Asymmetric Catalysis

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Hydrogen-Bond-Promoted Palladium Catalysis: Allylic Alkylation of Indoles with Unsymmetrical 1,3-Disubstituted Allyl Acetates Using Chiral Bis(sulfoxide) Phosphine Ligands**

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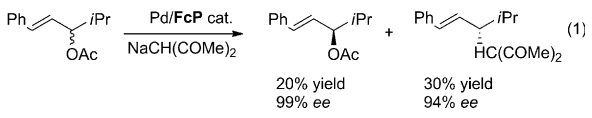
Dedicated to Professor Jingen Deng on the occasion of his 50th birthday

The palladium-catalyzed asymmetric allylic alkylation (AAA, Tsuji–Trost reaction) is a powerful strategy for construction of carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds.[1] Various ligands, such as monodentate phosphines, bidentate N,N-, P,N-, P,P-ligands, etc., have been used in this reaction, especially for symmetric 1,3-disubstituted allylic substrates.[1g,2] To date, asymmetric alkylation (C–C bond formation) of racemic, unsymmetric 1,3-disubstituted substrates have been rarely reported,[3] and a kinetic resolution is the only approach for providing the AAA products with a maximum of yield of 50% [Eq. (1) and (2); see Figure 1 for catalyst structures; **FcP** = (*R*)-*N*-methyl-*N*-bis(hydroxylmethyl)methyl-1-[(*S*)-1′,2-bis(diphenyl)phosphine]ferrocenylethylamine; TMS = trimethylsilyl].[4] However, the dynamic kinetic asymmetric transformation (DYKAT), as a straightforward method to transform racemic starting materials to optically pure products with a potential 100% yield, still remains a challenge.[5]

Hayashi and Ito 1986



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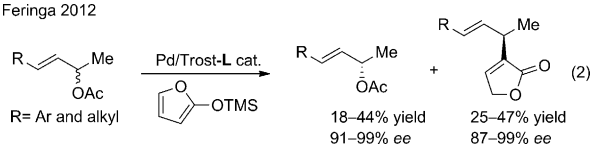

Transition-metal-catalyzed AAA using indole as a nucleophile is an attractive strategy for the synthesis of indoles containing stereocenters, compounds which are often found in biologically important natural products and pharmaceutical agents.[6] Various chiral palladium- and iridium-complexes have been developed to catalyze enantioselective inter- or intramolecular versions of the monosubstituted or symmetrically substituted allylic electrophiles.[7] To the best of our knowledge, the catalytic asymmetric indolylation of unsymmetrical 1,3-disubstituted allylic substrates has not been realized previously.

As part of our program to develop transition-metal-catalyzed asymmetric reactions, we designed several types of chiral ligands based on the stereogeometry and coordination properties of the *tert*-butylsulfinyl group.[8] Among these ligands, the sulfinyl moiety acts as a Lewis base which coordinates the metal. It is notable that the sulfinyl group can also readily form hydrogen bonds with some donors, like binol and indole.[9] Jacobsen and co-workers demonstrated that the hydrogen-bond interaction between the *tert*-butyl sulfinyl moiety of chiral urea catalysts and a protonated imine substrate effectively promoted an asymmetric [4+2] cycloaddition.[10] We envisioned that incorporation of an additional sulfinyl group into a bidentate ligand, like our previous sulfoxide phosphine ligand **L1** (Figure 1),[8a–c] might generate a new type of ligand which could perform cooperatively in

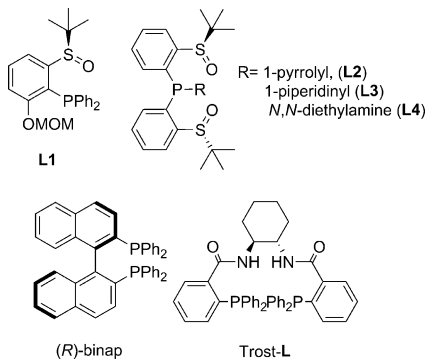

Figure 1. Chiral ligands used in this work. MOM = methoxymethyl.

