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C_1-Symmetric Dicyclopentadienes as New Chiral Diene Ligands for Asymmetric Rhodium-Catalyzed Arylation of *N*-Tosylarylimines

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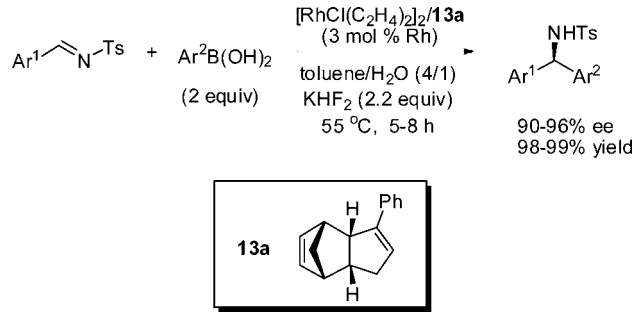
ABSTRACT



Monosubstituted C_1-symmetric dicyclopentadienes as a new class of diene ligands have been developed for asymmetric arylation of *N*-tosylarylimines in excellent yields (98−99%) with high enantioselectivities (90−96%). The preparation of these diene ligands relied on an efficient lipase-catalyzed resolution as the key step.

Specifically designed ligands play a key role in transition-metal-catalyzed asymmetric reactions.[1] Thanks to the seminal work of Hayashi and Carreira,[2] the rapid development of chiral dienes as steering ligands has paved a new avenue for ligand design. The chiral dienes have proven to be excellent ligands for transition-metal-catalyzed asymmetric reactions in terms of both catalytic activities and enantioselectivities.[3] However, the structural diversity of chiral diene ligands, which is very important to satisfy the demand of different asymmetric reactions, is still limited. The majority of chiral diene ligands used presently have a six-membered cyclohexadiene as the basic binding framework (Scheme 1, **1**−**3**),[4−6] and a few others have eight-membered cyclooctadiene (**4** and **5**).[7,8] The ligand framework is one of the crucial factors to determine the binding affinity and the binding angle toward a metal center, which in turn influences the catalytic activity and enantioselectivity of the catalyst.[3b] Compared with the tunability of steric and electronic issues

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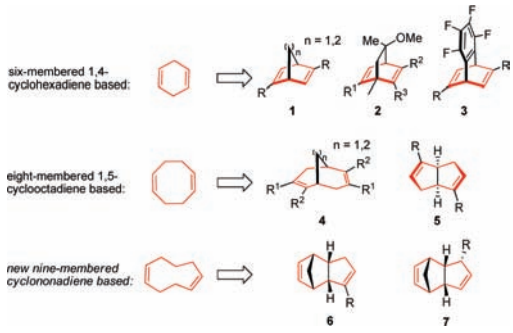
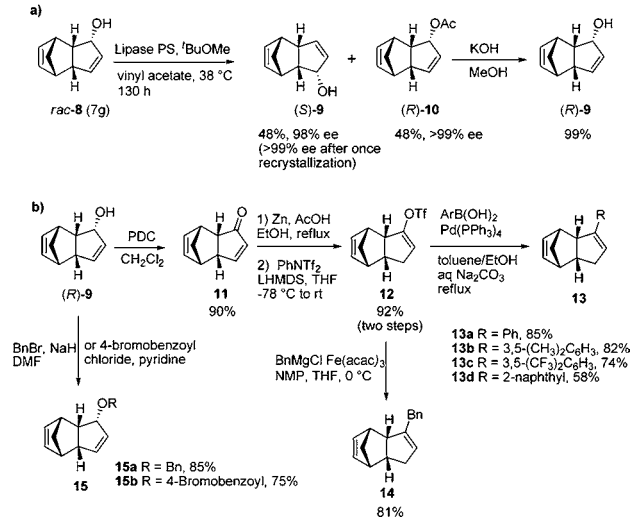
Scheme 1. Design of New Diene Ligands



Scheme 2. Preparation of New DCP-Based Dienes



of the diene ligands, the modification of the ligand framework is more difficult.[9] In 2007, we successfully introduced a series of diene ligands **5** with a nonbridged bicyclic skeleton.[8a−d] In our continuing interest in finding structurally novel diene ligands, several chiral dienes (**6** and **7**) with a dicyclopentadiene (DCP) backbone were designed. Though racemic DCP is one of the most common chelating diene ligands for transition-metal complexes with rigid structure,[10] no chiral diene ligand based on the DCP backbone has been reported yet. Herein, we report a class of C_1-symmetric monosubstituted chiral DCPs as the first type of chiral diene ligand with a nine-membered cyclononadiene as the basic binding framework.

