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Pd-Catalyzed Asymmetric Allylic Alkylation of Indoles and Pyrroles by Chiral Alkene-Phosphine Ligands

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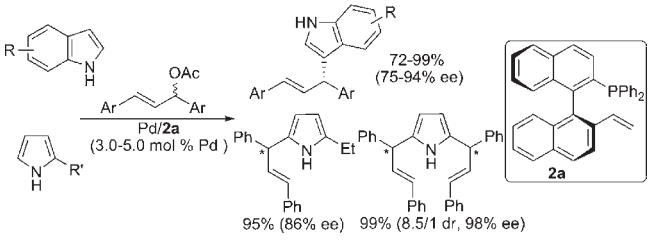
ABSTRACT



A variety of chiral binaphthyl-based terminal-alkene-phosphine hybrid ligands were synthesized in four steps with (*S*)-BINOL as a starting material and utilized for the Pd-catalyzed enantioselective allylic alkylations of indoles and pyrroles to afford the desired products in high yields with good to excellent ee's.

Indole moieties are present in a broad range of biologically and medically important compounds.[1] Regio- and enantioselective alkylations of indoles at the C-3 position through Lewis or Brønsted acids promoted Friedel–Crafts reactions[2] and transition-metal-catalyzed allylic alkylations[3] provide an efficient approach to afford optically active indole derivatives. As one of the most important methodologies to construct C–C bonds, great success has been achieved for Tsuji–Trost reactions.[4] However, Pd-catalyzed asymmetric allylic alkylation of indoles with 1,3-diphenyl-2-propenyl acetate was not realized until 2007 by Chan and co-workers with the use of chiral ferrocenyl P/S ligands to give the desired products in high ee's.[3h] In their study, various well-known bisphosphine or P/N ligands were also examined and found not suitable for this transformation. Hence, exploring other types of chiral ligands for this reaction is of great interest.

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Chiral alkenes as one novel type of ligands have received considerable attention and witnessed significant progress since Hayashi's group reported the first chiral diene ligand for transition-metal-catalyzed highly enantioselective reactions in 2003.[5,6] In addition to the rapid growth of chiral diene ligands,[7] some hybrid ligands combined alkenes with heteroatoms, such as phosphorus[8] or nitrogen[9] to improve the coordination ability to the metal, have also been developed for asymmetric conjugated addition or allylic substitution. As part of our ongoing efforts in exploring new, effective, and accessible chiral alkene ligands, we have discovered several flexible acyclic dienes possessing two terminal olefins as coordinating moieties which were effective for Rh-catalyzed asymmetric conjugated additions or arylations.[10] However, the coordination of an alkene to the metal was not observed in the NMR study in some cases, which may partially be attributed to the relatively weak coordination ability of the flexible dienes. Therefore, a strategy was adopted in our group for the development of a novel alkene-phosphine hybrid ligand by installing the terminal alkene and phosphorus atom on suitable chiral backbones (Figure 1). Ligand **1** was then developed and

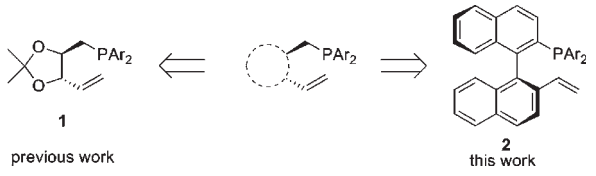
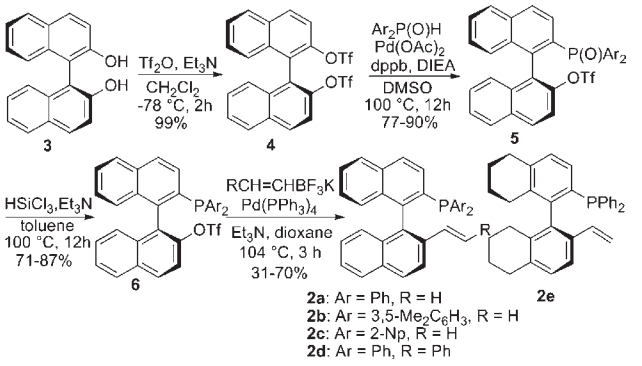


Figure 1. Strategy for exploring alkene-phosphine ligands.

found to be highly effective for palladium-catalyzed asymmetric allylic substitutions.[11] In this work, we wish to report our efforts on the development of binaphthyl-based chiral alkene-phosphine hybrid ligands for Pd-catalyzed enantioselective allylic alkylations of indoles and pyrroles.

