Metal-Containing Schiff Base/Sulfoxide Ligands for Pd(II)-Catalyzed Asymmetric Allylic C−H Aminations

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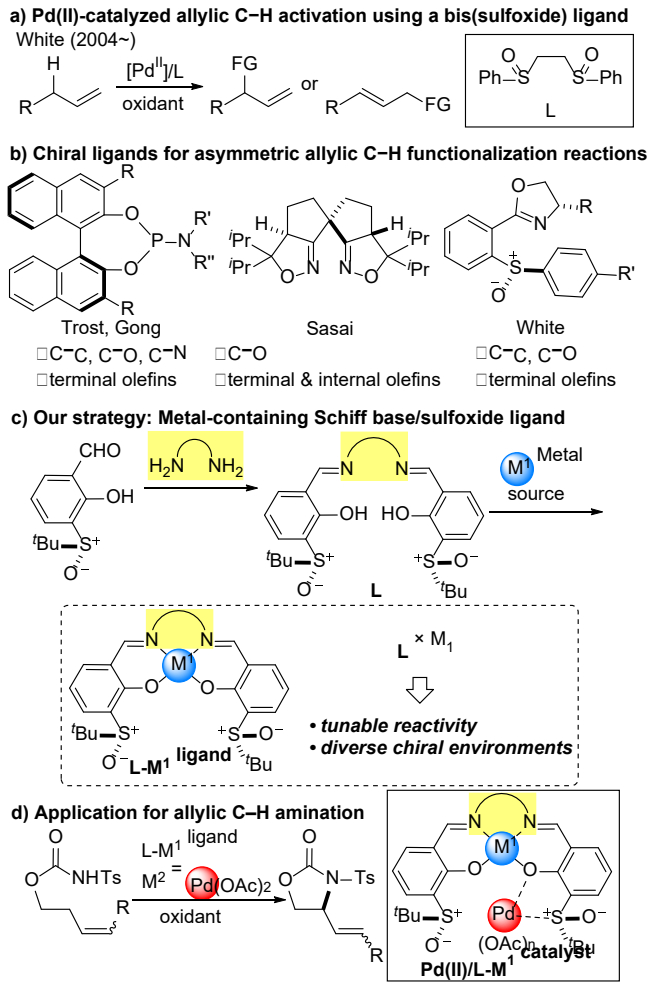
ABSTRACT: Metal-containing Schiff base/sulfoxides were developed as chiral ligands for Pd(II)-catalyzed asymmetric intramolecular allylic C−H amination reactions. The use of metal-containing Schiff base ligands allows tuning the selectivity and reactivity of the Pd(II)-catalyst, whereby a Schiff base-Cu(II)/sulfoxide ligand in combination with $Pd(OAc)_2$ showed the best performance. Both internal and terminal alkenes were applicable, and the C–H amination products were obtained in up to 91:9 er.

Palladium-catalyzed allylic C−H functionalization reactions have attracted great attention as an efficient tool for generating electrophilic π-allyl species without leaving groups such as halides, esters, or carbonates, which are required for typical Tsuji–Trost-type reactions.[1] In 2004, White demonstrated the utility of a bis(sulfoxide) ligand for the Pd-catalyzed allylic C−H bond cleavage (Scheme 1a).[2] This achiral bis(sulfoxide) ligand has been used to install a variety of synthetically versatile nucleophiles at the allylic positions of terminal olefins, often significantly streamlining the synthesis of complex molecules.[3]

On the other hand, chiral phosphoramidite ligands have often been used in combination with Pd to realize enantioselective variants of this transformation (Scheme 1b).[4,5,6] However, in most cases, the substrate scope is limited to activated allylic compounds, such as allylarenes, 1,4-dienes, or allyl esters.[5] Sasai has employed chiral bis(isoxazoline) ligands, but the reaction scope of the allylic C–H activation was limited to asymmetric C–O bond formation reactions.[7] Based on their high activity and stability under oxidative conditions, chiral sulfoxide ligands that bear a coordinating chiral sulfur center are attractive for Pd(II) catalysis.[8] Although the moderate coordinating ability of sulfoxide toward the Pd center complicates the construction of a rigid chiral environment, White elegantly overcame this limitation by introducing an additional σ-donor coordination unit.[9] The resulting chiral sulfoxide–oxazoline ligands showed excellent enantioselectivity (Scheme 1b).[10,11] Nonetheless, the number of chiral ligands available for Pd-catalyzed asymmetric allylic C–H functionalization reactions is still limited, and the development of new chiral ligand families to expand the reaction scope remains highly desirable.[12]

