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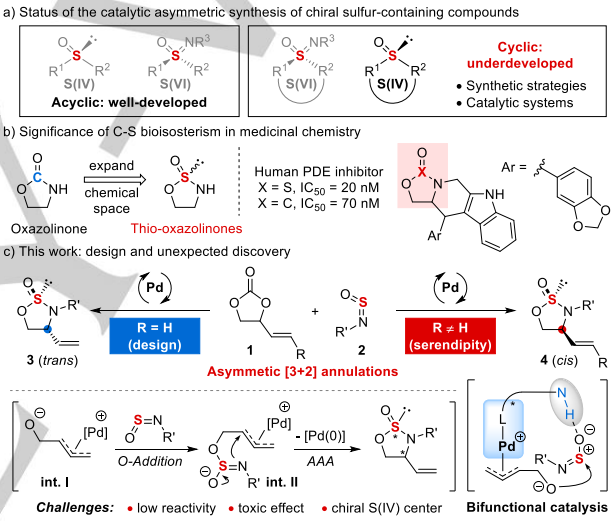
Synthesis of S(IV)-Stereogenic Chiral Thio-Oxazolidinones via Palladium-Catalyzed Asymmetric [3+2] Annulations

Bao-Cheng Wang,[a] Fang Hu,[b] Jiahui Bai,[c] Fen-Ya Xiong,[a] Peng Chen,[a] Jianye Li,[a] Ying Tan,[b] Yin-Long Guo,*[c] Wen-Jing Xiao,[a,d] and Liang-Qiu Lu*[a,e,f]

This paper is dedicated to the 60th birthday of the honourable Mr. Zuowei Xie.

Abstract: Organic molecules bearing chiral sulfur stereocenters exert a great impact on asymmetric catalysis and synthesis, chiral drugs, and chiral materials. Compared with acyclic ones, the catalytic asymmetric synthesis of thio-heterocycles has largely lagged behind due to the lack of efficient synthetic strategies. Here we establish the first modular platform to access chiral thio-oxazolidinones via Pd-catalyzed asymmetric [3+2] annulations of vinylethylene carbonates with sulfinylanilines. This protocol is featured by readily available starting materials, and high enantio- and diastereoselectivity. In particular, an unusual effect of a non-chiral supporting ligand on the diastereoselectivity was observed. Possible reaction mechanisms and stereocontrol models were proposed.

Organic molecules containing chiral sulfur stereocenters have received increasing interest from the synthetic community, as well as pharmaceutical and material chemists.[1] One of the most important reasons for this is that sulfur profoundly affects the physical, chemical, and biological performances of many chiral functional molecules including chiral catalysts, drugs, and material.[2,3] Therefore, the search for efficient strategies and catalytic systems for chiral sulfur-containing compounds is akin to a gold rush in modern synthetic chemistry.[4-6] Despite impressive advances in this field, most of the available methods focus on the preparation of acyclic chiral sulfur compounds, and comparatively limited success has been achieved for the cyclic ones by asymmetric [4+2] and [2+2] cycloadditions via Lewis acid or *N*-heterocyclic carbene catalysis,[6a,b] or sulfoximine-directed asymmetric C-H functionalization via rhodium and ruthenium catalysis (Scheme 1a).[6c-e] Given the great popularity of heterocyclic units in pharmaceutical agents[7] and the promising C-S bioisosterism in medicinal chemistry,[8] the development of efficient synthetic strategies and catalytic systems for sulfur-stereogenic chiral heterocycles is promising for greatly expanding the chemical space for drug discovery.



Scheme 1. Design plan for the synthesis of chiral thio-oxazolidinones. AAA, asymmetric allylic alkylation. PDE, phosphodiesterase.

