirocyclic oxindole **3aa** in 93% yield with 96% ee and 10:1 dr (Table 1, entry 1). Chiral rhodium complexes have been evaluated (entries 1−3); the catalyst **Λ-Rh1** is the superior one that affords the highest dr and ee values. Some Pd(II) catalysts have also been tested (entries 4−6), the reaction could be finished in the presence of $Pd(OAc)_2$ to give adduct **3aa** in only 87% ee (entry 4), and no reaction occurred in the case of $PdBr_2$ and $Pd(PPh_3)_2Cl_2$ used (entries 5, 6). A screen of solvents (entries 7−11) showed that CH_3CN could lead to the formation of **3aa** in the highest yield (99%) and ee (98%) within 12 h, although the diastereoselectivity was relatively lower (entry 7, 6:1 dr). Remarkably, the catalyst loading of $Pd_2(dba)_3{\cdot}CHCl_3$ can be reduced to 2.0 mol % without any significant influence on reactivity and stereoselectivity, only a slightly diminished yield (entry 12). Considering that the use of THF would lead to good diastereocontrol (entry 13), while CH_3CN gave better enantioselectivity, a mixed solvent of THF/CH_3CN (1:1) has been tried, and product **3aa** was obtained in 93% yield, 99% ee, and 9:1 dr (entry 14). Control experiments confirmed

Table 1. Optimization of Reaction Conditions[a]



entry	Λ-Rh	Pd-catalyst (mol%)	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	THF	93	10:1	96
2	Λ-Rh2	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	THF	91	8:1	36
3	Λ-Rh3	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	THF	99	3:1	86
4	Λ-Rh1	$Pd(OAc)_2$ (5.0)	THF	99	9:1	87
5	Λ-Rh1	$PdBr_2$ (5.0)	THF	0	n.a.	n.a.
6	Λ-Rh1	$Pd(PPh_3)_2Cl_2$ (5.0)	THF	0	n.a.	n.a.
7	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	CH_3CN	99	6:1	98
8	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	DCE	97	7:1	96
9	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	Toluene	93	8:1	84
10	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	DCM	99	7:1	96
11	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	CH_3OH	99	7:1	96
12	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.0)	CH_3CN	93	6:1	99
13	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.0)	THF	93	10:1	96
14	Λ-Rh1	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.0)	CH_3CN/THF 1:1	93	9:1	99
15	none	$Pd_2(dba)_3{\cdot}CHCl_3$ (5.0)	THF	0	n.a.	n.a.
16	Λ-Rh1	none	THF	0	n.a.	n.a.

[a]Unless otherwise noted, reactions were carried out by using **1a** (0.10 mmol), **2a** (0.12 mmol), **Λ-Rh** (0.002 mmol, 2.0 mol %), and Pd-catalyst (0.005 mmol, 5.0 mol %) in solvent (0.5 mL) at 50 °C under argon atmosphere. [b]Isolated yields of diastereomeric mixtures. [c]Diastereomeric ratio, determined via ^1H NMR analysis of diastereomeric mixtures. [d]Enantiomeric excess of the major isomer, determined by chiral HPLC analysis. n.a. = not available.

that both $Pd_2(dba)_3{\cdot}CHCl_3$ and **Λ-Rh1** are essential in this reaction. No target molecule could be obtained without the Pd catalyst or chiral Rh(III) complex (entries 15−16).

Using the optimal reaction conditions (Table 1, entry 14), the generality of the substrate *α,β*-unsaturated 2-acyl imidazoles **2** was examined by using SVCP-oxindole **1a** as the coupling partner. As summarized in Table 2, different substituents (e.g., methyl, isopropyl and phenyl, entries 1−3) on imidazole were tolerated in the title reaction, and the highest yield and stereoselectivity were obtained by using *N*-isopropyl substrate **2a** (entry 1). *β*-Aryl substituents bearing electron-donating or -withdrawing groups were evaluated (entries 4−9), delivering the corresponding products in excellent yields (up to 99%) with high stereoselectivities (99% ee, up to 9.4:1 dr). *β*-Naphthyl and heteroaryl (e.g., furyl and thienyl) substrates were also suitable (entries 10−12), leading to the formation of the target molecules in excellent yields (up to 99%) and enantioselectivities (up to 99% ee), and moderate to high diastereoselectivities (up to 12.4:1 dr). In the case of *β*-2-(5-Br)-furyl substrate **2m** (entry 13), a low yield (**3am**, 27%) was obtained. A rationalized explanation is that bromide could interact with the Pd(0)-catalyst to inhibit its catalytic activity toward ring opening of SVCP-oxindole. Further replacing *β*-aryl groups with ester or methyl substituents was also well tolerated (entries 14−15), providing