The synthesis of new diene ligands was illustrated in Scheme 2. Both enantiomerically pure (>99%) (*S*)-**9** and (*R*)-**10** were prepared via an efficient lipase-catalyzed resolution of racemic alcohol **8**, which was made from the readily available DCP in three steps.[11] Hydrolysis of (*R*)-**10** followed by oxidation afforded the enone **11** in high yield. Selective reduction[12] of **11** and subsequent treatment with the *N*-phenyltriflimide[13] gave the triflate **12**. The following cross-coupling with arylboronic acids or Grignard reagents afforded a serial ligand **13** and **14** with different substitutes on the double bond. The derivatization of (*R*)-**9** generated **15a** and **15b** in moderate yields. The absolute stereochemical assignment of compounds **9**−**15** was based upon the single-crystal X-ray diffraction analysis of *p*-bromobenzoate **15b**.[14]

Compared with the common diene ligands, C_1-symmetric monosubstituted chiral dienes have only one bulky substitutent on the diene binding framework, which makes the ligand synthesis easier. Though these ligands have exhibited good performance in rhodium-catalyzed asymmetric conjugate additions,[15] further application in other rhodium-catalyzed reactions has not been reported yet. In order to test the ability of our new ligands as well as explore the new application of the C_1-symmetric monosubstituted chiral dienes, a rhodium-catalyzed arylation of *N*-tosylarylimines with arylboronic acids was carried out.[16,17]

Under the standard conditions,[8a] the reaction of phenylboronic acid with *N*-tosylimine **16** in the presence of dienes **9**−**11** or **15a** proceeded sluggishly, and low enantioselectivities (4−64% ee) were obtained (entries 1−4 in Table 1). To our delight, when a phenyl-substituted chiral diene **13a** was screened, the excellent enantioselectivity appeared (93%

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(14) See the Supporting Information for details.

(15) (a) References 4b,c and 6c. (b) Gendrineau, T.; Genet, J. P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486. (c) Gendrineau, T.; Genet, J. P.; Darses, S. *Org. Lett.* **2010**, *12*, 308.

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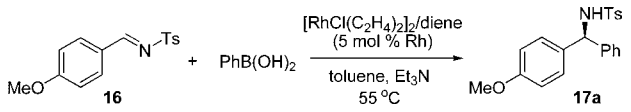
Table 1. Ligand Screening in the Rhodium-Catalyzed Phenylation of *N*-Tosylarylimine **16**[a]



entry	ligand	time (h)	yield[b] (%)	ee[c] (%)
1	(*R*)-**9**	24	6	6
2	(*R*)-**10**	24	32	17
3	**11**	24	72	64
4	**15a**	24	77	4
5	**13a**	6	92	93
6[d]	**13a**	6	92	93
7	**13b**	6	91	90
8	**13c**	6	93	88
9	**13d**	6	94	91
10	**14**	8	86	32

[a] The reaction was carried out with **16** (0.2 mmol), phenylboronic acid (0.4 mmol), Et_3N (0.4 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol), and chiral dienes (0.011 mmol) in toluene (1.2 mL) at 55 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Catalyst loading was reduced to 3 mol %.

ee for entry 5). Replacing the phenyl group with other more sterically bulky aryl groups resulted in a slight decrease of enantioselectivities (entries 7−9). A significant loss of enantioselectivity was observed when ligand **14**, which had a benzyl group on the double bond (entry 10), was used. When the catalyst loading was reduced to 3 mol %, the yield and enantioselectivity were maintained (entry 6).

