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RESEARCH ARTICLE

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Enantio- and Diastereodivergent Synthesis of Spirocycles through Dual-Metal-Catalyzed [3+2] Annulation of 2-Vinyloxiranes with Nucleophilic Dipoles

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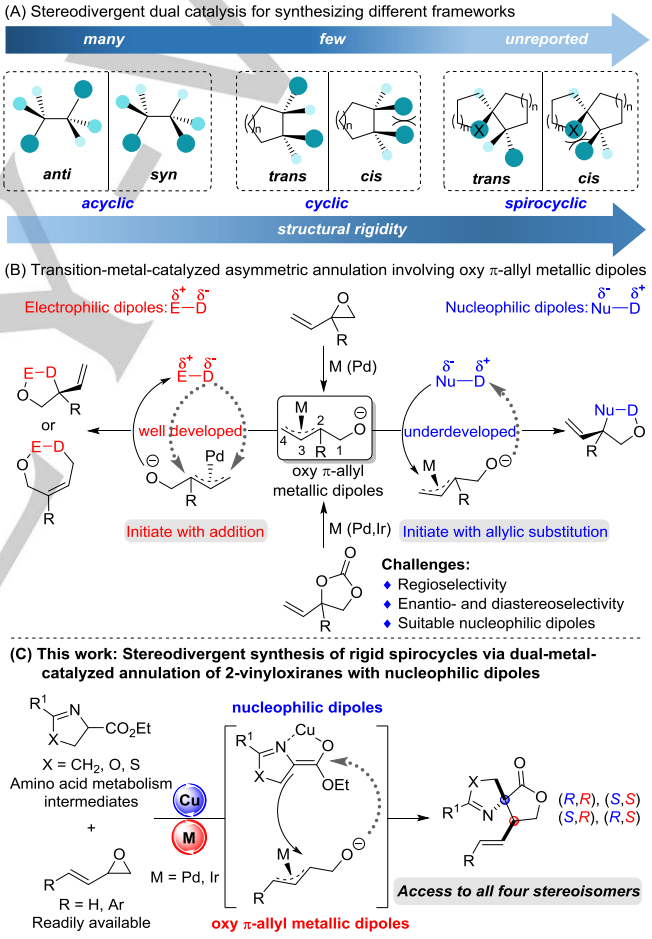
Abstract: The development of efficient and straightforward methods for obtaining all optically active isomers of structurally rigid spirocycles from readily available starting materials is of great value in drug discovery and chiral ligand development. However, the stereodivergent synthesis of spirocycles bearing multiple stereocenters remains an unsolved challenge owing to steric hindrance and ring strain. Herein, we report an enantio- and diastereodivergent synthesis of rigid spirocycles through dual-metal-catalyzed [3+2] annulation of oxy π-allyl metallic dipoles with less commonly employed nucleophilic dipoles (imino esters). A series of spiro compounds bearing a pyrroline and an olefin were easily synthesized in an enantio- and diastereodivergent manner (up to 19:1 dr, >99% ee), which showed great promise as a new type of *N*-olefin ligand. Furthermore, preliminary mechanistic studies including kinetic isotope effects (KIE), competitive experiment, and visual kinetic analysis were also carried out to understand the process of this bimetallic catalysis.

Introduction

Stereodivergent dual catalysis has emerged as a hot research topic in organic synthesis because it provides an attractive and powerful approach to prepare all possible stereoisomers of structural motifs bearing two stereogenic centers.[1] To date, such approaches mainly focus on the stereodivergent synthesis of vicinal stereocenters in acyclic frameworks using metal/organo dual catalysis,[2] dual metal catalysis,[3] and dual organocatalysis.[4] Importantly, the generally unfavored *syn*-diastereomers in acyclic frameworks could be smoothly obtained by appropriate permutations of the enantiomers of the two chiral catalysts. However, the stereodivergent synthesis of cyclic molecules is still underdeveloped due to the obvious energy difference between *cis*- and *trans*-configurations of cyclic molecules.[5] Furthermore, the stereodivergent synthesis of the much more rigid spirocycles containing multiple stereocenters remains unreported and more challenging mainly because of the difficulties associated with steric hindrance and ring strain (Scheme 1A). It's worth noting that the incorporation of spirocyclic scaffolds into pharmaceutical candidates could impart increased pharmacokinetic properties, such as potency, selectivity, protein binding affinities, and metabolic stability.[6] Therefore, the development of dual catalysis for the stereodivergent synthesis of the privileged spirocycles is highly desirable.



Scheme 1. Stereodivergent synthesis of rigid spirocycles via dual-metal-catalyzed annulation of 2-vinyloxiranes with nucleophilic dipoles.

Transition-metal-catalyzed asymmetric annulation reactions to access a modular library of complex cyclic frameworks and rigid spirocyclic skeletons have been recognized as a reliable methodology.[7] In this regard, the annulation reaction involving oxy π-allyl palladium dipoles is a convenient and powerful method for the rapid assembly of optically active oxy-heterocycles with multiple stereocenters.[8] The utility of this methodology lies in

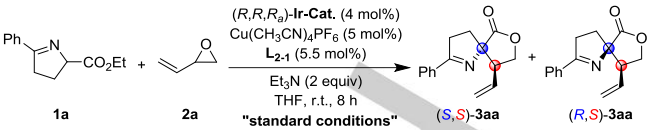
the fact that the oxy π-allyl palladium dipoles generated by oxidative addition of Pd(0) catalysts with vinylethylene carbonates or 2-vinyloxiranes can react with a variety of electrophilic dipoles including imines,[9] aldehydes,[10] α,β-unsaturated carbonyl compounds,[11] and other species[12] through a sequential addition/annulation fashion, efficiently constructing a wide range of enantioenriched 5- to 9-membered heterocyclic molecules (Scheme 1B, left). Nevertheless, the asymmetric annulations of oxy π-allyl metallic dipoles with nucleophilic dipoles, which undergo sequential allylic substitution/annulation, have received less attention and remain challenging due to the difficulty in control of regio-, enantio-, and diastereoselectivity and lack of suitable nucleophilic dipoles (Scheme 1B, right).[13]

