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Enantioselective Pd-Catalyzed Allylic Alkylation of Indoles by a New Class of Chiral Ferrocenyl P/S Ligands

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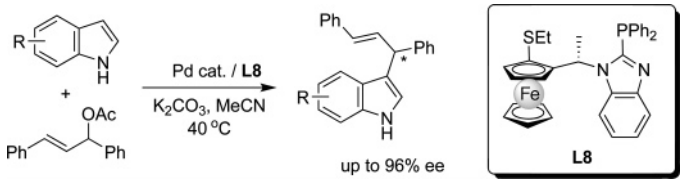
ABSTRACT



Chiral ferrocenyl heterobidentate P/S ligands bearing both central and planar chirality were prepared from (*S*)-Ugi's amine via a three-step modular synthesis. Through systematic screening and optimization, L8 was found to be the best ligand for Pd-catalyzed asymmetric allylic alkylation of indoles with ee's up to 96% being attained.

Stereoselective functionalization of indoles is a subject of significance because of the common occurrence of indole moieties in many bioactive natural products and pharmaceuticals.[1] Lewis acid promoted Friedel−Crafts reactions have been explored extensively for enantioselective alkylation of indoles at the C-3 position, and high catalyst loading (10 mol %) was often required for achieving satisfactory yields and enantiopurities.[2] While Pd-catalyzed asymmetric allylic alkylation is a powerful approach for stereoselective C−C bond formation,[3] its application in enantioselective indole functionalization has limited precedent in the literature.

In 1999, Kočovský and co-workers first reported that electron-rich aromatics (including indoles) could be alkylated with allyl acetates under the Mo(II)-catalyzed conditions.[4a] Recently, Umani−Ronchi and co-workers documented an elegant study on Pd-catalyzed indole alkylation with allylic carbonates,[4b] and the related intramolecular enantioselective reactions[4c] have been accomplished. As part of our continuing effort in designing new catalyst systems for the enantioselective C−C bond formation,[5] herein we describe an efficient Pd-catalyzed asymmetric allylic alkylation of indoles by a new class of chiral P/S ligands **L1**−**L8** based on ferrocene and heterocyclic scaffolds. Heterobidentate chiral P/S ligands have received considerable interest in recent years.[5a,6] By

(1) (a) Bentley, K. W. *Nat. Prod. Rep.* **2004**, *21*, 395. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. (c) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559.

(2) For examples, see: (a) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621. (b) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739. (c) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (d) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901. (e) Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511. (f) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309.

(3) For reviews on asymmetric allylic substitutions, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. II, Chapter 24, p 833.

(4) (a) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kočovský, P. *J. Org. Chem.* **1999**, *64*, 2751. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199. (c) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424.

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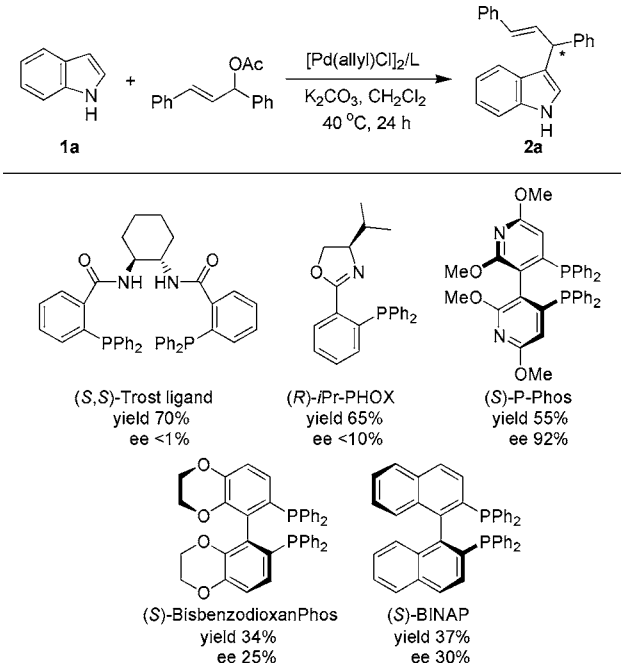
virtue of the steric and electronic differences of the P/S donor sets, some highly enantioselective catalytic reactions including allylic substitution,[5a,6c,6e] hydrogenation,[6d] Diels−Alder,[6b] and 1,3-dipolar cycloaddition[6a] reactions have been developed. In this work, we employed enantiopure (*S*)-Ugi's amine[7b] as a chiral building block to create some structurally diverse ferrocene-based heterobidentate P/S ligands via a modular synthetic route. Through systemic evaluation of the ligand library and optimization studies, **L8** was found to be the best ligand for the enantioselective indole alkylation with product enantioselectivity up to 96% ee.