Oxazolidinone is an important heterocyclic pharmacophore that is widely used in many drugs and pesticides.[9] Often, the use of its bioisostere, thio-oxazolidinone, can significantly affect the chemical and biological processes.[10] For example, the replacement of oxazolidinone with thio-oxazolidinone in a human PDE inhibitor can significantly improve the activity (Scheme 1b).[10d] However, the effect of sulfur stereochemistry has not yet been investigated in many cases because of the lack of efficient synthetic protocols for such promising thio-oxazolidinones. To our knowledge, the stereogenic-at-S(IV) thio-oxazolidinones have traditionally been prepared from chiral amino alcohols.[11] Following our focus on the catalytic asymmetric synthesis of chiral heterocycles,[12] we herein disclose a modular synthetic platform[13] for chiral thio-oxazolidinones via Pd-catalyzed asymmetric [3+2] annulations of vinylethylene carbonates (VECs)[13e,14] and sulfinylamines (Scheme 1c, up).[15] The availability of starting materials, and high enantio- and diastereoselectivity make this protocol attractive for synthetic chemistry and pharmaceutical studies. A brief design of the oxygen addition of Pd-containing 1,3-dipolar intermediates to

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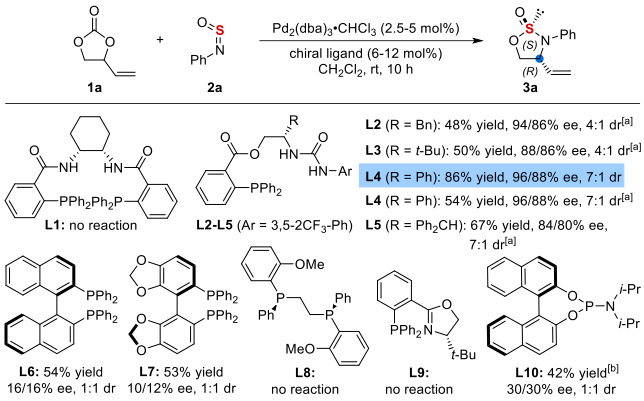
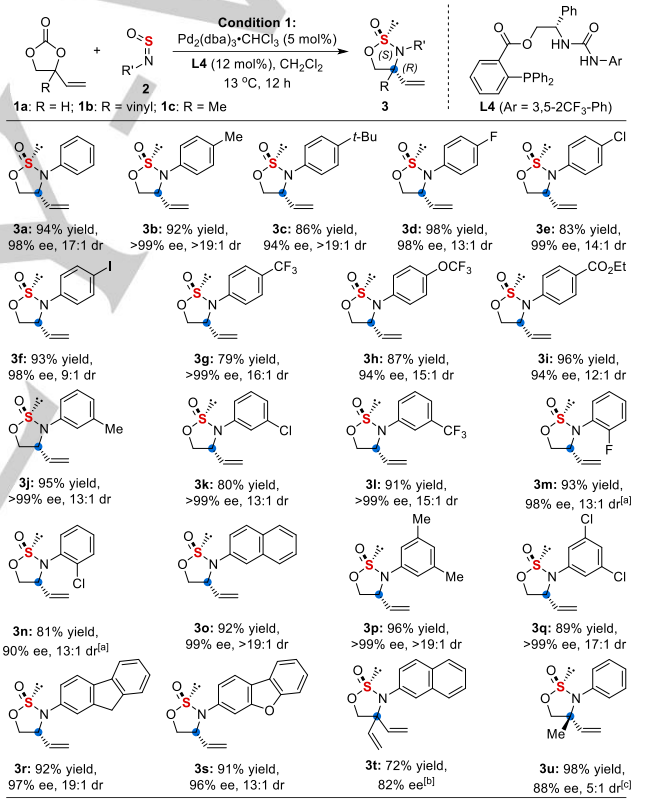
sulfinylamine reagents, followed by the intramolecular allylic substitution is illustrated in Scheme 1c (down). Although reasonable in principle, the low electrophilic reactivity of sulfinylamines, the potential toxic effect of sulfur atoms on palladium, and the fine control of the S(IV) stereogenic center would hinder this designed protocol. Considering the polarized characteristics of sulfinylanilines, we employed the strategy of bifunctional H-bonding/Pd catalysis,[16] in which additional H-bond donors help activate these reagents and induce their spatial orientation, to address these challenging issues.