Given the potential ability of bimetallic catalysis for developing catalytic reactions[14] and in our efforts towards dual metal catalysis for stereodivergent synthesis,[3] we envisioned using this strategy to develop the asymmetric annulation of oxy π-allyl metallic dipoles with less commonly employed nucleophilic dipoles for stereodivergent synthesis of rigid spirocycles. On the one hand, the introduction of the second chiral metal catalyst is beneficial to exploiting the novel nucleophilic dipoles for asymmetric annulation. On the other hand, dual chiral metal catalytic systems might offer an efficient strategy for overcoming the challenges related to regio-, enantio-, and diastereoselectivity in the asymmetric annulations with the nucleophile dipoles. Herein, we report our studies on the unexplored stereodivergent synthesis of rigid spirocycles through the dual-metal-catalyzed asymmetric annulation of 2-vinyloxiranes with nucleophilic dipolar imino esters (Scheme 1C). A series of privileged *N*-azaspiro-γ-butyrolactones bearing vicinal tertiary and quaternary stereocenters were easily synthesized in high yields with high to excellent enantio- and diastereoselectivities, the structural motif of which widely exists in alkaloids, natural products, and pharmaceuticals (e.g., amathaspiramide, spirohydantoin, and rolapitant).[6a,15] Additionally, these spiro products could be directly utilized in Rh-catalyzed asymmetric reactions as the chiral spiro *N*-olefin ligands with satisfactory catalytic results. It should be noted that there is no report so far in iridium-catalyzed asymmetric allylic substitution with simple 2-vinyloxiranes and in transition-metal-catalyzed asymmetric allylic substitution with 2-arylvinyloxiranes.[16]

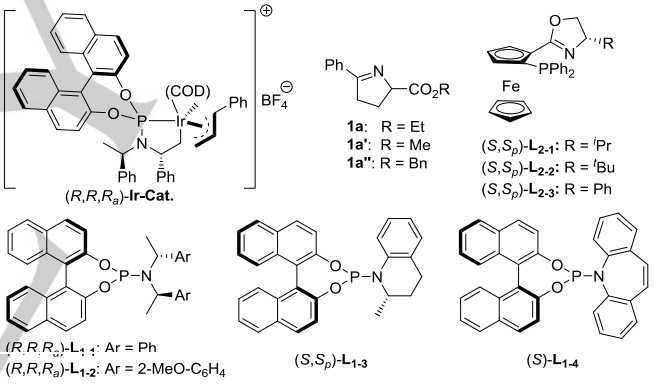
Results and Discussion

To verify the feasibility of our hypothesis, the substrate of amino acid metabolic intermediate **1**[17] was chosen as nucleophilic dipoles. The versatile and readily available 2-vinyloxirane **2a** was selected as oxy π-allyl metallic dipolar precursor for investigating the asymmetric [3+2] annulation to construct rigid spirocycles by dual metal catalysis. These results are summarized in Table 1. After systematic exploration, it was found that a bimetallic catalytic system comprising (*R*,*R*,R_a)-**Ir-cat**. (4 mol%), chiral copper catalyst (5 mol% $Cu(CH_3CN)_4PF_6$ + 5.5 mol% $\mathbf{L_{2\text{-}1}}$), and Et_3N (2 equiv) in THF (0.1 M) at room temperature was the optimal reaction conditions. The [3+2] annulation of 2-vinyloxirane **2a** with nucleophilic dipole **1a** proceeded smoothly under the optimal reaction conditions, delivering the spiro product *N*-azaspiro γ-butyrolactone (*S*,*S*)-**3aa** in 82% isolated yield with 13:1 dr and >99% ee (Table 1, entry 1). To explore the effect of

Table 1. Optimization of the reaction conditions.[a]



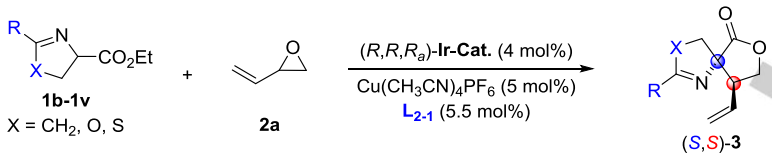
Entry	Variation from standard conditions	Yield of **3aa** (%)[b]	dr[c]	ee (%) (config.)[d]
1	none	86(82)	13:1	>99% (*S*,*S*)
2	**1a'** replace **1a**	77	10:1	>99% (*S*,*S*)
3	**1a''** replace **1a**	58	9:1	>99% (*S*,*S*)
4[e]	$[Ir(cod)Cl]_2$:$\mathbf{L_{1\text{-}2}}$	60	9:1	>99% (*S*,*S*)
5[e]	$[Ir(cod)Cl]_2$:$\mathbf{L_{1\text{-}3}}$	40	7:1	>99% (*S*,*S*)
6[e]	$[Ir(cod)Cl]_2$:$\mathbf{L_{1\text{-}4}}$	46	4:1	>99% (*S*,*S*)
7	$\mathbf{L_{2\text{-}2}}$ replace $\mathbf{L_{2\text{-}1}}$	44	10:1	>99% (*S*,*S*)
8	$\mathbf{L_{2\text{-}3}}$ replace $\mathbf{L_{2\text{-}1}}$	32	7:1	>99% (*S*,*S*)
9	Toluene replace THF	21	6:1	>99% (*S*,*S*)
10	DCM replace THF	19	5:1	>99% (*S*,*S*)
11	DME replace THF	58	11:1	>99% (*S*,*S*)
12	Dioxane replace THF	64	10:1	>99% (*S*,*S*)
13	50 °C replace r.t.	78	10:1	>99% (*S*,*S*)
14	-10 °C replace r.t.	39	12:1	>99% (*S*,*S*)
15	no **Ir-cat**.	n.d.	-	-
16	no [Cu] catalyst	n.d.	-	-
17	no Et_3N	n.d.	-	-
18	***ent*-$\mathbf{L_{2\text{-}1}}$** replace $\mathbf{L_{2\text{-}1}}$	80(75)	1:9	>99% (*R*,*S*)