Initially, chiral alkene-phosphine ligands **2** were obtained in reasonable yields through a straightforward four-step synthetic route using (*S*)-BINOL (**3**) as a starting material (Scheme 1). Wherein, the coupling reaction between compounds **6** and potassium alkenyltrifluoroboroates was the key step and $Pd(PPh_3)_4$ was found to be the most suitable catalyst for this transformation giving pure ligands **2** without inseparable impurities. Ligand **2e** bearing a partially reduced binaphthyl backbone was also obtained under the same procedure.

Scheme 1. Synthesis of Alkene-Phosphine Hybrid Ligands



Subsequently, chiral ligands **1** (Ar = 3,5-$Me_2C_6H_3$) and **2a** were subjected to the asymmetric allylic alkylation of indole (**7a**) with 1,3-diphenyl-2-propenyl acetate (**8a**) in the presence of $[Pd(C_3H_5)Cl]_2$ and K_2CO_3 in CH_2Cl_2 at room temperature. We were pleased to find that both of them were effective for this reaction to give the desired product **9a** accompanied with a small amount of *C*,*N*-dialkylation byproduct in high conversions and promising ee's, and ligand **2a** gave a relatively better result (Table 1, entries 1 and 2). In order to further improve the enantioselectivity and reduce the amount of byproducts, various reaction conditions including base, solvent, and temperature were then optimized (Table 1, entries 3−11). When this reaction was carried out under the catalysis of a Pd/**2a** complex (3.0 mol % Pd) in CH_2Cl_2 at 0 °C using Na_2CO_3 (2.0 equiv) as base, the corresponding product **9a** can be obtained in 92% ee with only a little amount of byproduct (Table 1, entry 11). Under the same condition, ligands **2b**−**e** were examined. It was found that all of these chiral ligands modified Pd catalysts can promote this reaction to give the corresponding product in 44−99% conversions and 79−90% ee (Table 1. entries 12−15). It was noteworthy that ligand **2d** containing an internal C−C double bond gave the product with a reverse absolute configuration in moderate conversion (Table 1, entry 14). Overall, ligand **2a** gave the highest conversion and ee. When the catalyst

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(8) For leading references on chiral phosphine-alkene hybrid ligands, see: (a) Deblon, S.; Grützmacher, H.; Schönberg, H. WO 03/048175 A1, 2003. (b) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem.—Eur. J.* **2004**, *10*, 4198. (c) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (d) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130. (e) Kasák, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084. (f) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (g) Mariz, R.; Briceño, A.; Dorta, R.; Dorta, R. *Organometallics* **2008**, *27*, 6605. (h) Štěpnička, P.; Císařová, I. *Inorg. Chem.* **2006**, *45*, 8785. (i) Stemmler, R. T.; Bolm, C. *Synlett* **2007**, 1365. (j) Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2009**, *11*, 4212.

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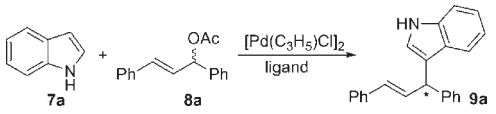
Table 1. Evaluation of Ligands and Optimization of Reaction Conditions[a]



entry	L	base	solvent	temp (°C)	time (h)	conv (%)[b]	ee (%)[c]
1[d]	**1**	K_2CO_3	CH_2Cl_2	rt	12	95 (19/1)	80
2	**2a**	K_2CO_3	CH_2Cl_2	rt	6	99 (5/1)	88
3	**2a**	Cs_2CO_3	CH_2Cl_2	rt	11	99 (6/1)	85
4	**2a**	Et_3N	CH_2Cl_2	rt	11	80	85
5	**2a**	Na_2CO_3	CH_2Cl_2	rt	11	99 (10/1)	87
6	**2a**	Na_2CO_3	MeCN	rt	11	74	87
7	**2a**	Na_2CO_3	THF	rt	11	77 (8/1)	87
8	**2a**	Na_2CO_3	toluene	rt	11	82 (4/1)	77
9[e]	**2a**	Na_2CO_3	CH_2Cl_2	rt	9	76	86
10[f]	**2a**	Na_2CO_3	CH_2Cl_2	rt	9	98 (11/1)	87
11	**2a**	Na_2CO_3	CH_2Cl_2	0	24	**97 (19/1)**	**92**
12	**2b**	Na_2CO_3	CH_2Cl_2	0	24	99 (13/1)	87
13	**2c**	Na_2CO_3	CH_2Cl_2	0	24	99 (10/1)	90
14	**2d**	Na_2CO_3	CH_2Cl_2	0	24	44	−79
15	**2e**	Na_2CO_3	CH_2Cl_2	0	24	79	83
16[g]	**2a**	Na_2CO_3	CH_2Cl_2	0	48	97 (10/1)	90