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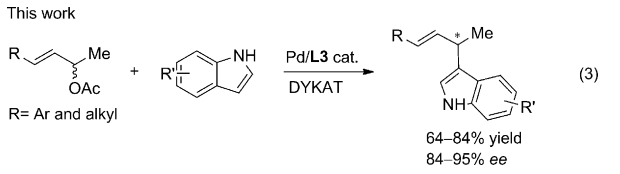
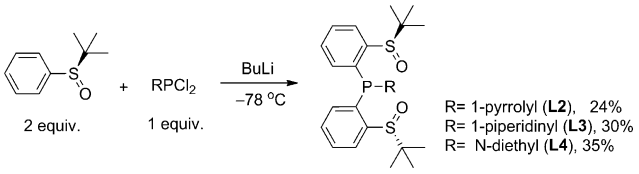
catalysis,[11] that is, serve 1) as a Lewis base to bind a metal, 2) as a hydrogen-bond acceptor to activate a substrate, and 3) to provide more of a chiral environment. Herein, we report a new class of chiral bis(sulfoxide) phosphine(BiSO-P) ligands, and employ them in an unprecedented palladium-



catalyzed DYKAT of racemic unsymmetrical 1,3-disubstituted allylic acetates with indoles [Eq. (3)].



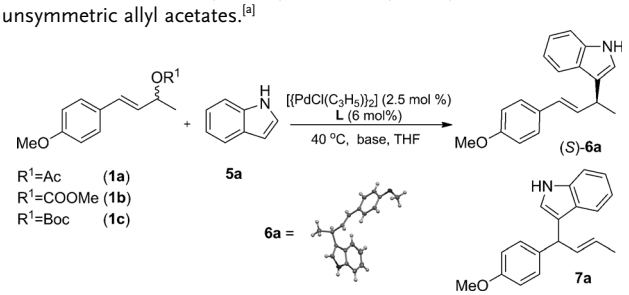
Scheme 1. Synthesis of BiSO-P ligands.

The ligands **L2**–**L4** were synthesized as shown in Scheme 1. Under an inert gas atmosphere and at −78 °C, two equivalents of phenyl *tert*-butyl sulfoxide was deprotonated by *n*-butyllithium and then reacted with one equivalent of the substituted (pyrrolyl, piperidinyl, and N-diethyl) phosphine dichloride. After workup, the bis(sulfoxide) phosphines (BiSO-P) were obtained as white solids in 24–35 % yields.

With the novel BiSO-P ligands in hand, we initially attempted the asymmetric indolylation of **1a** in the presence of $[\{PdCl(C_3H_5)\}_2]$ and K_2CO_3 at 40 °C. The previous sulfoxide phosphine **L1** resulted in a low yield and *ee* value (Table 1, entry 1). The new ligands **L2**–**L4** improved both the reactivity and enantioselectivity significantly (Table 1, entries 2–4) and provided (*S*)-**6a**, whose absolute configuration was determined by analysis of the single-crystal X-ray structure.[12] In contrast, (*R*)-binap was also tested in this model reaction and led to 27 % *ee* of the product with a rather low reactivity (Table 1, entry 5). Trost-**L** catalyzed the reaction of allylic carbonates **1b** and **1c** with indole to give nearly racemic products (Table 1, entries 6–8). In the presence of the best ligand, **L3**, the base Cs_2CO_3 was found to efficiently improve reactivity, albeit with a small reduction in enantioselectivity (Table 1, entry 12). Fortunately, an excellent *ee* value (94 %) and yield (94 %; 84 % for isolated product) of **6a** were obtained at 15 °C with four equivalents of Cs_2CO_3 as the base (Table 1, entry 13; (for detailed screening of reaction conditions, see the Supporting Information). From these results, it appears that the reaction can be realized through a deracemization (DYKAT or dynamic kinetic resolution) pathway promoted by the BiSO-P ligands.