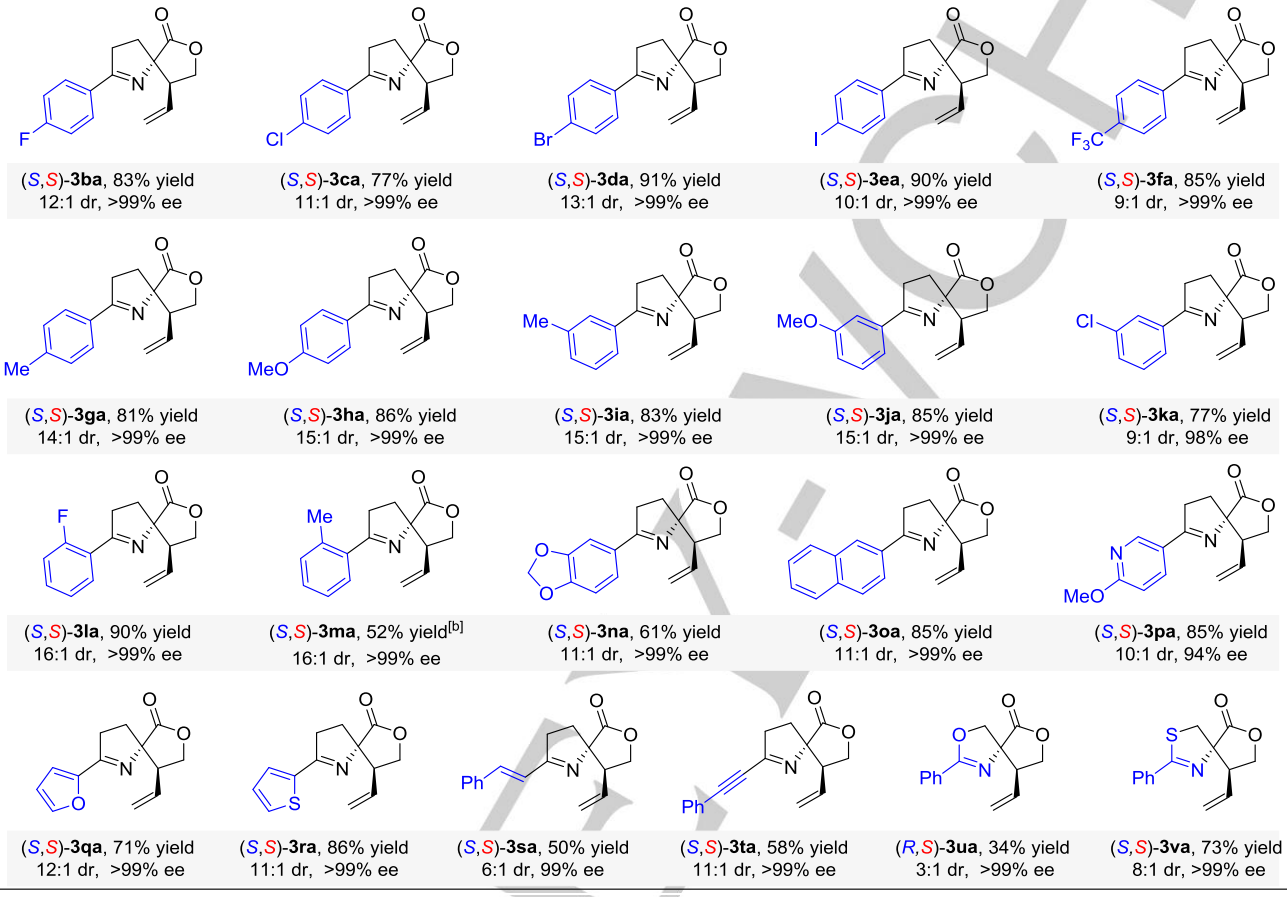


[a] The reaction was performed with **1a** (0.1 mmol), **2a** (0.25 mmol), (*R*,*R*,R_a)-**Ir-cat**. (4 mol%), $Cu(CH_3CN)_4PF_6$ (5 mol%), $\mathbf{L_{2\text{-}1}}$ (5.5 mol%), Et_3N (0.2 mmol) in THF (1 mL), at r.t. for 8 h. [b] Determined by ^1H NMR analysis of the crude reaction mixtures using mesitylene as internal standard; The value in parenthesis represents isolated yield. [c] Determined by ^1H NMR analysis of the crude reaction mixtures. [d] Determined by HPLC analysis. ***ent*-$\mathbf{L_{2\text{-}1}}$** = (*R*,R_p)-$\mathbf{L_{2\text{-}1}}$. [e] $[Ir(cod)Cl]_2$:**L** = 1:2.