entry	solvent	T/°C	time/h	1a:2a	yield/%[b]	ee/%[c]	dr[b]
1	CH_2Cl_2	25	10	1:2	86	96/88	7:1
2[d]	CH_2Cl_2	25	10	1:2	NR	ND	ND
3	PhCl	25	10	1:2	43	60/54	2:1
4	CH_3CN	25	10	1:2	NR	ND	ND
5	THF	25	6	1:2	93	64/52	1:1
6	DMF	25	10	1:2	NR	ND	ND
7	CH_2Cl_2	13	10	1:2	82	98/ND	15:1
8	CH_2Cl_2	0	10	1:2	37	98/ND	15:1
9	CH_2Cl_2	-10	10	1:2	trace	ND	ND
10	CH_2Cl_2	13	18	1:2	91	98/ND	15:1
11	CH_2Cl_2	13	10	2:1	95	99/ND	16:1
12	CH_2Cl_2	13	10	1.5:1	96 (94)[e]	98/ND	17:1

Scheme 2. Condition optimization. Conditions: **1a** (0.23 mmol, 1.5 equiv.), **2a** (0.15 mmol, 1.0 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00375-0.0075 mmol, 2.5-5 mol%), and chiral ligand (0.009-0.018 mmol, 6-12 mol%) in CH_2Cl_2 at rt. [a] Performed for 3 h. [b] 24 mol% of **L10** was used. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by chiral HPLC analysis of the purified product. [d] $[Pd(allyl)Cl]_2$ was used instead of $Pd_2(dba)_3{\cdot}CHCl_3$. [e] Isolated yield was shown in parentheses. rt, room temperature; dr, diastereomer ratio; ee, enantiomer excess; THF, tetrahydrofuran; DMF, *N*,*N*-dimethyl formamide; NR, no reaction; ND: not determined.

Initially, the Pd-catalyzed asymmetric [3+2] annulation was optimized using VEC **1a** and sulfinylaniline **2a** as model substrates (Scheme 2). The classic Trost ligand **L1**[17] containing two amide motifs as H-bonding donors was first tested; however, no reaction occurred. When Zi's phosphine ligands **L2**-**L5**[18] containing chiral urea motifs were used, to our delight, high enantioselectivity and moderate diastereoselectivity were achieved. In particular, the use of phenyl-substituted ligand **L4** afforded the chiral product **3a** in 86% yield and with 96% ee and 7:1 dr. The absolute configuration of the major stereoisomer **3a** was determined to be 2*S*,4*R* by analyzing the X-ray single-crystal diffraction of its analog, **3s** (see Section 8 in Supporting Information for the details). In comparison, other chiral ligands without H-bonding donors that have been widely used in Pd-catalyzed asymmetric annulations, such as the axially chiral bisphosphine ligands **L6** and **L7**, the stereogenic-at-P(III) chiral biphosphine ligand **L8**, chiral P,N ligand **L9**, and the chiral phosphoramidite ligand **L10**, did not give better results in terms of reaction efficiency and stereocontrol. Subsequently, the effect of [Pd] sources (Scheme 2, entries 1 and 2) and solvents (Scheme 2, entries 3-6) were studied and $Pd_2(dba)_3{\cdot}CHCl_3$ and CH_2Cl_2 were identified as the optimal precursor and solvent, respectively. Reactions carried out in the solvents such as CH_3CN and DMF failed to give the product **3a** with the starting materials unconverted, possibly because these solvents could destroy the H-bonding interactions or competitively coordinate with Pd. To further improve the results, the reaction temperature and ratio of the two substrates were finely tuned (Scheme 2, entries 7-12). Under the optimal conditions of the reaction temperature of 13 °C and a ratio of **1a**/**2a** = 1.5, the desired product **3a** was easily obtained in 94% isolated yield with 98% ee and 17:1 dr (Scheme 2, entry 12). Perhaps more importantly, the success of chiral urea-containing ligand **L4** experimentally supported our working hypothesis based on the concept of bifunctional H-bonding/Pd catalysis.



Scheme 3. Substrate scope of the *trans*-selective asymmetric annulation. Condition 1: the same with entry 12 in Scheme 2; isolated yields. The dr value was determined by ^{1}H NMR analysis of the crude reaction mixtures and the ee value of the major diastereoisomer was determined by chiral HPLC analysis. [a] Performed for 48 h at 0 °C. [b] Using **L3** as the chiral ligand. [c] Using **L3** as the chiral ligand at 40 °C.