The substrate scope of this palladium-catalyzed allylation is summarized in Table 2. Various 4-substituted but-3-en-2-yl

Table 1: Palladium-catalyzed asymmetric allylic alkylation of **5a** with unsymmetric allyl acetates.[a]



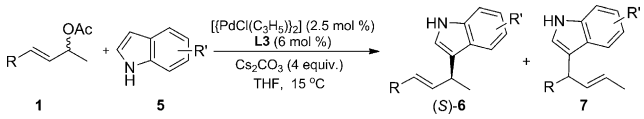
Entry	L	1	Base	6a/7a[b]	Yield [%][c]	*ee* [%][d]
1	**L1**	**1a**	K_2CO_3	97:3	20	43
2	**L2**	**1a**	K_2CO_3	95:5	76	80
3	**L3**	**1a**	K_2CO_3	95:5	72	90
4	**L4**	**1a**	K_2CO_3	90:10	72	60
5	(*R*)-binap	**1a**	K_2CO_3	85:15	12	27
6	Trost-**L**	**1a**	K_2CO_3	n.d.	trace	n.d.[e]
7	Trost-**L**	**1b**	K_2CO_3	86:14	70	*rac*
8	Trost-**L**	**1c**	K_2CO_3	95:5	63	*rac*
9	**L3**	**1b**	K_2CO_3	85:15	70	44
10	**L3**	**1c**	K_2CO_3	85:15	72	65
11	**L3**	**1a**	Na_2CO_3	98:2	29	89
12	**L3**	**1a**	Cs_2CO_3	94:6	82	88
13[f]	**L3**	**1a**	Cs_2CO_3	96:4	90(84)[g]	94

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), base (0.4 mmol), $[\{PdCl(C_3H_5)\}_2]$ (0.005 mmol; 2.5 mol %), ligand (0.012 mmol; 6 mol %) and THF (2 mL). Reactions were conducted under argon at 40 °C for 48 h. [b] Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. [c] Combined yields of **6a** and **7a** based on **1**. [d] The *ee* value of **6a** was determined by HPLC analysis using a chiral stationary column. [e] Not detected. [f] 15 °C, 4 equiv of Cs_2CO_3 was used as base. [g] Yield of isolated **6a**. Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran.

acetates could react with 1H-indole to get highly regioselective 3-allylindoles with excellent yields. Electron-rich substituents on the phenyl ring, such as *para*-, *meta*-, and *ortho*-methoxy groups, as well as *meta*- and *para*-methyl groups gave higher enantioselectivities. The major products **6a**–**6e** were afforded with excellent *ee* values (87–95 %) and high yields (76–84 %) of the isolated products. Substrates with electron-deficient phenyl rings (*para*-chloro, *para*-bromo, and *meta*-fluoro) also proceeded well and provided the major products with good enantioselectivities (84–87 %) and yields (70–78 %). In addition, the heteroaromatic substrate thiophenyl was quite reactive and provided **6j**. Particularly, some of 1,3-dialkyl allylic acetates were also suitable substrates for this transformation. For instance, when R was *n*Pr (**1m**), *i*Pr (**1n**), and cyclohexyl (**1o**), the corresponding 3-allylindoles **6k**, **6l**, and **6m** were obtained with good to excellent regioselectivities, as well as high enantioselectivities (Table 2, entries 11–13).[13]

We next investigated the scope of indole nucleophiles (Table 2, entries 14–24). Various 4-, 5-, 6-, or 7-substituted indoles (**5b**–**5l**) smoothly reacted with 4-(4-methoxyphenyl) but-3-en-2-yl acetate (**1a**) to deliver highly optically active 3-allylical indole derivatives (84–95 % *ee*), with good yields (63–83 %) of the isolated products. The electronic properties of the indole nucleophiles show no significant impact on the

Table 2: Highly regio- and enantioselective synthesis of 3-allylic indole derivatives.[a]