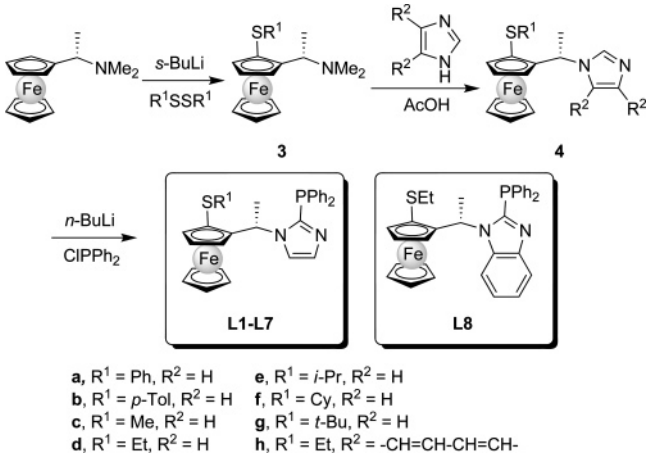
Initially, we examined a panel of well-established chiral phosphine ligands for effecting alkylation of unsubstituted indole with 1,3-diphenyl-2-propenyl acetate under catalytic conditions: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), ligands (5 mol %), and K_2CO_3 (2 equiv) in CH_2Cl_2 for 24 h. In most cases, the alkylated product was produced in low enantioselectivity (<30% ee), and the best result (55% yield and 92% ee) was obtained by employing the (*S*)-P-Phos ligand (Scheme 1).

Scheme 1. Pd-Catalyzed Asymmetric Allylic Alkylation of Indole **1a** with 1,3-Diphenyl-2-propenyl Acetate



In search of more effective chiral ligands for the enantioselective indole alkylation, we considered chelating P/S ligands based on ferrocenyl sulfides containing central and planar chirality to be valuable candidates because these ligands are known to promote enantioselective Pd-catalyzed allylic substitution reactions.[6e] In this work, we prepared a new class of chiral ferrocene-based P/S ligands **L1**−**L8** by a three-step synthesis (Scheme 2). Diastereoselective *ortho*-lithiation of (*S*)-Ugi's amine[7] followed by quenching with various disulfides gave the amino-thioethers **3**. Heating **3** with imidazole or benzimidazole in AcOH afforded **4** with retention of configuration at the central chirality. Phosphination of **4** afforded ligands **L1**−**L8** in 48−76% yields. **L1**−**L8** are air-stable compounds and can be handled in air.

Scheme 2. Preparation of P/S Ligands



At the beginning, we set out to test **L1**-containing imidazole and SPh moieties for the indole alkylation reaction. Treatment of **1a** (0.3 mmol) and 1,3-diphenyl-2-propenyl acetate (0.36 mmol) with **L1** (5 mol %) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) in CH_2Cl_2 in the presence of K_2CO_3 (2 equiv) for 18 h produced the desired adduct **2a** in 60% yield and 38% ee (Table 1, entry 1). Having established the catalytic activity of the chelating P/S ligand, we subsequently turned to examining the effect of the thioether (SR) group [R = *p*-Tol (**L2**), Me (**L3**), Et (**L4**), *i*-Pr (**L5**), Cy (**L6**), and *t*-Bu (**L7**)] on the reactivity and enantioselectivity.

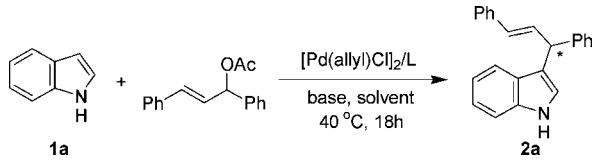
Table 1 depicts the results of the alkylation of indole upon variation of the thioether group. Ligand **L2** with a *p*-tolyl substituent afforded the alkylated product in 65% yield and 32% ee (entry 2), comparable to the results of **L1** (cf. entry 1). Employing ligands with primary alkyl substituents (i.e.,

(5) (a) Lam, F. L.; Au-Yeung, T. T.-L.; Cheung, H. Y.; Kok, S. H. L.; Lam, W. S.; Wong, K. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2006**, *17*, 497. (b) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413. (c) Lu, G.; Kwong, F. Y.; Ruan, J.-W.; Li, Y.-M.; Chan, A. S. C. *Chem.−Eur. J.* **2006**, *12*, 4115. (d) Kwong, F. Y.; Li, Y.-M.; Lam, W. H.; Qiu, L.; Lee, H. W.; Yeung, C.-H.; Chan, K. S.; Chan, A. S. C. *Chem.−Eur. J.* **2005**, *11*, 3872. (e) Ji, J.-X.; Wu, J.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11196.