After achieving the optimal conditions, we began to probe the generality of the Pd-catalyzed asymmetric [3+2] annulation. As summarized in Scheme 3, various *N*-aryl-substituted sulfinylamines were suitable for this transformation. Variations in the electronic character of the substituents at the *para*-position of the benzene ring did not have obvious effects on the enantio- and diastereoselectivities (**3a**–**3i**, 79–98% yields, up to >99% ee,

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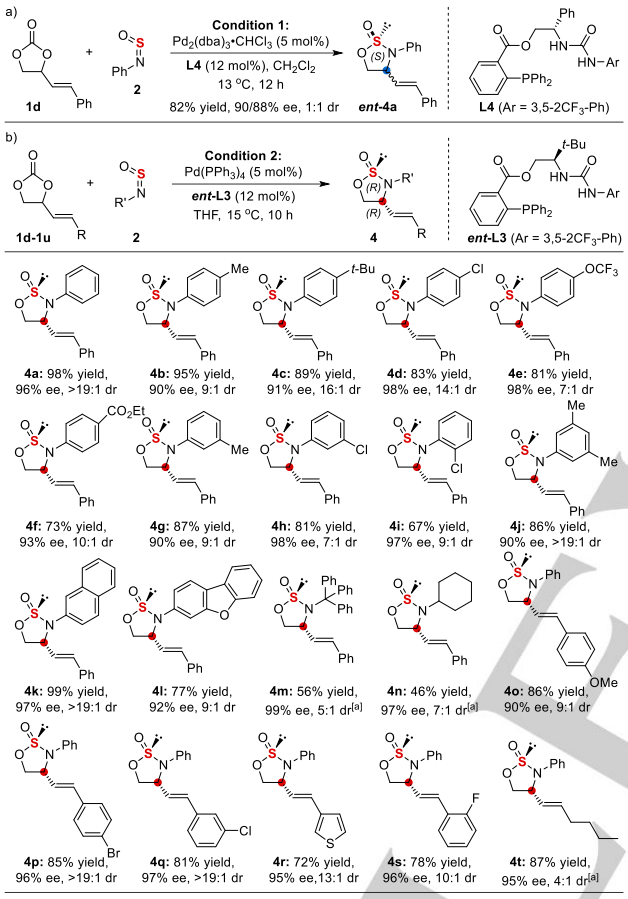
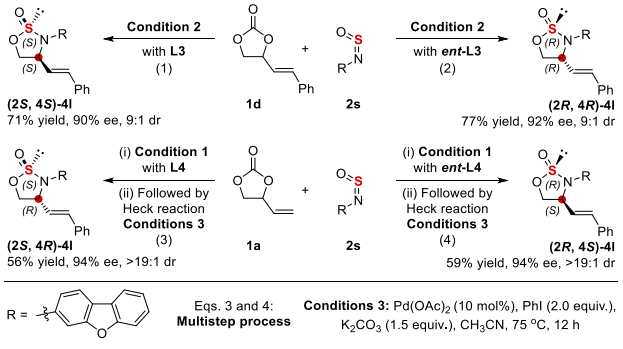
and >19:1 dr). Many significant functional groups such as halides, CF_3, CF_3O, and esters were tolerated. *N*-Aryl sulfinylamines with different substituents at the *meta*- and *ortho*-positions of the benzene ring were proven applicable in 80–96% yields, with up to >99% ee, and >19:1 dr. In addition to VEC **1a**, substrate **1b** with two vinyl groups was also tested under the similar conditions, successfully affording the corresponding product **3t** in 72% yield and 82% ee. When VEC **1c** with a methyl group at the allylic position was applied, the desired product **3u** was successfully afforded in 98% yield with 88% ee and 5:1 dr.



