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Design of bifunctional chiral phenanthroline ligand with Lewis basic site for palladium-catalyzed asymmetric allylic substitution

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Conceptually new bifunctional chiral ligands were developed. The axially chiral N,N-bidentate phenanthroline ligand (*S*)-1 was found to be effective for Pd-catalyzed asymmetric allylic substitution of allyl acetate and dialkyl malonate. The intramolecular Lewis basic group from the hydroxybinaphthyl structure of (*S*)-1 played a pivotal role in the high reactivity and enantioselectivity.

Since the pioneering investigations into chiral metal complexes by Shibasaki, the concept of "cooperative bifunctional chiral ligands" has been recognized as a powerful strategy to realize precise metal-catalyzed asymmetric syntheses.[1] Intramolecular non-coordinative functionalities (*i.e.*, Lewis/Brønsted acidic or basic groups to activate prenucleophiles) within a single complex exert a synergistic effect in cooperation with a catalytically active metal center to realize unique reactivity and selectivity (Figure 1).[2] New conceptual strategies for development of bifunctional chiral ligands has attracted attention recently.[3]

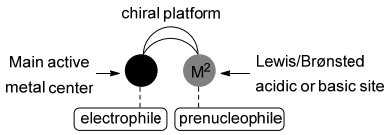
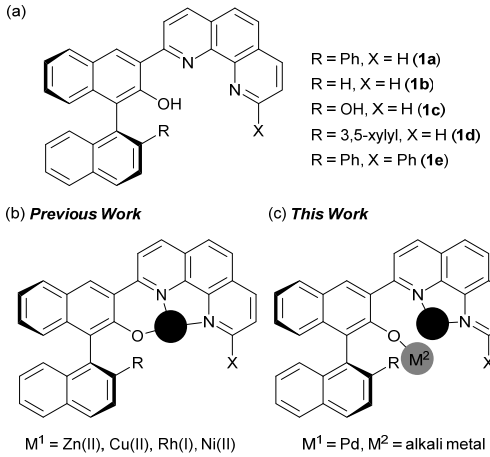


Figure 1. Concept of cooperative bifunctional chiral ligand

1,10-Phenanthroline (phen) is a common N,N-bidentate chelating reagent that is a candidate for metal ligands.[4] Despite the general applicability of phen in metal-catalyzed reactions, few studies on phen as chiral ligands have been reported.[5] In this context, we recently developed an axially chiral ligand (*S*)-**1** composed of phen and binaphthyl moieties (Figure 2a).[6] The compounds (*S*)-**1** were designed as versatile chiral ligands with a broad range of metal cations and were successfully applied to several enantioselective transformations catalyzed by metals including Zn(II),[7a,b] Cu(II),[7c,d] Rh(I)[7e] and Ni(II).[7f] In these reactions, the (*S*)-**1** was converted to the corresponding N,N,O-tridentate complex with metal cations (Figure 2b). To further broaden the utility of (*S*)-**1**, its advanced application as a bifunctional chiral ligand was investigated. The presence of separated coordination sites of the N,N-bidentate phen structure and O-monodentate hydroxybinaphthyl backbones enabled selective incorporation of two different metals, thus creating bifunctional catalysts (Figure 2c).

Figure 2. (a) Chiral phenanthroline ligand (*S*)-**1**. (b) N,N,O-



tridentate coordination of (*S*)-**1** (c) Combination of N,N-bidentate phen group and O-monodentate phenolic hydroxyl group in (*S*)-**1**

As the proof of concept, palladium-catalyzed asymmetric allylic substitution[8] was selected because phen can provide the

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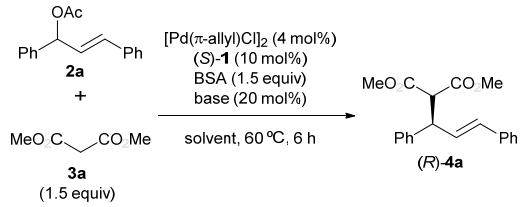
corresponding N,N-bidentate complexes, and allylic substitution using them has been investigated,[9] including a limited number of chiral phen ligands.[10] Therefore, (*S*)-**1** was expected to provide the corresponding N,N-bidentate Pd complexes while leaving the internal hydroxyl group non-coordinated. Since Pd-catalyzed allylic substitution is usually conducted under basic conditions, this hydroxyl group was expected to act synergistically with the Pd center as Lewis base.[11]

Table 1. Optimization of reaction conditions for Pd-catalyzed asymmetric allylic substitution of allyl acetate **2a** and dimethyl malonate **3a** [a]