[a] All reactions were carried out with **7a** (0.20 mmol), **8a** (0.24 mmol), Pd/L = 1/1 (3 mol % Pd), base (0.40 mmol), and solvent (1.0 mL) unless otherwise stated. [b] The conversion was determined by crude ^{1}H NMR. The ratios of **9a** and *C*,*N*-dialkylation product were noted in parentheses. [c] The ee values were determined by chiral HPLC with the *N*-Boc-protected derivative of **9a**. [d] 5.0 mol % Pd was used. [e] Na_2CO_3 (1.0 equiv) was used. [f] Na_2CO_3 (3.0 equiv) was used. [g] 1.0 mol % Pd was used.

loading was further decreased to 1.0 mol %, the reaction still went smoothly with only a slightly lower ee (Table 1, entry 16).

To evaluate the effect of alkene moieties of **2a**, ligand **10** bearing an ethyl group instead of a vinyl group and a well-known MOP ligand **11** were subjected to this reaction respectively (Scheme 2).[12] However, no desired product at all was observed, which strongly suggests that the vinyl group of ligand **2a** played a crucial role in both reactivity

Scheme 2. Palladium-Catalyzed Asymmetric Allylic Alkylation of Indole **7a**

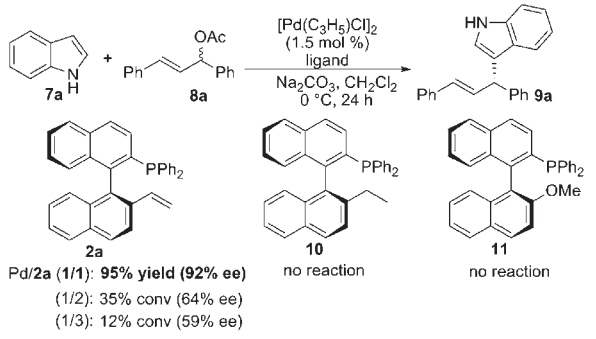


Table 2. Pd/**2a**-Catalyzed Asymmetric Alkylation of Indoles[a]

entry	indole (7)	product (9)[b]	yield (%)[c]	ee (%)[d]
1	**7a**		95	92
2	**7b**		99	83
3	**7c**		73	93
4	**7d**: R = Me		79	92
5	**7e**: R = OMe		83	90
6	**7f**: R = OBn		72	90
7	**7g**: X = F		83	93
8	**7h**: X = Cl		84	92
9	**7i**: X = Br		82	92
10	**7j**		81	94
11	**7k**		87	75
12	**7a**	**9l**: Ar = 4-ClC_6H_4	87	80
13		**9m**: Ar = 4-MeC_6H_4	89	86
14		**9n**: Ar = 3-ClC_6H_4	84	89

[a] All reactions were carried out with **7** (0.20 mmol), **8** (0.24 mmol), $[Pd(C_3H_5)Cl]_2$ (0.003 mmol), **2a** (0.006 mmol), Na_2CO_3 (0.40 mmol), and CH_2Cl_2 (1.0 mL) at 0 °C for 24 h. [b] The absolute configuration was tentatively assigned by analogy with **9j**. [c] Isolated yield. [d] The ee values were determined by chiral HPLC with the *N*-Boc-protected derivatives of **9a**−**n** (see Supporting Information).

and enantioselectivity. Importantly, the ratio of Pd/**2a** was found to be another factor to affect this reaction. The conversion and ee dropped sharply when the ratio of Pd and **2a** was tuned to 1/2 and 1/3 (Scheme 2). The reasoning was related to the phosphorus atom's strong coordination ability to palladium resulting in some amount of ligand **2a** to only act as ineffective monophosphine ligands.[11]

(12) For leading references on ligands **10** and **11**, see: (a) Hattori, T.; Shijo, M.; Kumagai, S.; Miyano, S. *Chem. Express* **1991**, *6*, 335. (b) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887.