the substituent group of the imino esters on the reaction, the substrates **1a'** and **1a''** substituted with Me and Bn groups were subjected to the reaction. The desired products were obtained with slightly decreased diastereoselectivities and yields (77% yield, 10:1 dr; 58% yield, 9:1 dr, entries 2 and 3). Subsequently, some representative and commercially available chiral ligands with respect to Ir and Cu were evaluated (entries 4-8). Different results were obtained ranging from 4:1 dr to 10:1 dr and from 32% yield to 60% yield. No further improvement of yield or dr was observed, even after screening various solvents, temperature, and different bases (entries 9-14 and see Supporting Information for details). Subsequently, a set of control experiments were performed to understand the role of each catalyst in this bimetallic catalytic system. The reaction did not proceed in the absence of iridium catalyst (entry 15). Without copper catalyst or Et_3N, none of the desired product was obtained and only imino ester **1a** was recovered (entries 16 and 17). These results suggest that the

Table 2. Substrate scope for the synthesis of (*S*,*S*)-spirocycles.[a]





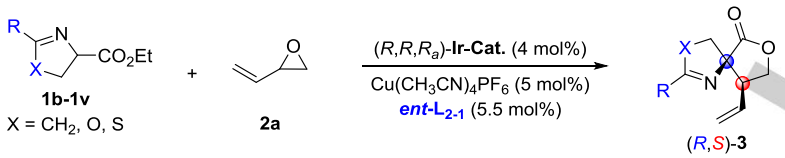
[a] Reaction conditions: See Table 1, entry 1. The yield is isolated yield. [b] The reaction was performed for 16 h.

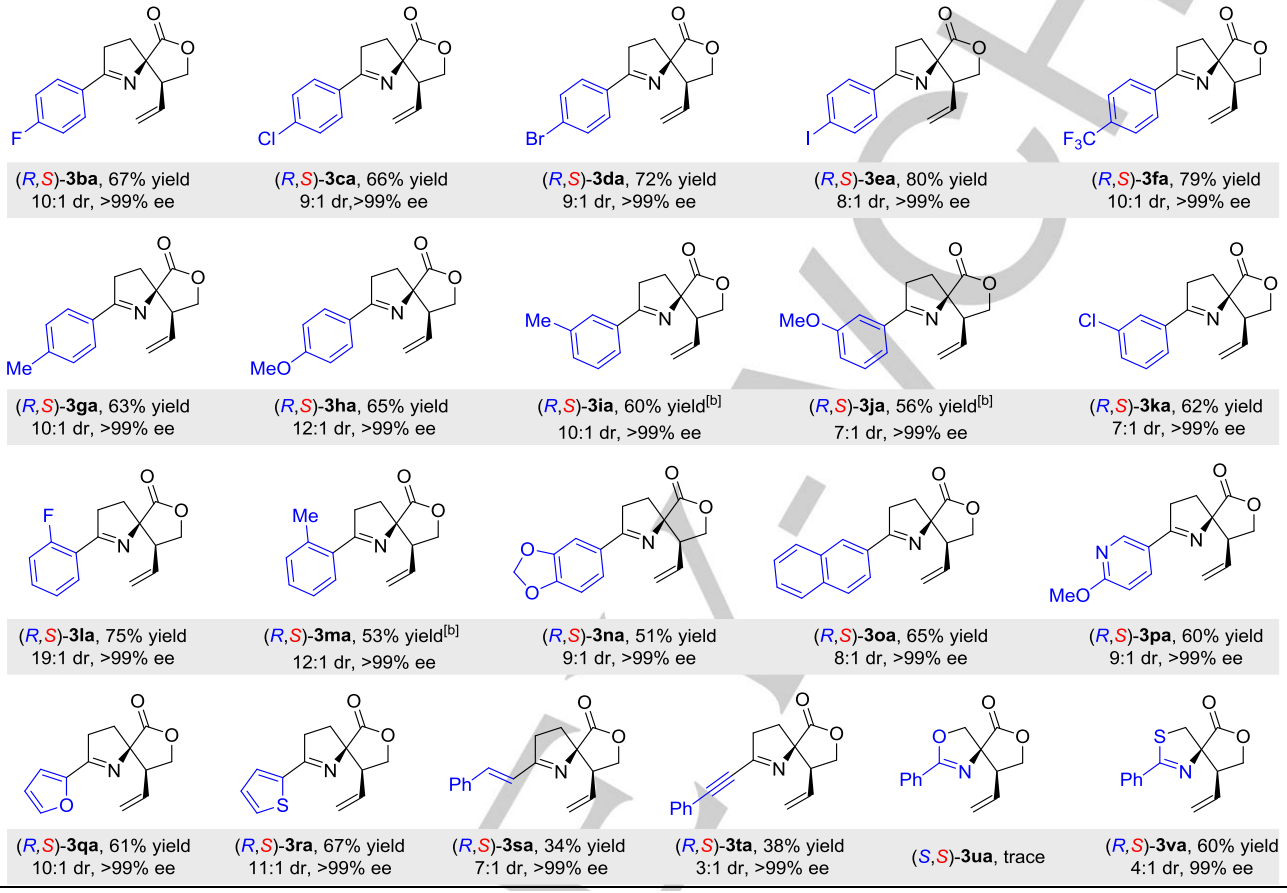
bimetallic catalysts and base played an indispensable role in allowing the annulation reaction to proceed efficiently. To our delight, the complementary diastereomer (*R*,*S*)-**3aa** was obtained in 75% isolated yield with 9:1 dr and >99% ee by using (R,R_p)-^{i}Pr-phosferrox instead of (S,S_p)-^{i}Pr-phosferrox, demonstrating the feasibility of diastereodivergent synthesis (entry 18).