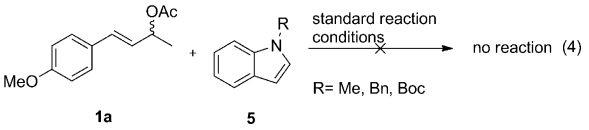


Entry	R (**1**)	R′ (**5**)	**6**	**6**/**7**[b]	**6** Yield [%][c]	**6** *ee* [%][d]
1	*p*-MeOC$_6$H$_4$ (**1a**)	H (**5a**)	**6a**	96:4	84	94
2	*o*-MeOC$_6$H$_4$ (**1d**)	H (**5a**)	**6b**	93:7	78	95
3	*m*-MeOC$_6$H$_4$ (**1e**)	H (**5a**)	**6c**	93:7	76	92
4	*m*-MeC$_6$H$_4$ (**1f**)	H (**5a**)	**6d**	93:7	83	87
5	*p*-MeC$_6$H$_4$ (**1g**)	H (**5a**)	**6e**	91:9	81	93
6	Ph (**1h**)	H (**5a**)	**6f**	95:5	84	89
7	*p*-ClC$_6$H$_4$ (**1i**)	H (**5a**)	**6g**	90:10	73	84
8	*p*-BrC$_6$H$_4$ (**1j**)	H (**5a**)	**6h**	93:7	70	87
9	*m*-FC$_6$H$_4$ (**1k**)	H (**5a**)	**6i**	95:5	74	86
10	thiophen-2-yl (**1l**)	H (**5a**)	**6j**	94:6	76	94
11	*n*Pr (**1m**)	H (**5a**)	**6k**	78:22	67	88
12	*i*Pr (**1n**)	H (**5a**)	**6l**	94:6	64	87
13	cyclohexyl (**1o**)	H (**5a**)	**6m**	97:3	65	88
14	*p*-MeOC$_6$H$_4$ (**1a**)	4-MeO(**5b**)	**6n**	88:12	77	94
15	*p*-MeOC$_6$H$_4$ (**1a**)	5-MeO(**5c**)	**6o**	89:11	82	94
16	*p*-MeOC$_6$H$_4$ (**1a**)	6-MeO (**5d**)	**6p**	90:10	83	93
17	*p*-MeOC$_6$H$_4$ (**1a**)	7-MeO (**5e**)	**6q**	86:14	63	90
18	*p*-MeOC$_6$H$_4$(**1a**)	4-Me (**5f**)	**6r**	85:15	74	84
19	*p*-MeOC$_6$H$_4$ (**1a**)	5-Me (**5g**)	**6s**	88:12	82	94
20	*p*-MeOC$_6$H$_4$ (**1a**)	7-Me(**5h**)	**6t**	88:12	70	93
21	*p*-MeOC$_6$H$_4$(**1a**)	7-Et (**5i**)	**6u**	88/12	69	94
22	*p*-MeOC$_6$H$_4$ (**1a**)	5-BnO (**5j**)	**6v**	90:10	79	95
23	*p*-MeOC$_6$H$_4$ (**1a**)	5-Cl (**5k**)	**6w**	96:4	75	93
24	*p*-MeOC$_6$H$_4$ (**1a**)	7-F (**5l**)	**6x**	90:10	77	91

[a] General reaction conditions: Allylic acetate **1** (0.2 mmol), indole **5** (0.24 mmol), [{PdCl(C$_3$H$_5$)}$_2$] (0.005 mmol), **L3** (0.012 mmol), Cs_2CO_3 (0.8 mmol) and THF (2 mL), 48 h. [b] Determined by analysis of the crude reaction mixture by 1H NMR spectroscopy. [c] Yield of isolated **6**. [d] Determined by HPLC or SFC using a chiral stationary phase.

reactivity and selectivity of the allylation. This approach is potentially useful for construction of bioactive compounds containing an indole unit.

Experimental and spectroscopy investigations were used to probe the bifunctional properties of the BiSO-P ligand and gain some insights into the reaction mechanism. Firstly, N-



protected indoles were selected as a nucleophile and were found to be inert under the standard reaction conditions [Eq. (4)]. In addition, comparison of the data reported in entry 1 versus entry 3 of Table 1 show that the ligand without an additional sulfinyl moiety gave a poorer result. All the above observations support the existence of a hydrogen-bond interaction between the Pd^{II}/BiSO-P complex and the indole, and was further confirmed by the Job's method and ^{1}H NMR titration experiments (Figure 2).[14] The expected 1:1 binding stoichiometry for Pd^{II}/**L3** and indole **5a** was obtained by

