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Development of Binaphthyl-Based Chiral Dienes for Rhodium(I)-Catalyzed Asymmetric Arylation of *N,N*-Dimethylsulfamoyl-Protected Aldimines

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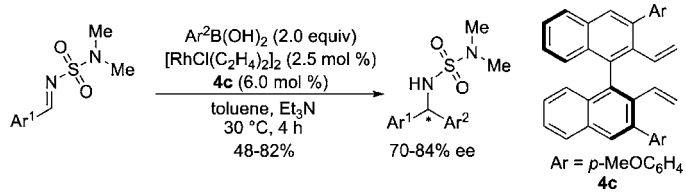
ABSTRACT



A variety of binaphthyl-based chiral dienes were synthesized and utilized as steering ligands for the enantioselective arylation of *N,N*-dimethylsulfamoyl-protected aldimines with arylboronic acids, and moderate to good yields and up to 84% ee were achieved.

Since the groups of Hayashi and Carreira independently reported their seminal work on the development of enantiomerically pure bicyclic dienes as steering ligands for metal-catalyzed asymmetric reactions in 2003 and 2004,[1] chiral olefins as one new class of promising ligands have attracted great attention,[2] and a few excellent chiral diene ligands with rigid cyclic frameworks have been successfully developed.[3−5] However, further expanding the scope of olefins as ligands to ensure their wide acceptance is still one of the most important subjects in this field.[2] As part of our general

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interest in exploring structurally new, effective, and accessible chiral diene ligands, we discovered that flexible acyclic dienes **1** and **2** can be used as effective ligands for Rh(I)-catalyzed asymmetric 1,4-additions with encouraging reactivity and enantioselectivity in our previous work (Figure 1).[6]

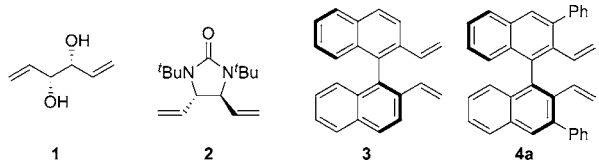


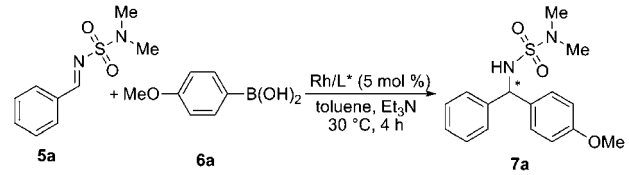
Figure 1. Acyclic chiral diene ligands.

It is well-known that C_2-symmetric binaphthyl frameworks are among the most successful chiral backbones in asymmetric catalysis.[7] Therefore, binaphthyl-based chiral dienes attracted our interest for their potential as ligands for metal-catalyzed reactions.

Rhodium-catalyzed asymmetric arylations of protected aldimines with organometallic reagents provide a powerful approach to afford optically active diarylmethylamines which are present in various biologically active molecules.[8−11] In 2006, de Vries, Feringa, Minnaard, and co-workers reported the first rhodium/phosphoramidite-catalyzed asymmetric arylation of *N*,*N*-dimethylsulfamoyl-protected aldimines with arylboronic acids to achieve excellent yields and ee's.[10c] In particular, *N*,*N*-dimethylsulfamoyl[12] was used as an inexpensive, low-molecular-weight, and easily removed protecting/activating group for this reaction. Herein, we report our efforts on the development of binaphthyl-based chiral dienes as ligands for Rh(I)-catalyzed enantioselective arylation of *N*,*N*-dimethylsulfamoyl-protected aldimines.