Inspired by an early report on the combined use of a chiral Cr-salen complex and an achiral Pd-bis(sulfoxide) complex,[4] we envisioned a new design involving chiral metal-

Scheme 1. Achiral and Chiral Ligands for Pd(II)-catalyzed Allylic C−H Functionalization Reactions



containing Schiff base/sulfoxide ligands for Pd-catalyzed asymmetric allylic C–H functionalization reactions. As we have previously demonstrated in other asymmetric reactions, bimetallic

Schiff base complexes are useful to rapidly construct a chiral environment that can be tuned by combining different modules, *i.e.*, a chiral amine with two metal sources.[13,14] Our basic strategy for metal-containing Schiff base/sulfoxide ligands (**L-M^1**) is illustrated in Scheme 1c. Starting from readily available salicylaldehyde, which contains a chiral sulfoxide unit (for synthetic details, see the Supporting Information), condensation with a chiral amine affords a dinucleating Schiff base ligand (**L**). The introduction of various metals M^1 into the inner N_2O_2 cavity should afford metal-containing Schiff base/sulfoxide ligands (**L-M^1**). By simply changing the chiral amines and M^1 sources, diverse chiral environments could be constructed around the sulfoxide unit in **L-M^1**. Furthermore, the reactivity of the Pd(II)/**L-M^1** catalyst would also be tuned as M^1 can be expected to affect the electronic properties of the σ-donor coordination unit in **L-M^1**. Based on this working hypothesis, we began our investigation of Pd(II)/**L-M^1**-catalyzed asymmetric allylic C–H amination reactions (Scheme 1d).

The use of non-cyclic internal olefins in Pd(II)-catalyzed asymmetric allylic C−H functionalization reactions is scarce (Scheme 1b).[7,12d,15,16] Furthermore, asymmetric allylic C−H amination reactions have rarely been investigated, with the only notable example being that of Gong, who has used a chiral phosphoramidite ligand.[5f] Thus, we selected the allylic C−H amination of internal alkenes as a model reaction to evaluate the efficiency of our metal-containing Schiff base/sulfoxide ligands (Table 1, Figure 1). We initiated optimization studies using Ts-protected carbamate **1a**,[17] $Pd(OAc)_2$, and 2,6-dimethylbenzoquinone (2,6-DMBQ), with adding $(PhO)_2PO_2H$.[10a,18] Using Cu(II) as M^1, we first screened the diamine unit of the Schiff base ligand. While a ligand with a planar achiral backbone (**L1**) afforded an almost racemic mixture of the product **2a** (entry 1), an ethylene-diamine-based ligand (**L2**) exhibited moderate enantioselectivity (76:24 er; entry 2). Among the chiral diamines screened (entries 3−10), the (*R*)-binaphthyl-diamine-based

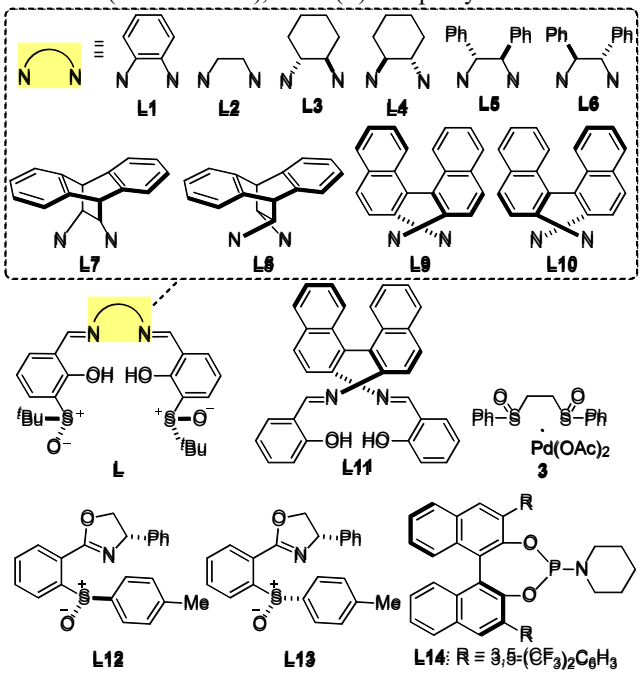
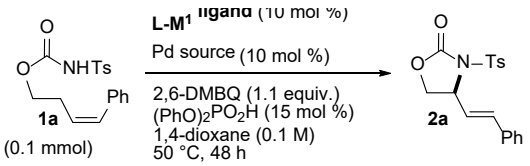