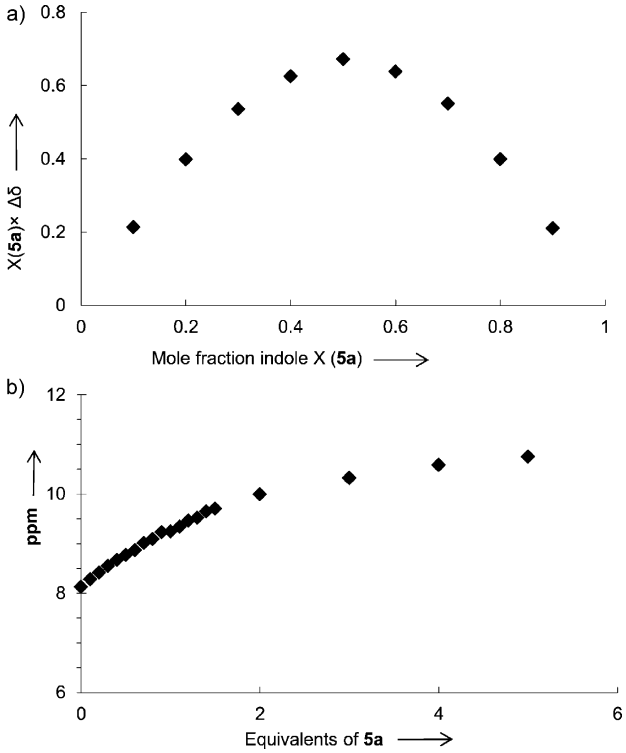


Figure 2. a) Job's method and b) ^{1}H NMR titration experiments.

applying Job's method of continuous variation to the NMR results for species in rapid exchange, and the association constant ($\log K_a = 1.20 \pm 0.23$) of the complex was determined by ^{1}H NMR titration experiments.[15] It is obvious that the indole H(N) interacts with the uncoordinated sulfinyl group of the Pd/BiSO-P complex as shown in Figure 3. In this

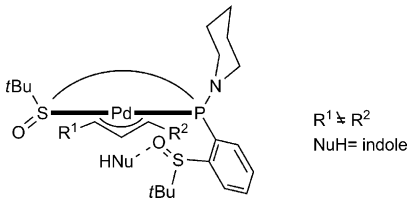
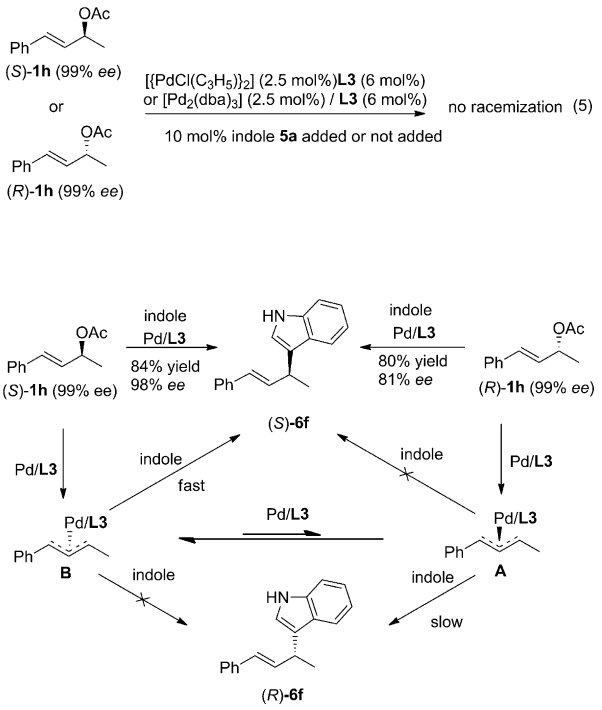


Figure 3. Hydrogen-bond activated model of allylation of indole.

complex, the two sulfoxide moieties of the ligand play different roles in the reaction. One serves as a metal-binding site and the other as a hydrogen-bond acceptor, which together promote the allylic alkylation by changing the reaction from an inter- to intramolecular reaction.