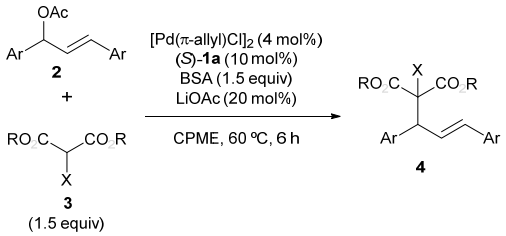
entry	(*S*)-**1**	base	solvent	% yield	% ee
1[b]	**1a**	KOAc	CH_2Cl_2	68	75
2[b]	**1b**	KOAc	CH_2Cl_2	94	-7
3[b]	**1c**	KOAc	CH_2Cl_2	92	23
4[b]	**1d**	KOAc	CH_2Cl_2	78	24
5[b,c]	**1e**	KOAc	CH_2Cl_2	84	-9
6	**1a**	KOAc	Toluene	40	63
7	**1a**	KOAc	DMF	10	68
8	**1a**	KOAc	THF	88	43
9	**1a**	KOAc	CPME	82	76
10	**1a**	LiOAc	CPME	70	**94**
11	**1a**	NaOAc	CPME	35	86
12	**1a**	CsOAc	CPME	68	74

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.15 mmol), [Pd(π-allyl)Cl]$_2$ (4 mol%), (*S*)-**1** (10 mol%), base (20 mol%), solvent (1 mL), 60 °C, 1 h, then BSA (0.15 mmol), 60 °C, 6 h. [b] Under reflux. [c] Reaction time: 24 h.

First, the reaction conditions for Pd-catalyzed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate (**2a**) and dimethyl malonate (**3a**) were optimized under reflux conditions in CH_2Cl_2 as the model reaction (Table 1). According to previous literatures,[9,10] [Pd(π-allyl)Cl]$_2$ was used as a palladium source, with a combined base of N,O-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc.

Reaction of **2a** and **3a** in the presence of Pd complex of the standard ligand (*S*)-**1a** with a phenyl group at the R position proceeded to give the target compound (*R*)-**4a** in 68% yield and with a moderate ee of 75% (entry 1). A previous study reported that the structure of the R group in hydroxybinaphthyl backbones affected both reactivity and enantioselectivity.[6,7] To improve the reaction results, the effect of substituents of (*S*)-**1** were examined (entries 2-5). However, all of the substituents resulted in a dramatic decrease in enantioselectivity, such as removal of the phenyl ring (entry 2), replacement of the phenyl ring with a hydroxyl group (entry 3), and the introduction of a bulky 3,5-xylyl group (entry 4). We recently report structural modification in a phen fragment that improved enantioselectivity.[7f] However, reaction with the modified ligand (*S*)-**1e** was not successful (entry 5). Screening of solvent revealed that conducting the reaction in cyclopentyl methyl ether (CPME) gave a better chemical yield and enantioselectivity (entries 6-9). Interestingly, the exchange of KOAc with other alkali metal acetates had a significant impact on the enantioselectivity (entries 10-12). Reaction using much weaker LiOAc proceeded to give (*R*)-**4a** in 70% yield and with the best ee of 94% (entry 10). Better enantioselectivity of (*R*)-**4a** was observed in the reaction with a weaker Lewis basic alkali metal acetate (order of Lewis basicity: CsOAc > KOAc > NaOAc > LiOAc.) More basic alkali metal acetates might work as stronger achiral Lewis base catalysts to furnish racemic **4a** and thus leading to poorer enantioselectivity.

Table 2. Scope of substrate for Pd-catalyzed asymmetric allylic substitution of allyl acetate **2** and dialkyl malonate **3** [a]



entry	Ar	R	X	% yield	% ee
1	Ph(**2a**)	Me	H(**3a**)	70(**4a**)	94(*R*)
2	Ph(**2a**)	Et	H(**3b**)	57(**4b**)	96(*R*)
3	Ph(**2a**)	*i*Pr	H(**3c**)	63(**4c**)	94(*R*)
4	Ph(**2a**)	*t*Bu	H(**3d**)	52(**4d**)	89(*R*)
5	Ph(**2a**)	Bn	H(**3e**)	62(**4e**)	98(*R*)
6	Ph(**2a**)	Et	Me(**3f**)	65(**4f**)	96
7	Ph(**2a**)	Et	Bn(**3g**)	59(**4g**)	86
8	*p*-tolyl(**2b**)	Me	H(**3a**)	55(**4h**)	87(*R*)
9	*p*-ClC_6H_4(**2c**)	Me	H(**3a**)	63(**4i**)	88(*R*)
10	*p*-BrC_6H_4(**2d**)	Me	H(**3a**)	67(**4j**)	88(*R*)
11	*m*-BrC_6H_4(**2e**)	Me	H(**3a**)	27(**4k**)	80(*R*)
12	*o*-BrC_6H_4(**2f**)	Me	H(**3a**)	8(**4l**)	25
13	2-Np(**2g**)	Me	H(**3a**)	38(**4m**)	70(*R*)
14	*p*-tolyl(**2b**)	Bn	H(**3e**)	60(**4n**)	97
15	*p*-ClC_6H_4(**2c**)	Bn	H(**3e**)	58(**4o**)	98(*R*)
16	*p*-BrC_6H_4(**2d**)	Bn	H(**3e**)	63(**4p**)	96(*R*)