With the best ligand **13a** obtained by screening, we further optimized the reaction conditions including solvents and additives. It was found that when dioxane or THF was used, high yields and enantioselectivities were maintained compared with the use of toluene (Table 2, entries 2 and 3 vs 1). A slight decrease in both activities and enantioselectivities occurred when DCE or acetone was used as the solvent (entries 4 and 5). Replacing Et_3N with aqueous K_3PO_4 resulted in a quick decomposition of *N*-tosylimine **16**, and only a trace of product **17a** was observed (entry 6). Gratifyingly, when aqueous KHF_2 was used as the additive, higher yield (99%) and improved enantioselectivity (95% ee) were achieved (entry 7).[18,19]

(17) For selected examples of the Rh(I)-catalyzed asymmetric arylation of aromatic imines using other catalysts, see: (a) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125. (c) Kuriyama, M.; Soeta, T.; Hao, X. Y.; Chen, O.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (d) Weix, D. J.; Shi, Y. L.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (e) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (f) Duan, H. F.; Jia, Y. X.; Wang, L. X.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 2567. (g) Nakagawa, H.; Rech, J. C.; Sindelar, R. W.; Ellman, J. A. *Org. Lett.* **2007**, *9*, 5155. (h) Kurihara, K.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2009**, *351*, 260. (i) Hao, X.; Kuriyama, M.; Chen, Q.; Yamamoto, Y.; Yamada, K.; Tomioka, K. *Org. Lett.* **2010**, *12*, 4470.

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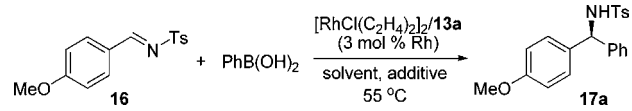
Table 2. Optimization of the Reaction Conditions[a]

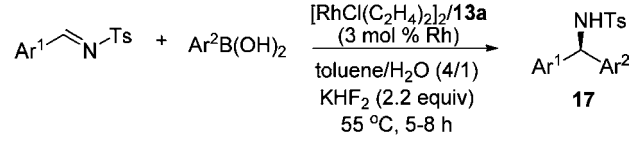


entry	solvent	additive	yield[b] (%)	ee[c] (%)
1	toluene	Et_3N	92	93
2	dioxane	Et_3N	92	93
3	THF	Et_3N	92	92
4	DCE	Et_3N	85	88
5	acetone	Et_3N	89	90
6	toluene	aq K_3PO_4[d]	trace	
7	toluene	aq KHF_2[d]	99	95

[a] The reaction was carried out with **16** (0.2 mmol), phenylboronic acid (0.4 mmol), Et_3N (0.4 mmol), $[RhCl(C_2H_4)_2]_2$ (0.003 mmol), and **13a** (0.0066 mmol) in solvent (1.2 mL) at 55 °C, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 1.5 M aqueous solution, 0.45 mmol.

Having established the optimal reaction conditions, arylation with other arylboronic acids and *N*-tosylarylimines was examined (Table 3). Compared with the previous results

Table 3. Asymmetric Rhodium-Catalyzed Arylation of *N*-Tosylarylimines with Arylboronic Acids[a]



entry	Ar^1	Ar^2	**17**	yield[b] (%)	ee[c,d] (%)
1	4-$MeOC_6H_4$	Ph	**17a**	99	95 (*S*)
2	4-MeC_6H_4	Ph	**17b**	99	94 (*S*)
3	4-ClC_6H_4	Ph	**17c**	99	94 (*S*)
4	4-BrC_6H_4	Ph	**17d**	98	95 (*S*)
5	2-MeC_6H_4	Ph	**17e**	98	96 (*S*)
6	2-$MeOC_6H_4$	Ph	**17f**	99	93 (*S*)
7	1-naphthyl	Ph	**17g**	99	95 (*S*)
8	4-$MeOC_6H_4$	4-MeC_6H_4	**17h**	99	95 (*S*)
9	4-$MeOC_6H_4$	4-$CF_3C_6H_4$	**17i**	99	94 (*S*)
10	4-$MeOC_6H_4$	4-ClC_6H_4	**17j**	99	94 (*R*)
11	4-$MeOC_6H_4$	3-MeC_6H_4	**17k**	99	93 (*R*)
12	4-$MeOC_6H_4$	3-$MeOC_6H_4$	**17l**	99	92 (*R*)
13	4-$MeOC_6H_4$	1-naphthyl	**17m**	98	90 (*R*)
14	Ph	4-$MeOC_6H_4$	**17a′**	98	93 (*R*)
15	Ph	4-MeC_6H_4	**17b′**	99	93 (*R*)
16	Ph	4-ClC_6H_4	**17c′**	98	94 (*R*)