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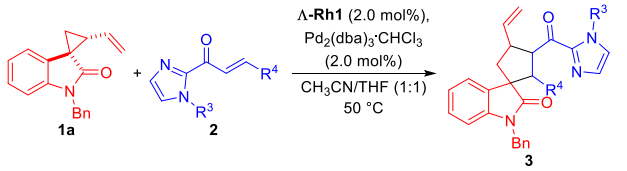
Table 2. Substrate Scope of α,β-Unsaturated 2-Acyl imidazoles[a]



entry	R^3	R^4	time (h)	3	yield (%)[b]	dr[c]	ee (%)[d]
1	^{i}Pr	Ph	12	**3aa**	93	9:1	99/54
2	Me	Ph	12	**3ab**	94	8.5:1	99/73
3	Ph	Ph	12	**3ac**	78	6.5:1	99/70
4	^{i}Pr	2-Me-C_6H_4	24	**3ad**	95	5.4:1	99/31
5	^{i}Pr	3-Me-C_6H_4	12	**3ae**	96	6:1	99/66
6	^{i}Pr	4−F-C_6H_4	17	**3af**	88	9.4:1	99/55
7	^{i}Pr	4−Cl-C_6H_4	12	**3ag**	91	7.6:1	99/70
8	^{i}Pr	4-OMe-C_6H_4	24	**3ah**	99	6.4:1	99/37
9	^{i}Pr	4-NO_2-C_6H_4	17	**3ai**	98	6:1	99/86
10	^{i}Pr	2-naphthyl	17	**3aj**	99	12.4:1	99
11	^{i}Pr	2-furyl	15	**3ak**	91	2.5:1	97/84
12	^{i}Pr	2-thienyl	17	**3al**	99	3.5:1	96/70
13	^{i}Pr	2-(5-Br)-furyl	34	**3am**	27	3:1	96/82
14	^{i}Pr	CO_2Et	36	**3an**	96	2:1	96/83
15	Me	Me	12	**3ao**	99	10:1	99/89
16	Me	2-naphthyl	12	**3ap**	91	12:1	99

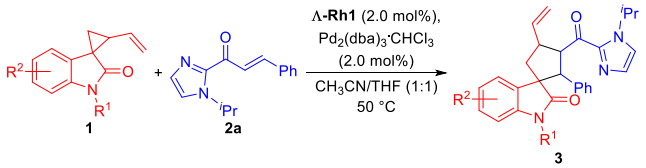
[a]Unless otherwise noted, reactions were carried out by using **1a** (0.10 mmol), **2** (0.12 mmol), **Λ-Rh1** (0.002 mmol, 2.0 mol %), and $Pd_2(dba)_3$·$CHCl_3$ (0.002 mmol, 2.0 mol %) in mixed CH_3CN/THF (1:1, 0.5 mL) at 50 °C under argon atmosphere. [b]Isolated yields of diastereomeric mixtures. [c]Determined via ^{1}H NMR analysis of diastereomeric mixtures. [d]The ee of the major/minor isomer, determined by chiral HPLC analysis.

the corresponding products **3an** and **3ao** in excellent yields and enantioselectivities. However, reactions involving β-heteroaryl or β-ethyl formate substituted substrates (**2k**−**2n**) gave relatively low diastereoselectivities (entries 11−14). A *N*-methyl (R^3 = Me) and β-2-naphthyl (R^4 = 2-naphthyl) substituted substrate **2p** has been checked in the title reaction with SVCP-oxindole **1a** using the optimal conditions (entry 16), and the corresponding product **3ap** was obtained in high yield (91%) with excellent stereoselectivity (99% ee, 12:1 dr). A cyclic substrate **2q** and an α-methyl substituted substrate **2r** have also been checked;[15] however, no target molecule was obtained, and substrates were totally recovered. This may be because the substituent hinders the activation of double bond by chiral Lewis acid or the steric hindrance prevents the bond formation.

Further investigation of the substrate scope of SVCP-oxindoles **1** was carried out under optimal conditions with **2a** (Table 3). SVCP-oxindoles **1** with various electron-rich and -deficient arenes were examined (entries 1−8). In almost all cases, high yields (up to 99%) and excellent stereoselectivities (up to 99% ee, 20:1 dr) could be achieved, except for substrates 5-OMe-**1c** and 5-NO_2-**1d**, the dr values of their corresponding products (**3ca** and **3da**) dramatically decreased. SVCP-oxindoles **1** with some other protecting groups on nitrogen (e.g., methyl, allyl, and 4-^{t}Bu-benzyl) also worked very well under the optimal conditions (entries 9−11).