(6) For recent examples on chiral P/S ligands, see: (a) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456. (c) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905. (d) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534. (e) Mancheño, O. G.; Priego, J.; Cabrera, S.; Arrayás, R. G.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679. (f) Priego, J.; Mancheño, O. G.; Cabrera, S.; Arrayás, R. G.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, 2512.

(7) (*S*)-Ugi's amine was prepared by asymmetric hydrogenation of acetylferrocene in a 150 g scale followed by nucleophilic substitution. See: (a) Lam, W. S.; Kok, S. H. L.; Au-Yeung, T. T.-L.; Wu, J.; Cheung, H. Y.; Lam, F. L.; Yeung, C.-H.; Chan, A. S. C. *Adv. Synth. Catal.* **2006**, *348*, 370. (b) Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.* **1972**, *37*, 3052.

Table 1. Optimization of Reaction Conditions[a]



entry	ligand	solvent	base	yield (%)[b]	ee (%)[c]
1	**L1**	CH_2Cl_2	K_2CO_3	60	38
2	**L2**	CH_2Cl_2	K_2CO_3	65	32
3	**L3**	CH_2Cl_2	K_2CO_3	69	61
4	**L4**	CH_2Cl_2	K_2CO_3	73	65
5	**L5**	CH_2Cl_2	K_2CO_3	43	80
6	**L6**	CH_2Cl_2	K_2CO_3	63	75
7	**L7**	CH_2Cl_2	K_2CO_3	65	4
8	**L8**	CH_2Cl_2	K_2CO_3	78	86
9[d]	**L8**	CH_2Cl_2	K_2CO_3	45	83
10	**L8**	THF	K_2CO_3	63	62
11	**L8**	toluene	K_2CO_3	79	59
12	**L8**	DCE	K_2CO_3	72	66
13	**L8**	DME	K_2CO_3	70	58
14	**L8**	EtOAc	K_2CO_3	77	81
15	**L8**	CH_3CN	K_2CO_3	74	95
16	**L8**	CH_3CN	Li_2CO_3	49	56
17	**L8**	CH_3CN	Na_2CO_3	69	71
18	**L8**	CH_3CN	Cs_2CO_3	22	92
19	(*S*)-P-Phos	CH_3CN	K_2CO_3	34	96

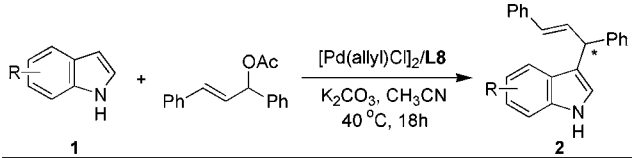
[a] Conditions: indole **1a** (0.3 mmol), [Pd(η^3-C_3H_5)Cl]$_2$ (2.5 mol %), ligand (5 mol %), 1,3-diphenyl-2-propenyl acetate (1.2 equiv), base (2 equiv) in solvent (2 mL). [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC with the *N*-Boc-protected derivative of **2a** (see Supporting Information). [d] Methyl 1,3-diphenyl-2-propenyl carbonate was used instead of 1,3-diphenyl-2-propenyl acetate.

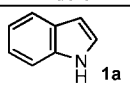
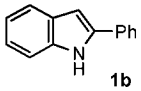
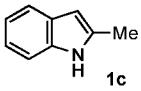
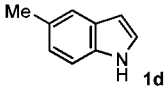
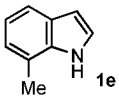
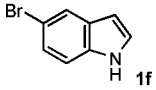
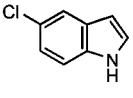
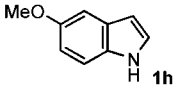
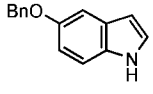
L3 and **L4**) led to progressively improved product yields of 69% and 73% and higher enantioselectivities of 61% ee and 65% ee, respectively (entries 3 and 4). Enantioselectivities of 80% and 75% were attained with ligands **L5** (R = *i*-Pr) and **L6** (R = Cy) with the product yields being 43% and 63%, respectively (entries 5 and 6). However, employing ligand **L7** with a bulkier *t*-Bu substituent resulted in poor enantioselectivity of 4% ee (entry 7).