Figure 1. Chiral ligands used in this study.

Table 1. Optimization Studies



entry	L-M^1 ligand		M^2 metal	yield (%)[b]	er
	L	M^1 source[a]	Pd source[a]		
1	**L1**	$Cu(OAc)_2$	$Pd(OAc)_2$	18	52/48
2	**L2**	$Cu(OAc)_2$	$Pd(OAc)_2$	55	76/24
3	**L3**	$Cu(OAc)_2$	$Pd(OAc)_2$	15	62/38
4	**L4**	$Cu(OAc)_2$	$Pd(OAc)_2$	35	63/37
5	**L5**	$Cu(OAc)_2$	$Pd(OAc)_2$	42	70/30
6	**L6**	$Cu(OAc)_2$	$Pd(OAc)_2$	32	64/36
7	**L7**	$Cu(OAc)_2$	$Pd(OAc)_2$	39	58/42
8	**L8**	$Cu(OAc)_2$	$Pd(OAc)_2$	1	51/49
9	**L9**	$Cu(OAc)_2$	$Pd(OAc)_2$	56[c]	90/10
10	**L10**	$Cu(OAc)_2$	$Pd(OAc)_2$	41	56/44
11	**L9**	$Co(OAc)_2$	$Pd(OAc)_2$	15	87/13
12	**L9**	$Ni(OAc)_2$	$Pd(OAc)_2$	7	82/18
13	**L9**	$ZnEt_2$	$Pd(OAc)_2$	22	70/30
14	**L9**	$Pd(OAc)_2$	$Pd(OAc)_2$	70	70/30
15	**L9**	$Pd(OAc)_2$	-	ND	-
16	**L11**	$Cu(OAc)_2$	$Pd(OAc)_2$	ND	-
17	**L11**	$Cu(OAc)_2$	catalyst **3**	7	50/50
18		**L12**	$Pd(OAc)_2$	9	52/48
19		**L13**	$Pd(OAc)_2$	1	-
20		**L14**	$Pd(OAc)_2$	1	-
21[d]	**L9**	$Cu(OAc)_2$	$Pd(OAc)_2$	75[c]	91/9
22[e]	**L9**	$Cu(OAc)_2$	$Pd(OAc)_2$	84[c]	89/11

[a]Ligands **L1**−**L11** were mixed with the M^1 source ($Cu(OAc)_2·H_2O$, $Co(OAc)_2·4H_2O$, $Ni(OAc)_2·4H_2O$, $ZnEt_2$ 1.0 M solution in hexane, or $Pd(OAc)_2$) in THF at 40 °C. After removing the solvent, the Pd source ($Pd(OAc)_2$ or catalyst **3**) and other reagents were added to the mixture. [b]Determined by ^{1}H NMR analysis of the crude mixture using dimethylsulfone as the internal standard. [c]Isolated yield after purification by column chromatography on silica gel. [d]*trans,trans*-Dibenzylideneacetone (10 mol %) was added. [e]$Pd(OAc)_2$ (15 mol %) was used.