Scheme 4. Pd-catalyzed asymmetric [3+2] annulations. a) A preliminary result for the reaction of **1d** and **2a** under condition 1. b) Substrate scope of the *cis*-selective asymmetric annulation under condition 2. Condition 2: **1a** (0.20 mmol, 2.0 equiv.), **2a** (0.10 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (0.005 mmol, 5 mol%), ***ent*-L3** (0.012 mmol, 12 mol%) in THF at 15 °C; isolated yields. The dr value was determined by ^1H NMR analysis of the crude reaction mixtures and the ee value of the major diastereoisomer was determined by chiral HPLC analysis. [a] Performed at 25 °C.

When the above reaction conditions were applied to the reaction with phenyl-substituted VEC **1d**, 1:1 dr was observed with 82% yield and 90/88% ee (Scheme 4a). After further optimization of the conditions (see Tables S6-13 in Supporting Information (SI) for the details), a combination of $Pd(PPh_3)_4$ and chiral ligand ***ent*-L3** was identified as the best catalyst, giving the desired product **4a** in 98% yield and with >19:1 dr and 96% ee. The absolute configuration of product **4a** was established through the X-ray diffraction analysis of the enantiomer of its analog **4u** (see Section 8 in Supporting Information for the details). It is worth noting that the relative configuration of the S(IV) stereocenter and the allylic carbon center in product **4a** was inverse to that of product **3a**, which was tentatively attributed to the different configuration of the π-allyl Pd species reacting with sulfinylamine **2a** (see below for details). With these new optimal conditions in hand, we explored the substrate scope of both VEC and sulfinylamine moieties. As summarized in Scheme 4b, the chiral products **4a**–**4t** were obtained in 46–99% yields, with up to >19:1 dr and 99% ee. The protocol was quite efficient for various sulfinylamines and VECs, including those having aryl groups with *para*- (**4b**–**4f**: 73–95% yields, up to 16:1 dr and 98% ee), *meta*- (**4g**: 97% yield, 9:1 dr and 90% ee; **4h**: 93% yield, 7:1 dr and 98% ee), and *ortho*-substituents (**4i**: 67% yield, 9:1 dr and 97% ee), whether electron-donating or electron-withdrawing. Furthermore, identical transformations with *N*-3,5-dimethylphenyl, *N*-2-naphthyl, or *N*-heteroaryl sulfinylamines proceeded smoothly (**4j**: 86% yield, >19:1 dr, and 90% ee; **4k**: 99% yield, >19:1 dr, and 97% ee; **4l**: 77% yield, 9:1 dr, and 92% ee). Unlike the reaction with VEC **1a**, where no conversion was observed, *N*-alkyl-substituted sulfinylamines, such as triphenylmethyl or cyclohexyl, could be incorporated into the reaction of phenyl VEC **1d** (**4m**: 56% yield, 5:1 dr, and 99% ee; **4n**: 46% yield, 7:1 dr, and 97% ee). Toslyl-substituted and phthalimide-substituted sulfinylamines (**2w** and **2x**) were not suitable for this annulation at the current stage (see Figure S1 in SI). VECs **1** with different substituents were suitable for the Pd-catalyzed [3+2] annulation. Electronically diverse aryl, heteroaryl, and alkyl groups were tolerated, and the corresponding cycloadducts were obtained in moderate to good yields, diastereoselectivities, and high enantioselectivities (**4o**-**4t**: 72-87% yields, up to >19:1 dr and 97% ee). Notably, the efficiencies and enantioselectivities of these annulations were not affected by variations in the alkenyl groups.

The inverse relative configuration between products **3a** and **4a** provides an opportunity to prepare all four stereoisomers of thio-oxazolidinones. As shown in Scheme 5, the reactions of phenyl-substituted VEC **1d** and *N*-heteroaryl sulfinylamine **2s** were carried out in an enantio- and diastereo-divergent manner under the optimal reaction conditions. Two enantiomers of thio-oxazolidinones, **(2*S*,4*S*)-4l** and **(2*R*,4*R*)-4l**, were prepared in good yields with high diastereo- and enantioselectivities (Eqs. 1 and 2). Then, when VEC **1a** and sulfinylamine **2s** were used as the starting materials, a two-step operation involving Pd-catalyzed asymmetric [3+2] annulation and the Heck reaction[19] was carried out to obtain the other pair of enantiomers, **(2*S*,4*R*)-4l** and **(2*R*,4*S*)-4l**, in moderate yields and with excellent diastereo- and enantioselectivities (Eqs. 3 and 4).