To understand the deracemization (DYKAT or DKR) pathway of this transformation and examine the stereocontrolling ability of the BiSO-P ligands, the pure, optically active (*S*)- and (*R*)-4-phenylbut-3-en-2-yl acetate [(*S*)-**1h** and (*R*)-**1h**, respectively] do not racemize under the standard reaction conditions [Eq. (5); dba = dibenzylideneacetone], and do react with 1*H*-indole catalyzed by [PdCl(C$_3$H$_5$)]$_2$/**L3** (Scheme 2). The product **6f** obtained from either starting material has the same *S* configuration albeit with different



Scheme 2. The transformation of optically pure **1h** catalyzed by [{PdCl-(C_3H_5)}$_2$]/**L3**.

ee values [98% from (*S*)-**1h** versus 81% from (*R*)-**1h**]. This data indicates that the ligand can dominate the stereochemical outcome of the reaction, regardless of the optical purity of the starting material. Moreover, the results also shows that **L3** matches with (*S*)-**1h** and mismatches with (*R*)-**1h**, thus the allylpalladium species **A** derived from (*R*)-**1h** appropriately epimerizes before attack by the indole nucleophile. Given that unsymmetrical 1,3-disubstituted ally1 systems do not racemize through a π-σ-π allyl rearrangement, we propose a DYKAT mechanism in which there is a palladium(0)-promoted epimerization of the allylpalladium species (Scheme 2).[16] In the presence of **L3**, the palladium(0) complex ionizes the racemic substrate **1h** by stereospecific(inversion) oxidative addition[17] and generates a mixture of diastereomeric allylpalladium species, **A** and **B**, which are interconvertible through nucleophilic displacement by the palladium(0) species under these reaction conditions. The major enantiomer of the product, (*S*)-**6f**, is generated through nucleophilic attack by indole on the diastereomer **B**.

In summary, we developed a new class of bis(sulfoxide) phosphine (BiSO-P) ligands, based on the concept of cooperative catalysis. These ligands, for the first time, promoted a palladium-catalyzed DYKAT of racemic unsymmetrical 1,3-disubstituted allylic acetates with indoles, and demonstrated a unique stereocontrolling ability. ^{1}H NMR titration experiments proved the existence of a hydrogen bond between the free sulfinyl group of ligand and the indole substrate. Studies on the details of the mechanism of the reaction are ongoing.

Experimental Section

Under an argon atmosphere, [{PdCl(C_3H_5)}$_2$] (1.8 mg, 0.005 mmol), **L3** (5.7 mg, 0.012 mmol), allylic acetate **1** (0.2 mol), 1*H*-indole (0.24 mol), Cs_2CO_3 (266 mg, 0.8 mmol), and 2.0 mL tetrahydrofuran (THF) were added to a 10 mL Schlenk tube. The mixture was then stirred at 15 °C for 48 h, after which the solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate 200:1 as the eluent, to afford the adducts.

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Communications

Asymmetric Catalysis

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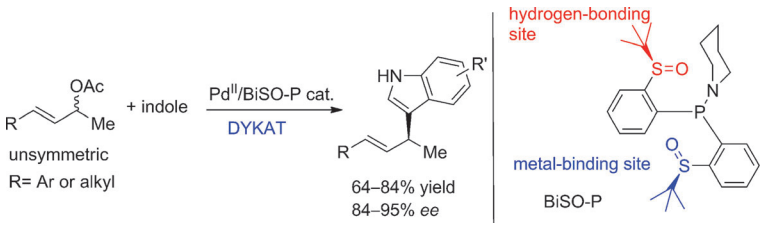
Hydrogen-Bond-Promoted Palladium Catalysis: Allylic Alkylation of Indoles with Unsymmetrical 1,3-Disubstituted Allyl Acetates Using Chiral Bis(sulfoxide) Phosphine Ligands



A DYKAT die hard: A new class of chiral BiSO-P ligands were effective for an unprecedented palladium-catalyzed asymmetric allylic alkylation of indoles with the racemic title acetates through a dynamic kinetic asymmetric transformation (DYKAT). The hydrogen bond formed between the sulfinyl group of the ligand and NH of indole plays an important role in the reaction.