ligand **L9** furnished **2a** in the highest enantioselectivity (90:10 er, entry 9). The mismatched **L10**, which incorporated an (*S*)-binaphthyl diamine and (*R*)-chiral sulfoxide, resulted in a poor er of 56:44 (entry 10), indicating that both chiral sulfoxide and chiral diamine units are required for good enantio-induction. The choice of the M^1 source was also important, with Cu(II) giving the best selectivity (entry 9 vs 11−14). Entries 15–17 represent control experiments that were carried out to clarify the importance of each of the components of Pd(II)/**L9-Cu**. A catalyst prepared from **L9** and $Pd(OAc)_2$ without $Cu(OAc)_2$ did not furnish any product (entry 15). The system was unreactive when a ligand without chiral sulfoxide units (**L11**) was used (entry 16). When the achiral bis(sulfoxide) Pd(II) catalyst **3** was used in combination with **L11** and $Cu(OAc)_2$, the yield and selectivity were poor (entry 17). We also examined other chiral ligands that were used in the previously reported asymmetric allylic C–H functionalization reactions (entries 18−19). A small amount of product **2a** was obtained with (*S*,*R*)-SOX ligand (**L12**),[10a] but the enantioselectivity was low (9%, 52:48 er; entry 18). The

reaction hardly proceeded with (*S*,*S*)-SOX ligand (**L13**)[10b] and phosphoramidite ligand (**L14**)[5f] (entries 19, 20). These results demonstrated the utility of our newly developed metal-containing Schiff base/sulfoxide ligand. Further optimization studies (*cf.* Tables S1−S3 in the Supporting Information) suggested that the yield was improved by adding *trans,trans*-dibenzylideneacetone, which might stabilize the Pd(0) species to prevent undesired catalyst deactivation (entry 20). The yield was also improved upon increasing the amount of $Pd(OAc)_2$ (15 mol %), albeit that the enantioselectivity of **2a** simultaneously decreased slightly (entry 21).

To gain insight into the catalyst structure, we performed a conformational structure search using Grimme's xtb/crest program[19] and further structure optimization with density functional theory (DFT) calculations at the M06L/def2-SVP level of theory. The calculations suggested that chelation of the palladium complex by the sulfoxide and phenoxide lone pair are energetically favored (Figure 2).

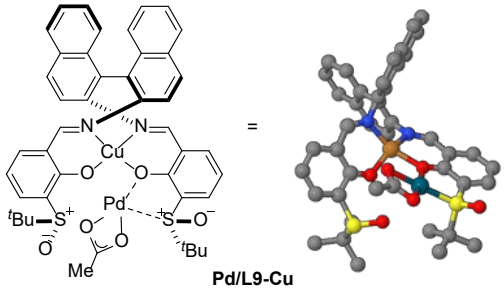
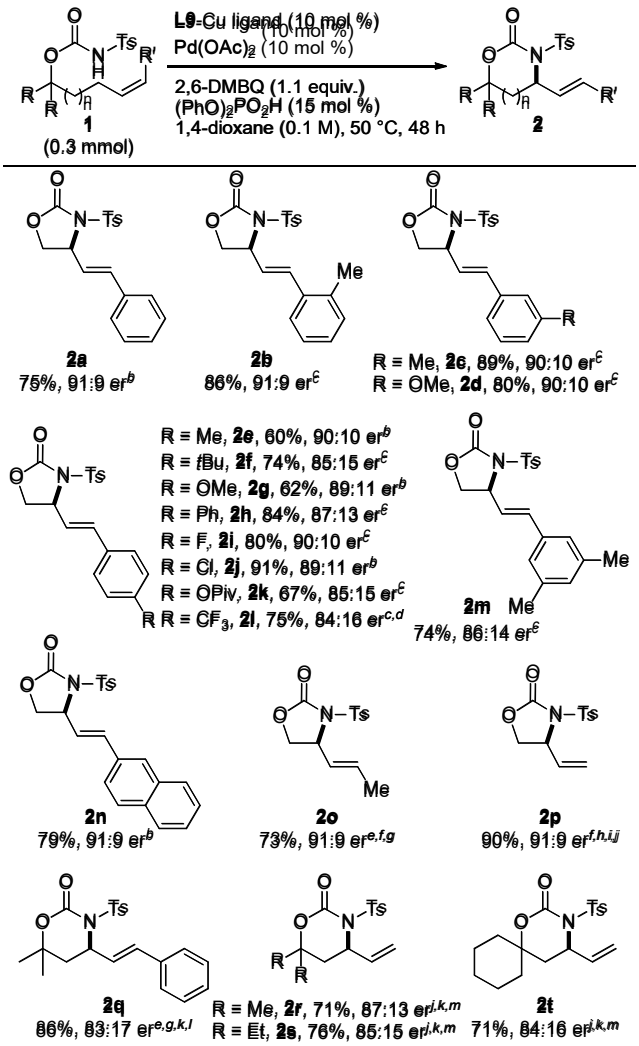


Figure 2. Possible catalyst structure based on DFT calculations at the M06L/def2-SVP level of theory.