Scheme 5. Stereoselective access to all four stereoisomers.

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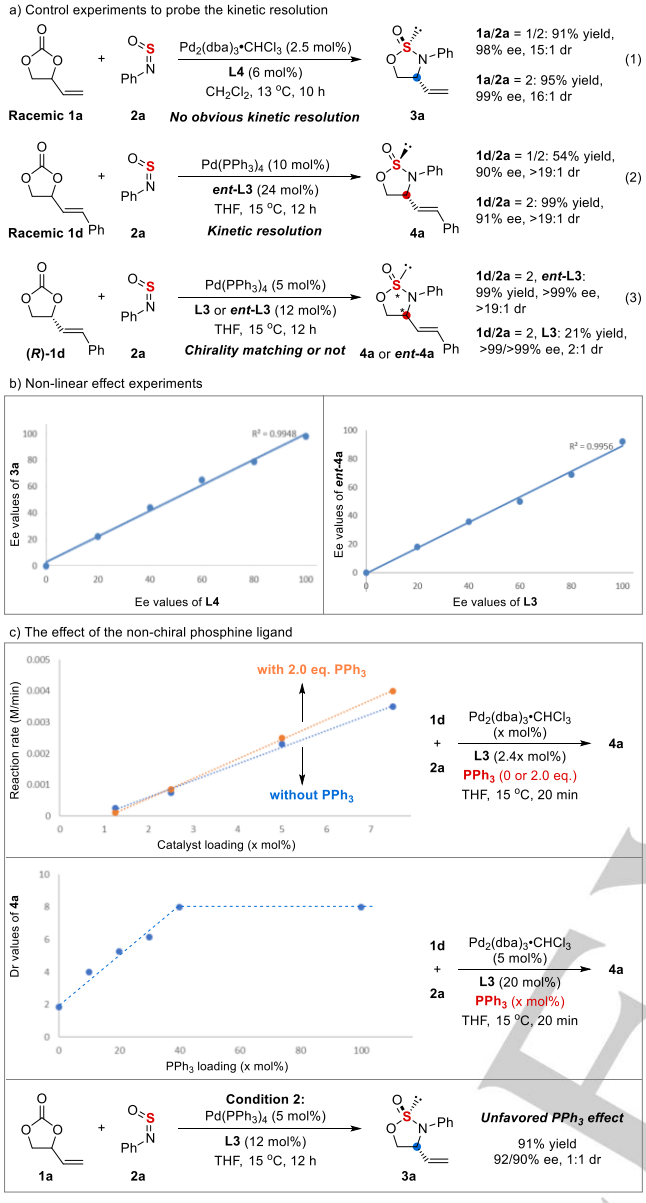

Scheme 6. Mechanism investigations.