[a] The reaction was carried out with *N*-tosylarylimine (0.2 mmol), arylboronic acid (0.4 mmol), 1.5 M aq KHF_2 (0.45 mmol), $[RhCl(C_2H_4)_2]_2$ (0.003 mmol), and **13a** (0.0066 mmol) in toluene (1.2 mL) at 55 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configurations were determined by comparing with the known optical rotations $[\alpha]_D$ in the literature. The configurations of **17i**, **17k**, and **17l** were tentatively assigned by consideration of the stereochemical pathway.

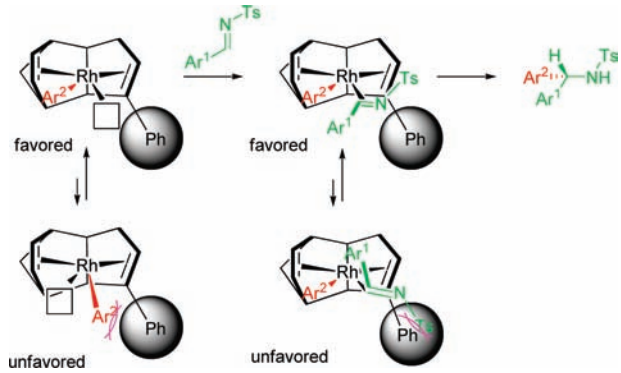
obtained with other diene ligands, the diarylmethyltosylamide products **17** were generated in higher yields (98−99%) but

with slightly lower enantioselectivities (90−96% ee). The phenylation of substituted benzaldimines with both electron-withdrawing and electron-donating groups at the para position gave the desired products in 94−95% ee (entries 1−4). The additions of more sterically hindered imines derived from 2-MeC_6H_4CHO, 2-$MeOC_6H_4CHO$, and 1-naphthaldehyde proceeded equally well with high enantioselectivities (entries 5−7). High enantioselectivities (90−95%) were also observed in the addition of a variety of arylboronic acids bearing different substituents to **16** (entries 8−13). Similar results were obtained when the corresponding aryl acceptor and donor were switched, constituting a flexible apporach for chiral diarylmethylamine synthesis (entries 1 vs 14, 2 vs 15, and 3 vs 16).

The stereochemical defining pathway in our arylation of imines with **13a** as the ligand is assumed to be consistent with the similar model proposed by Hayashi[16b] and Darses[4b] (Scheme 3). After the initial transmetalation step, the aryl group will occupy the position far away from the phenyl groups on the diene ligand to minimize a potential steric repulsion. In the following step, the sterically bulky phenyl groups on the double bond efficiently recognize the enantioface of the imine when it coordinates to the rhodium center. Accordingly, the aryl group in the metal center attacks the activated aldimine from the *Si* face to give the corresponding adduct.

In summary, a new class of monosubstituted C_1-symmetric diene ligands with a DCP backbone has been developed. With an efficient lipase-catalyzed resolution as the key step, the ligand synthesis is convenient and high yielding. These new ligands were successfully applied in the rhodium-catalyzed asymmetric arylation of *N*-tosylarylimines. The reaction proceeded smoothly and resulted in the corresponding diarylmethyltosylamides with excellent yields (98−99%) and high enantioselectivities (90−96%). Further application of the new ligands in asymmetric synthesis is currently underway.

Scheme 3. Stereochemical Defining Pathway with Rh−**13a** Complex



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Supporting Information Available: Experimental procedures and characterization data, copies of ^1H and ^{13}C NMR spectra, HPLC profiles, and X-ray data of **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For the example of KHF_2 used as an additive in arylboronic acid participated reactions, see: Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980.