[a] Reaction conditions: **2** (0.1 mmol), **3** (0.15 mmol), [Pd(π-allyl)Cl]$_2$ (4 mol%), (*S*)-**1a** (10 mol%), LiOAc (20 mol%), CPME (1 mL), 60 °C, 1 h, then BSA (0.15 mmol), 60 °C, 6 h.

Once optimized conditions were obtained, the scope of asymmetric allylic substitution of various allyl acetate **2** and dialkyl malonate **3** was investigated (Table 2). Reaction of **2a** with several dialkyl malomate compounds **3a-e** was investigated (entries 1-5). Regardless of the size of the alkyl group, target products **4a-e** were obtained with high ee (89-98% ees). Bulky α-substitued diethyl malonate **3f** and **3g** also were tolerated to give compounds **4f** and **4g** having quaternary

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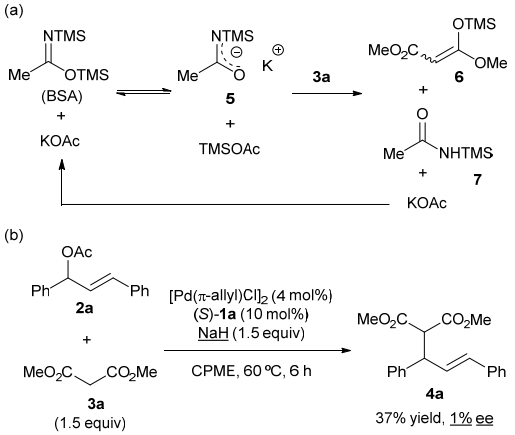
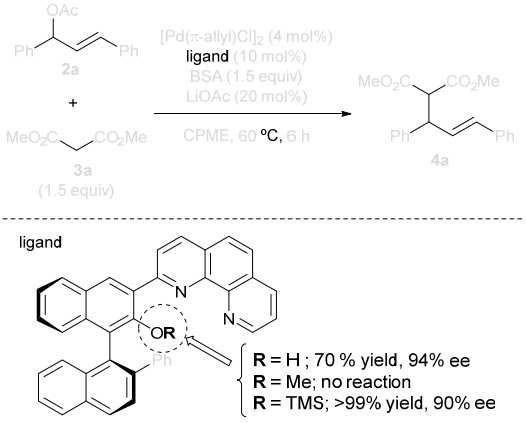
carbon with 96% and 86% ee, respectively (entries 6 and 7). The scope of 1,3-diaryl-2-propenyl acetate **2b-f** also was examined (entries 8-16). Use of a *para*-substituted aryl group on the phenyl ring of **2a** (**2b-d**) gave the corresponding products **4h-j** with 87-88% ee (entries 8-10). In contrast, reaction of **2e** and **2f** with a *meta*- or *ortho*-substituted aryl group tended to reduce both yield and ee (entries 11 and 12). Similarly, reaction of 1,3-di(2-naphthyl)-2-propenyl acetate **2g** also led to a decrease in ee (entry 13). For the reaction of **2b-d**, the use of dibenzyl malonate (**3e**) instead of **3a** improved enantioselectivity to 96-98% ee (entries 14-16).



Scheme 1. (a) Possible mechanism of generation of ketene silyl acetal **6** with BSA/KOAc. (b) Reaction with NaH instead of BSA.

To shed light on the mechanism of the present reaction, several control experiments were conducted. Reaction of BSA and catalytic KOAc was reported to generate a mild silylating reagent through potassium base **5** and TMSOAc (Scheme 1a).[12] Thus, dimethyl malonate **3a** should be converted to the corresponding ketene silyl acetal **6** with the generation of N-trimethylsilylacetamide **7** and KOAc. The silyl enolate **6** generated *in situ* is an important intermediate for asymmetric induction because the control reaction using sodium enolate prepared from **3a** and NaH resulted in complete loss of enantioselectivity (Scheme 1b). This control experiment suggests that the catalytic Lewis base-activated silyl enolate of **3** should attack with cationic Pd/π-allyl species in an enantioselective manner. The activation of trimethylsilyl nucleophiles with a Lewis base has been reported in the literature. [11,13]