Using the optimized reaction conditions, we subsequently investigated the substrate scope (Scheme 2). When a methyl group was introduced at the *o*-, *m*-, or *p*-position of the aryl group, **2b**, **2c**, and **2e** were obtained in 91:9-90:10 er. Both electron-donating and -withdrawing substituents were compatible, and **2d** and **2f**−**2n** were obtained in moderate to good er. For the methyl-substituted internal alkene **1o**, the ligand **L2-Cu** was more effective than **L9-Cu**, giving **2o** in 73% yield and 91:9 er. The C–H amination reaction also proceeded with terminal alkene **1p** to furnish **2p** in 90% yield and 91:9 er using $B(C_6F_5)_3$ as an additive. Substrates for six-membered ring formation were also applicable after minor modification of the reaction conditions, giving **2q**−**2t** in moderate selectivity. The absolute configurations of **2a** and **2o** were determined by comparison with authentic samples synthesized from known compounds (for details, see the Supporting Information).

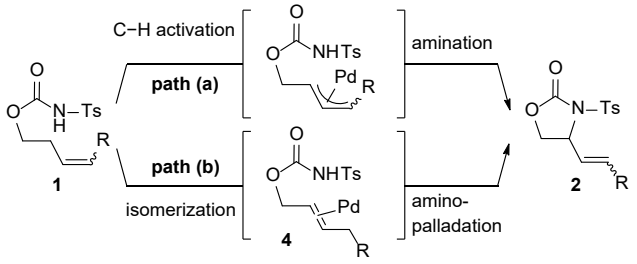
Two reaction pathways are possible for the present intramolecular allylic C–H amination. In addition to the standard allylic C−H activation pathway (Scheme 3; path a), isomerization of **1** into **4** followed by amino-palladation/β-H elimination would also generate **2** (path b).[20] To gain insight into the reaction pathway, we examined whether isomerized alkene **4** would be involved under the optimized reaction conditions. As the *E*/*Z* geometry of alkenes **1** and **4** could potentially affect the reaction outcome, **(*Z*)-1o**, **(*E*)-1o**, **(*E*)-4**, and **(*Z*)-4** were prepared independently and subjected to the previously established optimized reaction conditions (Scheme 4; 50 °C for 48 h). While **(*Z*)-1o** afforded **(*E,S*)-2o** as the major product (Scheme 4a; *S*:*R* = 91:9), **(*E*)-1o** gave **(*E,R*)-2o** in poor yield and enantioselectivity (Scheme 4b; 15% yield and *S*:*R* = 40:60). Both the yield and enantioselectivity were highly dependent on the geometry of **1**. The same was observed in Ph-substituted alkene **1a** (*cf.* Scheme S1)[21]. When the reaction was started from **(*E*)-4**, **(*E,S*)-2o** was obtained in only 28% yield and a diminished selectivity of 82:18 er, together with 14% of **(*Z*)-2o** (Scheme 4c). The reaction using **(*Z*)-4** provided **(*E,R*)-2o** in moderate yield and selectivity (Scheme 4d; 41% and *S*:*R* = 24:76). These results indicate that reaction path (a) in Scheme 3 via an allylic C–H activation is more plausible. In the isomerization/amino-palladation path (b), **(*Z*)-1o** can be expected to selectively isomerize to **(*E*)-4**. The enantiomeric ratio and *E*/*Z* selectivity from **(*E*)-4** was, however, lower than those from **(*Z*)-1o** (*cf.* Scheme 4a vs Scheme 4c). Moreover, **(*E*)-4** was not observed in the reaction of **(*Z*)-1o**, even though (*E*)-**4** is much less reactive than **(*Z*)-1o** under the applied reac-