To shed light on the reaction mechanism, control experiments were performed using VECs **1a** or **1d** and sulfinylaniline **2a** under optimal conditions. For the former, almost the same results were observed regardless of the ratio of **1a**/**2a** (Scheme 6a, Eq. 1), whereas the latter gave very different reaction yields, indicating the possible kinetic resolution of racemic phenyl-substituted VEC **1d** during the Pd-catalyzed asymmetric [3+2] annulation (Scheme 6a, Eq. 2). This hypothesis was further supported by the following control experiments. When enantiopure (*R*)-VEC **1d** and chiral ligand **L3** were used, the stereochemical matching made the annulation proceed very well in an almost quantitative yield, with >99% ee and >19:1 dr; otherwise, a low yield and diastereoselectivity were observed in the same time (Scheme 6a, Eq. 3). There are two possible reasons for this: 1) the stereochemical mismatch between the aryl-substituted VEC substrates and the chiral ligands **L3** would slow down the formation of the crucial π-allyl-Pd dipolar intermediates, and 2) although stereo-labile, the enlonged conjugated system of π-allyl-Pd species made the configuration transformation via π-σ-π interconversion difficult.[20] Subsequently, two sets of nonlinear effect experiments were performed with the two model reactions; linear relationships between the ee values of products and chiral ligands were found, indicating that the most effective palladium catalyst is a 1:1 ratio of Pd(0) and chiral ligand (Scheme 6b). Kinetic studies of the reaction between **1d** and **2a** were performed to investigate the function of the nonchiral supporting ligand.[21] The results showed that: 1) the reaction rate with respect to chiral Pd(0) catalysts is a first-order reaction, regardless of the presence or absence of PPh_3 (Scheme 6c, top; see details in Section 7.2 of the SI); 2) the reaction rates were not obviously changed by the introduction of PPh_3. Control experiments confirmed the positive effect of PPh_3 on the diastereoselectivity, and the use of PPh_3 over 4 equiv. to Pd could not further increase the dr value (Scheme 6c, middle). When the annulation reaction of VEC **1a** was performed under condition 2, a much reduced diastereoselectivity (Scheme 6c, bottom) was observed compared to the result shown in Scheme 3 (**3a**: 94% yield, 98% ee and 17:1 dr), indicating the reverse effect of the supporting non-chiral ligand on the diastereoselectivity compared to that of phenyl-VEC **1d**. In addition, control experiments with chiral ligands **L4a**–**L4c** were performed to demonstrate the importance of hydrogen bonds (Scheme 6d). Depending on whether one or both NH bonds were methylated, different effects on the reaction efficiency and enantio- and diastereoselectivities were observed, suggesting the importance of bis-hydrogen bonds in this annulation.

Based on these studies and the previous literatures,[14] a possible reaction mechanism was proposed for the two model reactions, as shown in Scheme 7a. First, the Pd(0) catalyst **A**, generated in situ from a Pd(0) precursor and chiral ligand, reacts with VEC **1a** or **1d** to form the chiral π-allyl-Pd dipolar intermediate **B** via oxidative addition and decarboxylation. Subsequently, this reactive intermediate captures sulfinylaniline **2a** through H-bonding interactions. Asymmetric *O*-addition to the electrophilic sulfur atom in the transient complex **C** proceeds to yield the intermediate **D**. Finally, the intramolecular allylic substitution of the nitrogen anion motif affords the intermediate **E**, which releases the desired product **3a** or **4a** and regenerates the Pd(0) catalyst **A** by ligand dissociation. Solvent-assisted electrospray ionization mass spectrometry (SAESI-MS) studies of the two reaction mixtures supported this reaction mechanism. The m/z signals of possible Pd-containing intermediates were observed (Scheme 7a, center). Their structural characterization suggested the formation of these transient species by performing a series of SAESI-MS/MS experiments (see details in Section 7.7 of the SI). In particular, the m/z signal at 1313 was assigned to the Pd(0) complex of chiral ligand ***ent*-L3** and nonchiral ligand PPh_3. This proposed complex agrees with the results of ^{13}C NMR spectroscopy (see details in Section 7.6 of SI). The chemical shift of the ester carbonyl in Pd(0)/***ent*-**