The Lewis basic metal phenoxide was assumed to play an important role in the activation of the silyl enolate of **3** because the chiral phen ligand (*S*)-**1a** possessed a phenoic hydroxyl group. To examine the importance of the internal hydroxyl group of (*S*)-**1a**, an additional control reaction was conducted with (*S*)-**1a** protected by a methyl group (Scheme 2). As expected, the reaction did not proceed. This result implies that the lithium phenoxide of (*S*)-**1a** actually acts as a Lewis basic activator of **6**, and that LiOAc cannot promote the reaction.[14] In addition, the bifunctional character of (*S*)-**1a** is crucial for both high reactivity and enantioselectivity. Furthermore, we found that TMS-protected (*S*)-**1a**[15] works as well as protecting group-free (*S*)-**1a** to give (*R*)-**4a** in 90% ee (Scheme 2). In this case, we observed the complete desilylation of TMS-protected (*S*)-**1a** to (*S*)-**1a** with ^{1}H NMR analysis of the crude reaction mixture.



Scheme 2. Control reactions with (*S*)-**1a** protected by a methyl group or a trimethylsilyl group.

A reasonable mechanism for the present asymmetric allylic substitution was illustrated on the basis of these control experimental results (Figure 3). Bifunctional Pd complex **A** with an internal lithium phenoxide reacts with allyl acetate **2** to provide the Pd/π-allyl complex **B**. Lithium phenoxide in **B** would activate the silyl enolate of **3** through the formation of five-coordinated silicate **C**. Subsequent nucleophilic addition to Pd/π-allyl species gives **4**. Here, the intramolecular cooperation between the Pd center and lithium phenoxide enables precise facial control to achieve high enantioselectivity. After removal of product **4**, complex **D** with a siloxy group[16] might be generated, followed by desilylation by LiOAc restore complex **A**.[17] The intervention of complex **D** was supported by the comtrol experiment of TMS-protected (*S*)-**1a** (Scheme 2).

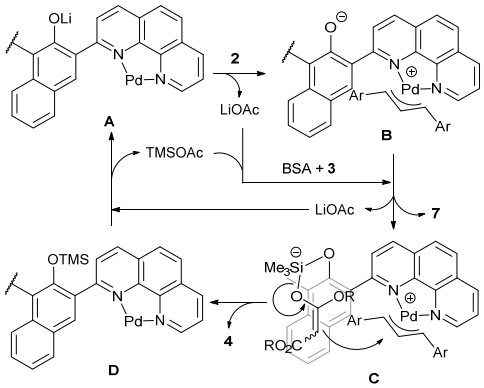


Figure 3. Possible catalytic cycle.

In conclusion, the Pd-catalyzed enantioselective allylic substitution of allyl acetate **2** and dialkyl malonate **3** was demonstrated using the chiral phen ligand (*S*)-**1a**. Under the reaction conditions, the Pd complex of (*S*)-**1a** with internal

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lithium phenoxide acted as a bifunctional chiral catalyst (*i.e.*, the Pd center activated the electrophilic allyl acetate **2** and lithium phenoxide activated the silyl enolate of **3**). Control experiments supported this unique synergistic reaction mechanism.[18] The present work provides an entirely different application of (*S*)-**1**, which has been investigated as an N,N,O-tridentate ligand,[6,7] and can provide an addition to the set of bifunctional chiral ligands.

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Conflicts of interest

There are no conflicts to declare.

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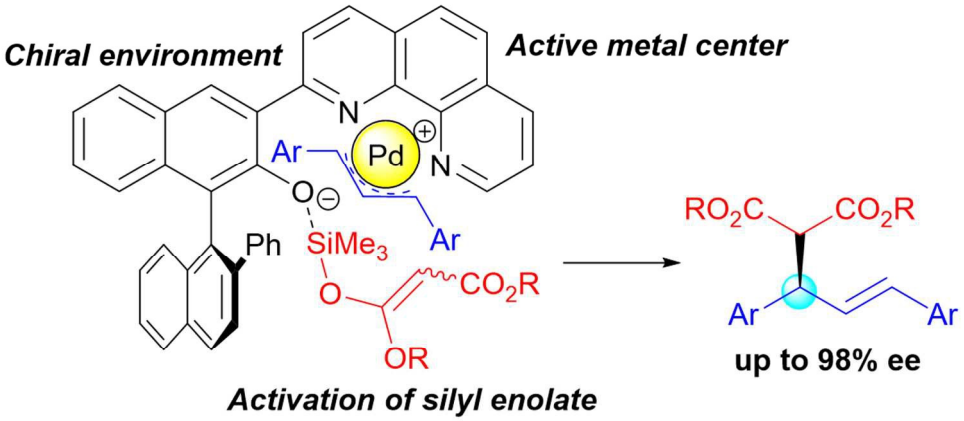

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