First, the substrate scope of the nucleophilic dipoles (imino esters) **1** was examined in an enantio- and diastereodivergent manner (Table 2 and 3). As expected, a wide range of imino esters **1** bearing electron-withdrawing or electron-donating groups at the aromatic ring could be employed in the annulation reaction, giving a series of chiral *N*-azaspiro-γ-butyrolactones (*S*,*S*)-**3ba-3ma** and their complementary diastereomers (*R*,*S*)-**3ba-3ma** in moderate to excellent yields and with high diastereoselectivities and enantioselectivities (up to 91% yield, 19:1 dr, and generally >99% ee). For example, halide, trifluoromethyl, methyl, and methoxyl functional groups at the *para*-position of the phenyl ring were all suitable for this transformation (**3ba-3ha**). In particular, the substrates bearing bromo and iodo groups, which are widely applied in transition-metal-catalyzed coupling reaction,[18] were also tolerated. And the desired products were obtained in high yields and stereoselectivities, implying the potential value of this transformation (**3da** and **3ea**). The substituents at the *meta* and *ortho* positions of the phenyl ring were also compatible, delivering the corresponding products in moderate to excellent yields (52-90%) with high levels of enantio- and diastereoselectivities (7:1-19:1 dr and >99% ee, **3ia-3ma**). Furthermore, polyaromatic and heteroaromatic substrates could efficiently participate in the reaction, giving the target products in 51-86% yields with 8:1-12:1 dr and generally >99% ee values (**3na-3ra**). Interestingly, imino esters derived from cinnamyl aldehyde, alkyne aldehyde, serines, and cysteines were suitable for this reaction as well, furnishing the corresponding products with excellent enantioselectivities, although the yields or diastereoselectivities were slightly lower (**3sa-3va)**.

2-Styryloxirane can be easily accessed from cinnamaldehydes via the Corey–Chaykovsky epoxidation and serve as an important building block for versatile transformations.[8b] However, this type of racemic 1,3-unsymmetric disubtituted allylic substrate has not been applied to metal-catalyzed asymmetric allylic substitution reactions, even for the construction of a single stereocenter. Therefore, we were curious about whether this substrate would be compatible with our present Ir/Cu bimetallic catalytic system for the enantio- and diastereodivergent synthesis of spiro products. Unfortunately, initial attempts and efforts were

Table 3. Substrate scope for the synthesis of the complementary diastereomer (*R*,*S*)-spirocycles.[a]





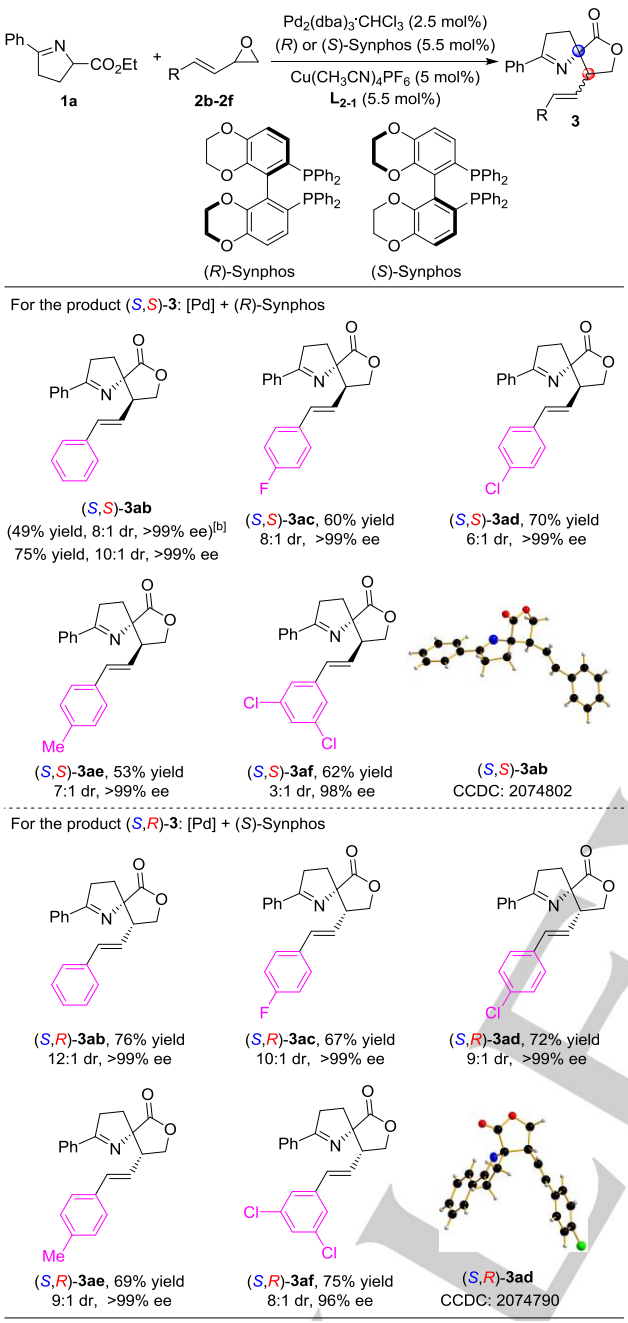
[a] Reaction conditions: See Table 1, entry 18. The yield is isolated yield. [b] The reaction was performed for 16 h.

unsuccessful for the asymmetric annulation of 2-styryloxirane **2b** with imino ester **1a**.[19] Inspired by our previous work on palladium-catalyzed asymmetric allylic alkylation reactions with unsymmetrical 1,3-disubstituted allyl substrates,[3h] we hypothesized that the asymmetric [3+2] annulation of 2-styryloxirane **2b** with imino esters might be successfully realized through synergistic Pd/Cu catalysis. As anticipated, the substrate **2b** could smoothly participate in this annulation reaction, giving the spirocycle (*S*,*S*)-**3ab** in 49% yield with 8:1 dr and >99% ee in the presence of [5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ + 5.5 mol% (*R*)-BINAP], [5 mol% $Cu(CH_3CN)_4PF_6$ + **L2-1**] and K_3PO_4 (Table 4).