Taking into account the steric requirement, we are gratified that the best results of 78% product yield and 86% ee were obtained when employing ligand **L8** bearing a benzimidazole scaffold and a SEt group for the indole alkylation reaction (entry 8). According to the report by Umani−Ronchi and co-workers, methyl 1,3-diphenyl-2-propenyl carbonate was a more effective substrate for the Pd-catalyzed indole alkylation reaction. In this work, when methyl 1,3-diphenyl-2-propenyl carbonate was treated with indole, **2a** was formed in comparable enantioselectivity (83% ee) vs the analogous reaction with 1,3-diphenyl-3-propenyl acetate (86% ee), albeit with lower product yield (45%, entry 9).

For further reaction optimization, the solvent effect was also investigated. The best results were obtained (95% ee and 74% product yield) with CH_3CN as solvent (entry 15). Moreover, Li_2CO_3, Na_2CO_3, and Cs_2CO_3 failed to give better enantioselectivities and yields than K_2CO_3 under identical

Table 2. Scope of Indoles[a]



entry	indole	2	yield (%)[b]	ee (%)[c]
1		**2a**	74	95
2		**2b**	77	92 (99.5)[d]
3		**2c**	78	95
4		**2d**	77	96
5		**2e**	75	96
6		**2f**	66	94
7		**2g**	61	96
8		**2h**	85	94
9		**2i**	56	94

[a] Conditions: indole **1** (0.3 mmol), [Pd(η^3-C_3H_5)Cl]$_2$ (2.5 mol %), ligand (5 mol %), 1,3-diphenyl-2-propenyl acetate (1.2 equiv), K_2CO_3 (2 equiv) in CH_3CN (2 mL). [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC with the *N*-Boc-protected derivatives of **2** (see Supporting Information). [d] After a single recrystallization.

reaction conditions (entries 16−18). The catalyst containing (*S*)-P-Phos are less active, though 96% ee was obtained (entry 19).

With the optimal catalyst combination and reaction conditions in hand, the scope of the reaction with different indoles **1b**−**i** was then investigated (Table 2). It is noteworthy that the 5-substituted and 7-substituted indoles with both electron-withdrawing (Cl, Br) and electron-donating (Me, OMe, OBn) groups, as well as 2-substituted indoles (Ph, Me), were well tolerated in the reaction, and the desired adducts **2b**−**i** were formed with only small differentiation of enantioselectivities (92−96%). Over 99.5% ee was also attained after a single recrystallization of Boc-protected adduct **2b** (entry 2).

The absolute configuration and binding mode of ligand **L8** was established by an X-ray crystallographic study. An ORTEP representation of the [Pd(**L8**)Cl_2] is shown in Figure

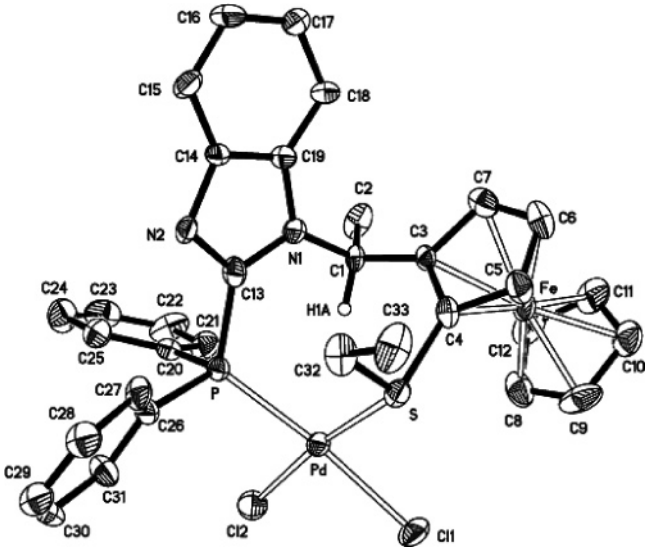


Figure 1. Molecular structure of [Pd(**L8**)Cl_2] at 35% probability level.

1. Only one epimer of the ethyl substituent on the sulfur donor was observed in an anti-orientation with respect to the iron atom of ferrocene. A similar structural observation has been reported by Carretero and co-workers.[6f] In addition, the stronger *trans* effect exerted by the phosphorus donor is reflected in the difference in Pd−Cl bond lengths *trans* to the phosphorus atom [2.353(1) Å] and *trans* to the sulfur atom [2.289(3) Å].

In summary, we have succeeded in preparing a new class of air-stable ferrocenyl P/S ligands with heterocyclic moieties, and their application in the enantioselective Pd-catalyzed allylic alkylation of indoles was achieved with high enantioselectivities (96% ee) irrespective of the steric or electronic nature of indoles.

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Supporting Information Available: Detailed experimental procedures, spectral data for all new compounds, and X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

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