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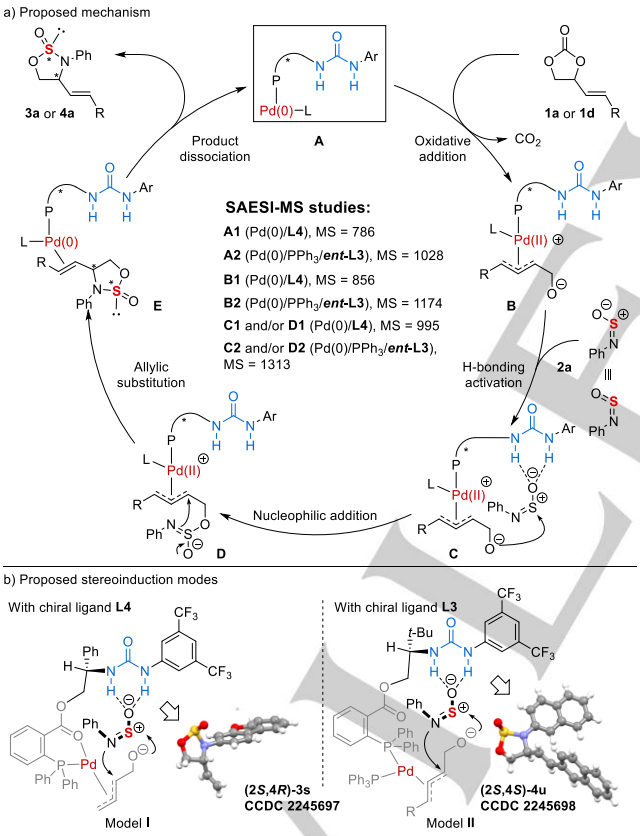
L3/PPh_3 was 166.2 ppm, which was close to the chemical shift of the free chiral ligand ***ent*-L3** (165.5 ppm), while the chemical shift of the ester carbonyl in Pd(0)/**L4** shifted to a higher field (142.3 ppm) in comparison with that of the free chiral ligand **L4** (167.5 ppm). These results indicate that in the annulation of vinyl substrate **1a**, the chiral ligand **L4** functions as a hybrid O/P ligand, while in the annulation of styryl substrate **1d**, chiral ligand ***ent*-L3** or **L3** functions as a monophosphine ligand. Thus, based on the results of MS and NMR experiments, the reported *cis*-configuration of sulfinylamines[22] and the absolute configurations of products **(2*S*,4*R*)-3s** and **(2*S*,4*S*)-4u**,[23] the two possible stereocontrol models, **I** and **II**, were proposed to explain the observed stereochemical results. As shown in Scheme 7b, first, similar hydrogen-bond activation modes have been proposed, directing the spatial orientation of the electrophilic sulfinylaniline **2a** to the π-allyl-Pd side for the less steric repulsion of the (*S*)-ligand units, thus resulting in the same S(IV)-stereogenic center. Second, the different coordination environments of the Pd centers in these two reaction systems may lead to two configuration-different π-allyl-Pd structures and the subsequent reversed allylic stereogenic carbon center, although further mechanistic studies are needed in the future.



Scheme 7. Proposed reaction mechanism and stereoinduction modes.

In conclusion, we developed a Pd-catalyzed asymmetric [3+2] annulation reaction between VECs and sulfinylamines. Chiral urea-containing phosphine ligands are critical for achieving high reaction efficiencies and stereoselectivities. In parallel, the nonchiral supporting ligand PPh_3 was unexpectedly found to play an important role in diastereo-control. Consequently, the catalytic asymmetric synthesis of thio-oxazolidinones, characterized by good reaction efficiency, high enantio- and diastereoselectivity, and readily available starting materials, was achieved for the first time. Moreover, the preliminary mechanistic insights based on control experiments, SAESI-MS studies, and NMR analysis were obtained to illustrate the bifunctional H-bonding/Pd catalysis and the origin of the observed stereochemical results. We believe that this study not only provides a promising avenue for chiral thiogenic heterocycles, but also significantly advances the frontiers of Pd-catalyzed asymmetric annulations.

Acknowledgements

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Keywords: asymmetric catalysis • [3+2] annulation • hydrogen bonding • palladium • sulfur chirality

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[23] CCDC 2259679, 2245697 and 2245698 contain the supplementary crystallographic data of substrate **(*R*)-1d** and products **(2*S*,4*R*)-3s** and **(2*S*,4*S*)-4u**, which can be downloaded for free (https://www.ccdc.cam.ac.uk).

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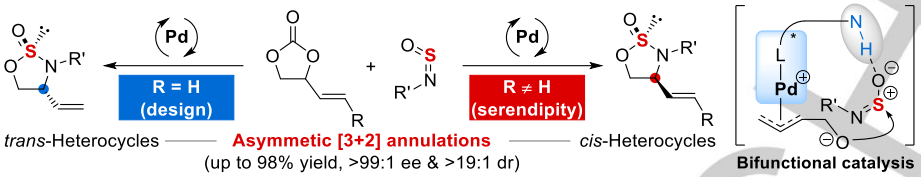

Two Pd-catalyzed asymmetric [3+2] annulations were disclosed, providing a modular platform for the enantioselective synthesis of chiral thio-oxazolidinones. Preliminary mechanistical studies were performed to rationalize the observed enantio- and diastereo-controls.

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