Then, all reaction parameters, including various types of bases, solvents, temperature, metallic salt and ligands were carefully investigated to improve yield and diastereoselectivity (See Supporting Information for more details). To our delight, a dual catalytic system containing [5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ + 5.5 mol% (*R*)-Synphos], [5 mol% $Cu(CH_3CN)_4PF_6$ + 5.5 mol% **L2-1**], K_3PO_4 (1 equiv) and in THF (2 mL) at 5 °C was determined to be the optimal reaction conditions, affording (*S*,*S*)-**3ab** in 75% isolated yield with 10:1 dr and >99% ee after 16 h (Table 4). Meanwhile, the complementary diastereomer (*S*,*R*)-**3ab** was obtained in 76% yield with 12:1 dr and >99% ee by only changing the absolute configuration of the palladium catalyst (Table 4). Then, several 2-arylvinyloxiranes were subjected to the annulation reaction for the construction of rigid spirocycles in an enantio- and diastereodivergent manner. As shown in Table 4, 2-arylvinyloxiranes substituted with fluoro, chloro, methyl, and 3,5-dichloro at the aromatic ring, were all compatible with this catalytic system, delivering the spirocylclic compounds and their complementary diastereomers in high yields and with high diastereoselectivities and excellent enantioselectivities (**3ac**-**3af**, up to 76% yield, 12:1 dr, and >99% ee). The absolute configuration of the products (*S*,*S*)-**3ab** and (*S*,*R*)-**3ad** were determined by X-ray crystallography.[20]

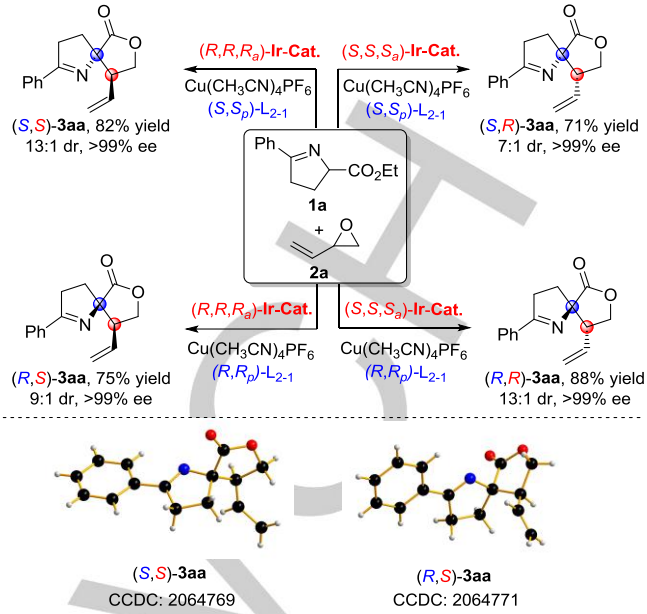
To further evaluate the stereodivergence of the established protocol, the reactions of **1a** and **2a** were carried out in an enantio- and diastereodivergent manner under the optimal reaction conditions. All four stereoisomers of the spiro products **3aa** could be prepared in excellent yields and with high levels of diastereoselectivities and enantioselectivities (up to 88% yield, 13:1 dr, and >99% ee, Scheme 2). Notably, the present protocol provides an attractive route to access all stereoisomers of spirocycles bearing two stereocenters. The absolute configuration of the product (*S*,*S*)-**3aa** and the complementary diastereomers (*R*,*S*)-**3aa** were determined by X-ray crystal diffraction.[20]

Table 4. Substrate scope of 2-arylvinyloxiranes.[a]



[a] The reaction was performed with **1a** (0.2 mmol), **2** (0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), (*R*)-Synphos or (*S*)-Synphos (5.5 mol%), $Cu(CH_3CN)_4PF_6$ (5 mol%), $\mathbf{L_{2\text{-}1}}$ (5.5 mol%), and K_3PO_4 (0.2 mmol) in THF (2 mL), at 5 °C for 16 h. The yield is based on isolated yield. The dr value is determined by GC-MS analysis of the crude reaction mixtures. The ee value is determined by HPLC analysis. [b] (*R*)-BINAP instead of (*R*)-Synphos.

To demonstrate the practicality of the bimetallic catalytic system, a scale-up experiment was performed (Scheme 3). To our delight, the product (*R*,*S*)-**3aa** was obtained in 73% yield and with 8:1 dr and >99% ee when the reaction was conducted on a 3 mmol scale. Fortunately, the (*R*,*S*)-**3aa** with >20:1 dr could be easily obtained after column chromatography. Then, different transformations with regards to the terminal alkene, pyrroline, and γ-butyrolactone of this rigid spirocyclic (*R*,*S*)-**3aa** were conducted. At first, hydroboration of the terminal alkene was conducted in the presence of $[Ir(COD)Cl]_2$ and DPPM, furnishing the *anti*-