During the characterization of these cycloaddition products, it has been found that some properties (e.g., solubilities and polarities) and ^{1}H NMR spectra of products **3an** and **3ao**, derived from β-alkyl substituted α,β-unsaturated 2-acyl imidazoles (Table 2, entries 14−15), were quite different from the others. On the basis of careful analysis of the NOE interactions, the relative configuration of the major diastereomers of **3an** and **3ao** was assigned as model **a** (Figure 2), and the major isomers of the other products were assigned as model **b** but model **a** for their minor isomers (for details, see the Supporting Information). This conclusion could be partially proved by the absolute configuration of the optically active **3ja** determined by X-ray crystallographic studies (Figure 2).[16] In theory, starting from (*E*)-alkenes, **2** would generate final products **3** with four pairs of diastereomers. Exper-

Table 3. Substrate Scope of SVCP-Oxindoles[a]



entry	R^1	R^2	time (h)	3	yield (%)[b]	dr[c]	ee (%)[d]
1	Bn	5-Me	17	**3ba**	93	10:1	99/52
2	Bn	5-OMe	16	**3ca**	88	2:1	99/75
3	Bn	5-NO_2	36	**3da**	99	1.4:1	95/47
4	Bn	5-F	17	**3ea**	92	8:1	99/23
5	Bn	5-Cl	20	**3fa**	91	6:1	99/43
6	Bn	4-Cl	16	**3ga**	89	13.5:1	99
7	Bn	6-Cl	20	**3ha**	97	14.5:1	99
8	Bn	7-Cl	20	**3ia**	98	20:1	99
9	Me	H	16	**3ja**	98	14:1	99
10	Allyl	H	16	**3ka**	99	12:1	99
11	4-^{t}Bu-benzyl	H	15	**3la**	95	15:1	99

[a]Unless otherwise noted, reactions were carried out by using **1** (0.10 mmol), **2a** (0.12 mmol), **Λ-Rh1** (0.002 mmol, 2.0 mol %), and $Pd_2(dba)_3$·$CHCl_3$ (0.002 mmol, 2.0 mol %) in mixed CH_3CN/THF (1:1, 0.5 mL) at 50 °C under argon atmosphere. [b]Isolated yields of diastereomeric mixtures. [c]Determined via ^{1}H NMR analysis of diastereomeric mixtures. [d]The ee of the major/minor isomer, determined by chiral HPLC analysis.

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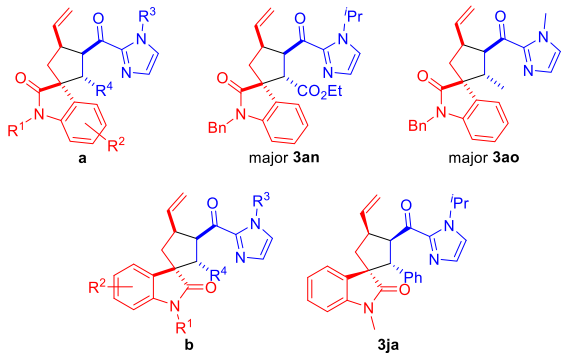
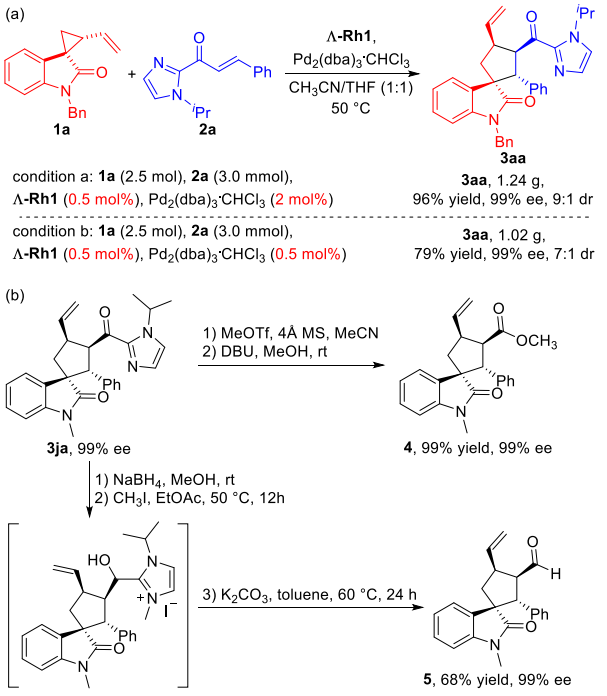


Figure 2. Structures of [3 + 2]-cycloaddition products.

imentally, more isomers could be observed in NMR spectra of a few compounds but too little to be characterized.