Scheme 2. Substrate Scope of the Asymmetric Allylic C−H Amination[a]

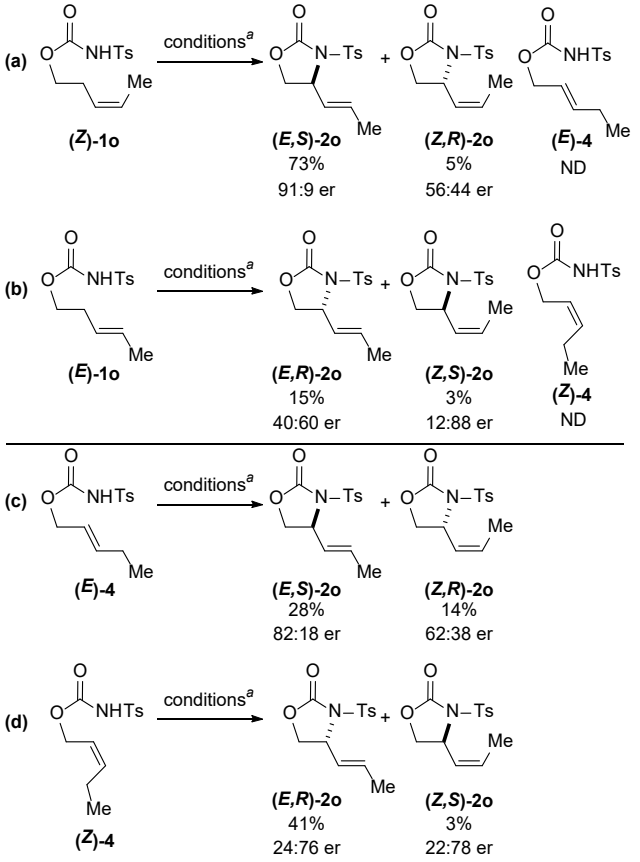


[a]Yields of isolated products are given. [b]Dibenzylideneacetone (10 mol %) was added. [c]$Pd(OAc)_2$ (15 mol %) was used. [d]0.2 mmol scale. [e]**L2** was used instead of **L9**. [f]2,6-DMBQ (1.5 equiv.). [g]$(PhO)_2PO_2H$ (4 mol %). [h]$B(C_6F_5)_3$ (15 mol %) was added instead of $(PhO)_2PO_2H$. [i]The reaction concentration was 1 M. [j]45 °C. [k]2,6-DMBQ (2.0 equiv.). [l]60 °C. [m]Without addition of $(PhO)_2PO_2H$.

Scheme 3. Two Possible Pathways for the Pd(II)-Catalyzed Amination Reactions



Scheme 4. Mechanistic Studies



[a]**L2** (10 mol %) was mixed with $Cu(OAc)_2 \cdot H_2O$ (10 mol %) in THF at 40 °C. After removing the solvent, $Pd(OAc)_2$ (10 mol %), $(PhO)_2PO_2H$ (4 mol %), 2,6-DMBQ (1.5 equiv.), 1,4-dioxane (0.1 M), and the substrate were added. The mixture was stirred at 50 °C for 48 h. Product yields were determined by ^1H NMR analysis of the crude mixture.

tion conditions. Based on these results, we concluded that the isomerization/amino-palladation pathway would most likely not be dominant. In addition, the reaction using deuterated **d$_2$-1o** provided product **d-2o** without any H/D scrambling. The result further supported that the isomerization/amino-palladation pathway is not plausible. (See, Supporting Information for detail).

In conclusion, we have demonstrated the synthetic utility of metal-containing Schiff base/sulfoxide ligands for Pd(II)-catalyzed asymmetric allylic C−H amination reactions. Both internal and terminal alkenes were applicable, and the combination of the Schiff base-Cu(II)/sulfoxide with $Pd(OAc)_2$ provided the C–H amination products in up to 91:9 er. As the ligand structure can be readily modified by changing the individual modules, investigation into further applications of the metal-containing Schiff base/sulfoxide ligands in other reactions are currently in progress in our group.

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge at http://pubs.acs.org.

Experimental procedures and characterization data for the synthesized compounds and ^1H, ^{13}C NMR spectra (PDF)

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