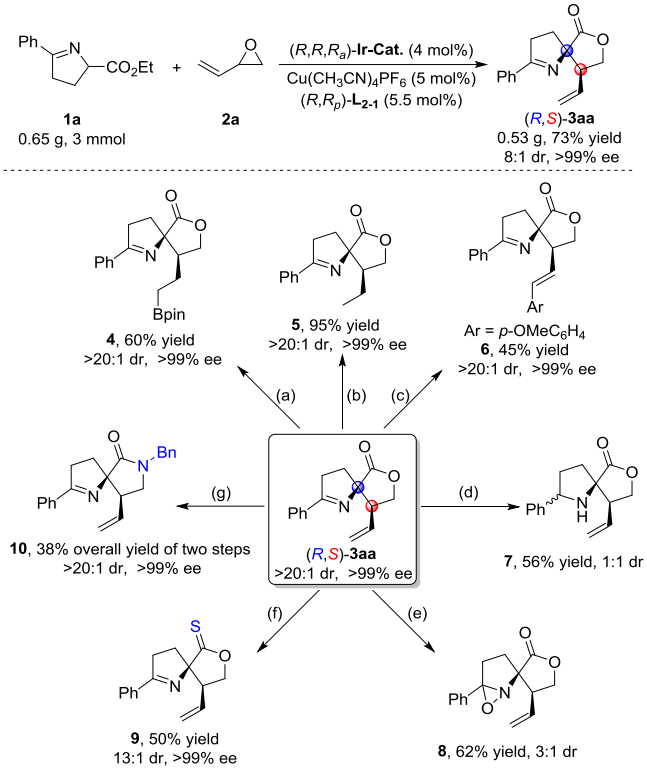


Scheme 2. Stereodivergent access to all four stereoisomers of **3aa**

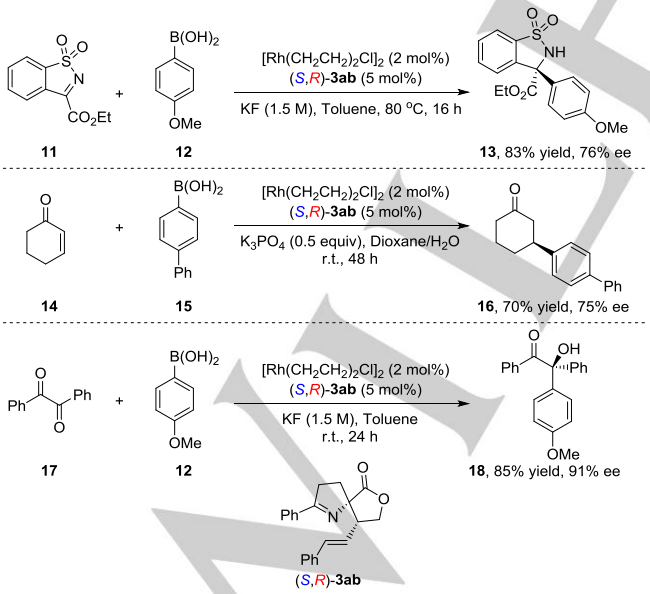
Markovnikov product **4** in 60% yield (Scheme 3a).[21] The product (*R*,*S*)-**3aa** could be selectively hydrogenated to give the product **5** in 95% yield (Scheme 3b). To our delight, the terminal alkene smoothly underwent cross-coupling with methyl 4-bromobenzoate, affording the Heck product **6** in moderate yield and with retention of diastereoselectivity and enantioselectivity (Scheme 3c). Secondly, selective imino reduction could be achieved by using $NaBH_3CN$ as a reducing reagent, delivering the product **7** in 56% yield and with 1:1 dr (Scheme 3d).[22] On the other hand, selective imino oxidation of (*R*,*S*)-**3aa** afforded oxaziridine derivatives **8** in 62% yield with 3:1 dr (Scheme 3e), which might have potential antimalarial activity.[23] Furthermore, (*R*,*S*)-**3aa** could be converted into the spirocylicthionate lactone **9** in 50% yield with 13:1 dr and >99% ee using Lawesson's reagent (Scheme 3f). Notably, *N*-azaspirolactam **10** could be smoothly obtained in 38% yield over two steps with retention of diastereoselectivity and enantioselectivity, which is a common structural core found in natural products and pharmaceuticals (Scheme 3g).[15b-d]

The development of chiral ligands with novel backbones is the central research topic in asymmetric catalysis. And the spiro backbone has been recognized as one of the privileged structures for the construction of chiral ligands. Accordingly, we are curious about whether our spiro products could be applied in transition-metal-catalyzed asymmetric reactions as the *N*-olefin ligands.[19d,24-25] To our delight, (*S*,*R*)-**3ab** was successfully utilized in Rh-catalyzed asymmetric arylation of cyclic ketimines **11**, *α*,*β*-unsaturated ketone **14**, and benzyl **17**.[26] And preliminary results were obtained with the addition products **13**, **16**, and **18** in 83% yield and 76% ee, 70% yield and 75% ee, 85% yield and 91% ee, respectively (Scheme 4).

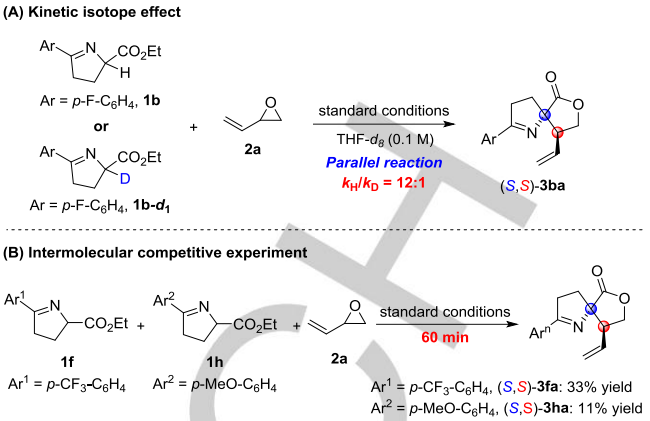
An array of mechanistic studies was subsequently performed in order to gain insight into the bimetallic catalytic system. In order to determine which step is the rate-determining step, the imino esters **1b** and **1b-*d*$_1$** were firstly studied under the standard reaction conditions by *in situ* ^{19}F-NMR monitoring. The value of the primary kinetic isotope effect was determined to be 12



Scheme 3. Scale-up experiment and transformation of the spirocycle. (a) HBpin (2 equiv), $[Ir(COD)Cl]_2$ (3 mol%), DPPM (6 mol%), DCM, r.t., 20 h; (b) H_2, Pd/C (5 mol%), MeOH, r.t., 4 h; (c) Methyl 4-bromobenzoate (1 equiv), $Pd(OAc)_2$ (5 mol%), P(*o*-toyl)$_3$ (20 mol%), Et_3N (1.5 equiv), DMF, 100 °C, 30 h; (d) $NaBH_3CN$ (5 equiv), conc. HCl/PrOH (v/v = 1:11), r.t., 24 h; (e) MMPP (3 equiv), MeOH, r.t., 5 h; (f) Lawesson's reagent (1 equiv), toluene, reflux, 24 h; (g) (1) $BnNH_2$ (1.3 equiv), MeOH, r.t., 12 h; (2) TsCl (1.5 equiv), pyridine (2 equiv), DCM, 0 °C, 6 h.