To illustrate the synthetic potential of current protocol, the cycloaddition of SVCP-oxindole **1a** (2.5 mmol) and *α,β*-unsaturated 2-acyl imidazole **2a** (3.0 mmol) was conducted on a gram-scale by employing 0.5 mol % of **Λ-Rh1** and 2 mol % $Pd_2(dba)_3{\cdot}CHCl_3$. Gratifyingly, product **3aa** was obtained in 96% yield (1.24 g) with 99% ee and 9:1 dr (Scheme 2a). Then

Scheme 2. Gram-Scale Experiments and Synthetic Transformations of Product 3ja



the catalyst loading of $Pd_2(dba)_3{\cdot}CHCl_3$ was further reduced to 0.5 mol %, which was equal to **Λ-Rh1** in this gram-scale reaction, and product **3aa** was formed with 99% ee, in a diminished yield (1.02 g, 79%), and decreased dr (7:1). Moreover, the product **3ja** could be transformed into optically active ester **4** and aldehyde **5** by removal of imidazole moiety in good yields without any loss in enantiomeric excess (Scheme 2b).[17]

On the basis of these experimental results, and literature precedents on chiral-at-metal octahedral rhodium catalysis[14] and palladium-catalyzed ring-opening annulation of VCPs,[7−9] a plausible mechanism is proposed in Figure 3. A Pd-stabilized

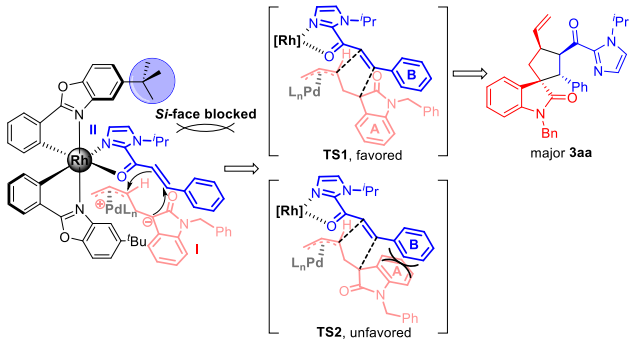


Figure 3. Proposed intermediate and plausible stereochemical outcome.

zwitterionic *π*-allylpalladium intermediate **I** is formed via a palladium-catalyzed ring opening of SVCP-oxindole **1a**. Meanwhile substrate **2a** coordinates with the rhodium complex **Λ-Rh1** to generate a bidentate *N,O*-coordinated intermediate **II**. The *Si*-face of the double bond of intermediate **II** is shielded by one of the *tert*-butyl groups, then *π*-allylpalladium intermediate **I** can attack from its *Re*-face. Presumably, during the bond formation, *π*−*π* stacking effect and antiattack of a nucleophile to *π*-allylpalladium leads to the same orientation of the vinyl group and the acyl imidazole, and the steric repulsion between two phenyl moieties (**A** and **B**) renders transition state **TS2** unfavorable and thus facilitates the generation of major isomer **3aa** via transition state **TS1**.

During our research, the diastereoselectivity of the title reaction is affected by many factors such as solvent, temperature, chiral rhodium catalyst, palladium catalyst, substituent, and so on. By now it is still very difficult to address the reason underlying the abnormalities in dr values (e.g., **3ak**−**3an** in Table 2, **3ca** and **3da** in Table 3). The configuration inversion that took place on spirocyclic of major diastereomers of **3an** and **3ao** (Figure 2) might be the result of replacing the *β*-aryl substituents with smaller ones such as ethyl formate group and methyl (Table 2, entries 14−15). With the disappearance of the steric repulsion, the phenyl moiety **A** (Figure 3) of oxindole tends to depart far away from rhodium complex and get close to *β*-alkyl groups of *α,β*-unsaturated 2-acyl imidazoles. The protecting group on oxindole nitrogen (R^1 in Table 3) could rotate around the carbon−nitrogen single bond and move far away from reaction center; thus, it does not affect diastereoselectivity much.

In conclusion, a highly efficient bimetallic synergistic catalysis for enantioselective [3 + 2]-cycloaddition reaction of SVCP-oxindoles with *α,β*-unsaturated 2-acyl imidazoles has been developed, with the combination of an achiral palladium(0) catalyst and a chiral rhodium(III) complex. A variety of biologically important 3-spirocyclopentane-2-oxindoles containing four contiguous stereocenters could be obtained in high yields with excellent enantiopurities. This work demonstrates the unique charm of the bimetallic catalytic system, presenting a bright prospect for development of chiral Lewis acid catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03588.

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X-ray data for compound **3ja**, experimental procedures, characterization data, analysis of NOE interactions, copies of ^{1}H, ^{13}C, and some two-dimensional NMR spectra, HPLC chromatograms for obtained compounds (PDF)

Accession Codes

CCDC 1998725 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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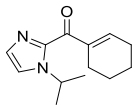
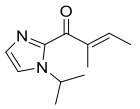
(16) CCDC 1998725 contains the supplementary crystallographic data for compound **3ja**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



2q



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