With the best ligand **2a** and optimal reaction conditions in hand, Pd-catalyzed asymmetric allylic alkylations of a variety of indoles **7** with 1,3-diaryl-2-propenyl acetate (**8**) were subsequently investigated. As shown in Table 2, all of the alkylation reactions proceeded efficiently to give the corresponding products **9** in 72−99% yields with 75−94% ee (Table 2, entries 1−14). The alkylations of 2-substituted and 7-substituted indoles gave high yields but with relatively lower ee's (Table 2, entries 2 and 11). Moreover, the substituents of 1,3-diaryl-2-propenyl acetate (**8**) were found to have some impact on both reactivities and enantioselectivities (Table 2, entries 1 vs 12−14). The absolute configuration of product **9j** was determined to be *S* by an X-ray structure of its derivatives (Figure 2), and the configurations of other products were tentatively assigned by analogy.

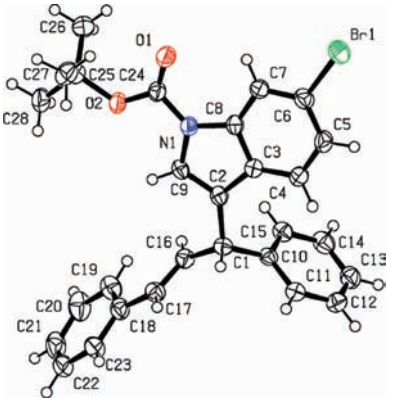


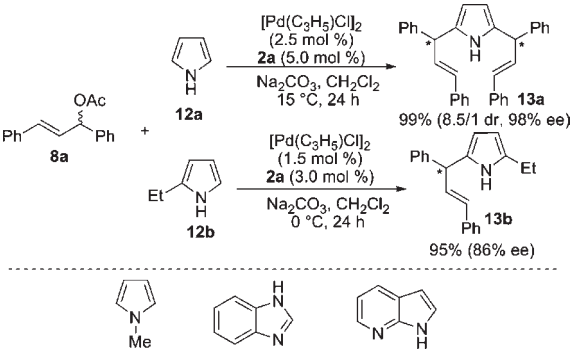
Figure 2. X-ray structure of *N*-Boc-protected (*S*)-**9j**.

To further expand the substrate scope, several *N*-heterocycles including pyrroles, 7-azaindole, and benzimidazole were subjected to this reaction. We were pleased to find that the reaction between pyrrole (**12a**) and 1,3-diphenyl-2-propenyl acetate (**8a**) under the catalysis of Pd/**2a** (5.0 mol %) proceeded smoothly to give a 2,5-dialkylation product **13a** in excellent yield with 8.5/1 dr and 98% ee (Scheme 3). When 2-ethylpyrrole was employed as a substrate, the alkylation reaction occurred at the 5-position to give the desired product **13b** in 95% yield with 86% ee (Scheme 3).

(13) For selected examples on asymmetric Friedel−Crafts alkylation of pyrroles, see: (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (b) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. (c) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (d) Li, G.; Rowland, G. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065. (e) Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438. (f) Wang, W.; Liu, X.; Cao, W.; Wang, J.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2010**, *16*, 1664.

Other *N*-heterocycles, such as 1-methylpyrrole, 7-azaindole, and benzimidazole, were not suitable for this reaction (Scheme 3). Although the substrate scope still awaits further expansion, to the best of our knowledge, the present work represents the first successful example of asymmetric allylic alkylation of pyrroles catalyzed by Pd complexes.[13]

Scheme 3. Palladium-Catalyzed Asymmetric Allylic Alkylation of Other *N*-Heterocycles



In summary, a variety of binaphthyl-based chiral alkene-phosphine hybrid ligands were successfully prepared through a straightforward four-step synthesis. Ligand **2a** was found to be highly effective for the Pd-catalyzed asymmetric allylic alkylation of indoles with 1,3-diaryl-2-propenyl acetate (**8**) to give the corresponding products in high yields with good to excellent ee's. Interestingly, the enantioselective alkylations of pyrroles catalyzed by Pd/**2a** were also realized with up to 98% ee. Expanding the substrate scope, searching for other effective terminal-alkene-phosphine hybrid ligands, and exploring their applications in asymmetric catalysis are currently underway in our lab.

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Supporting Information Available. The procedure for the synthesis of chiral ligands **2**; Pd-catalyzed asymmetric allylic alkylation; characterization of **9a**−**n**, their Boc-protected derivatives, and **13a**−**b**; and data for the determination of enantiomeric excesses of **9a**−**n** and **13a**−**b** along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.