Scheme 4. Preliminary results using the spiro product (*S*,*R*)-**3ab** as the *N*−olefin ligand in Rh-catalyzed asymmetric addition of cyclic ketimines, *α*,*β*-unsaturated ketones, and benzil with arylboronic acids.



Scheme 5. Kinetic isotope effect and competitive experiment.

(Scheme 5A). There is a tunneling effect in this process.[27] Furthermore, an intermolecular competitive experiment between **1f** and **1h** was also performed (Scheme 5B). The substrate **1f** bearing an electron-withdrawing group tended to be relatively more reactive than the substrate **1h** possessing an electron-donating group. These results implied that the extraction of hydrogen from the imino esters is the rate-determining step.

To further gain the information of the reaction order, visual kinetic analysis reported by Burés was adopted to investigate the reaction of 2-vinyloxirane **2a** and imino ester **1b** using ^{19}F-NMR spectroscopy.[28] By varying the concentration of the reaction components, the order of the corresponding reaction components was obtained by plotting the concentration of product against normalized time (Figure 1, See Supporting Information for more details). As shown in Figure 1, the experimental results showed that the Cu catalyst and the Ir catalyst were both first-order, which reflects that the Cu catalyst and the Ir catalyst participate in the reaction to activate the nucleophile and electrophile, respectively. The results are in good agreement with the control experiments shown in Table 1. The order of Et_3N was found to be approximate 0.5. It was proposed that Et_3N could abstract the proton of the

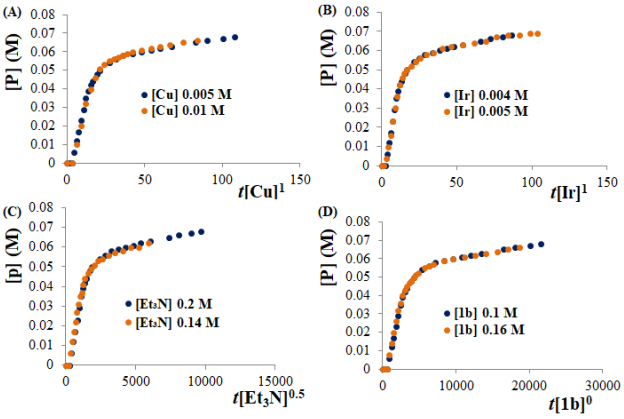


Figure 1. The profile for visual kinetic analysis. (A) Order in Cu catalyst, $t[Cu]^1$. (B) Order in Ir catalyst, $t[Ir]^1$. (C) Order in Et_3N, $t[Et_3N]^{0.5}$. (D) Order in imino ester **1b**, $t[\mathbf{1b}]^0$.

imino ester, generating Et_3NH^+. Next, the Et_3NH^+ might participate in the activation of 2-vinyloxiranes combining with the metal catalyst, affording the oxy π-allyl metallic dipoles. On the contrary, excess Et_3N might reduce the activating ability of Et_3NH^+ on the 2-vinyloxiranes. Furthermore, the reaction was shown to be zero order with respect to imino ester.

Conclusion

In summary, we have developed a dual-metal-catalyzed asymmetric [3+2] annulation of 2-vinyloxiranes with nucleophilic dipoles (imino esters), which was successfully applied to the stereodivergent synthesis of structurally rigid spirocyclic frameworks for the first time. A series of spiro compounds bearing vicinal tertiary and quaternary stereocenters were easily synthesized in an enantio- and diastereodivergent manner. This reaction features broad substrate scope, high reactivity, high to excellent stereoselectivity (up to 19:1 dr, >99% ee), and easy diversification, selectively affording a new family of chiral spiro ligands bearing *N*/olefin functionalities. This new type of spiro N/olefin ligand showed high asymmetric induction in Rh-catalyzed asymmetric addition reactions.

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Keywords: stereodivergent dual catalysis • bimetallic catalysis • spirocycles • allylation • *N*/olefin ligand

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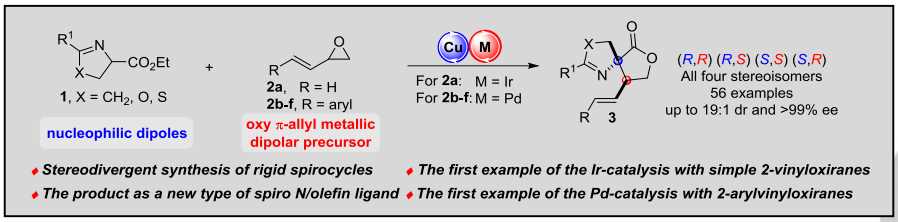

A dual-metal-catalyzed asymmetric [3+2] annulation of 2-vinyloxiranes with the challenging nucleophilic dipoles (imino esters) was achieved, which was successfully applied to the stereodivergent synthesis of structurally rigid spirocyclic framework for the first time. A series of spiro compounds bearing a pyrroline and an olefin were easily synthesized in an enantio- and diastereodivergent manner, which showed great promise as a new type of *N*-olefin ligand.

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