The initial studies were carried out with chiral dienes **1** and **2** as ligands for Rh(I)-catalyzed reactions of *N*,*N*-dimethylsulfamoyl-protected aldimine **5a** (1.0 equiv) and arylboronic acid **6a** (2.0 equiv) in the presence of Et_3N[13] (2.0 equiv) at 30 °C in toluene for 4 h. It was disappointing to find that only low conversions and ee's were obtained (Scheme 1). When (*S*)-2,2′-divinyl-1,1′-binaphthyl (**3**)[14]

Scheme 1. Rh(I)-Catalyzed Asymmetric Arylation of Aldimine **5a** with Arylboronic Acid **6a**[10c]



1: 5% ee (37% convn)
2: 13% ee (24% convn)
3: trace
4a: 77% ee (76% convn)

(Figure 1) was subjected to this reaction, only a trace amount of product **7a** was observed (Scheme 1), although we were pleased to find that (*S*)-3,3′-diphenyl-2,2′-divinyl-1,1′-binaphthyl (**4a**) modified rhodium catalyst led to a dramatic improvement for both reactivity and enantioselectivity (Scheme 1). ^{1}H NMR studies (see the Supporting Information) indicate that ligand **4a** can coordinate with rhodium(I) more efficiently to form the corresponding complex than ligand **3**, which may account for the observed difference for catalyst activity and selectivity (Scheme 1).

Encouraged by the promising result, a variety of binaphthyl-based chiral dienes (**4b**−**k**) bearing different aryl substituents at the 3,3′-positions were synthesized with (*S*)-diisopropyl-3,3′-dibromo-1,1′-binaphthyl-2,2′-dicarboxylate (**8**) as starting material, which was readily available by the reported methods.[15] After subsequent classic transformations without optimizations, including a Suzuki coupling reaction to afford **9**, reduction of **9** with $LiAlH_4$, oxidation with PCC to give dialdehyde **10**, and Wittig reaction, all chiral dienes **4b**−**k** can be obtained in reasonable yields (Scheme 2).

To search for more effective ligands, chiral dienes **4b**−**k** were then subjected to the Rh(I)-catalyzed arylation reactions between aldimine **5a** and arylboronic acid **6a**, and all of the

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(10) For leading references on catalytic rhodium-catalyzed arylations of imines with arylboron reagents, see: (a) References 3a and 5e. (b) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (c) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (d) Trincado, M.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5623. (e) Kurihara, K.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2009**, *351*, 260.

(11) For leading references on rhodium-catalyzed arylations of imines with other organometallic reagents, see the following. Sn: (a) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. Zn: (b) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692. Ti: (c) Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125.

(12) For leading references on the *N*,*N*-dimethylsulfamoyl protecting group, see: (a) Huisman, M.; ten Have, R.; van Leusen, A. M. *Synth. Commun.* **1997**, *27*, 945. (b) ten Have, R.; Huisman, M.; Meetsma, A.; van Leusen, A. M. *Tetrahedron* **1997**, *53*, 11355. (c) Jagt, R. B. C.; Toullec, P. Y.; Schudde, E. P.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *J. Comb. Chem.* **2007**, *9*, 407. (d) Hietanen, A.; Saloranta, T.; Rosenberg, S.; Laitinen, E.; Leino, R.; Kanerva, L. T. *Eur. J. Org. Chem.* **2010**, 909.

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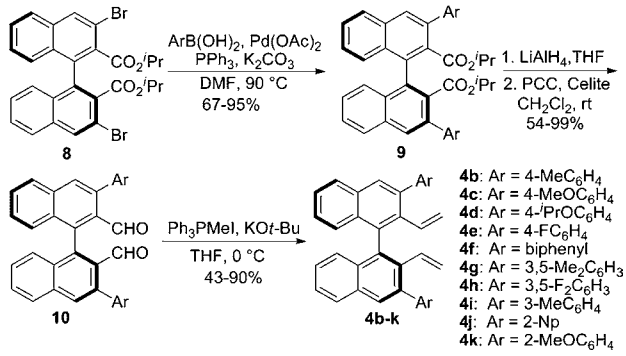
(14) For a reference on *rac*-2,2′-divinyl-1,1′-binaphthyl, see: Collins, S. K.; Grandbois, A.; Vachon, M. P.; Côté, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2923.

(15) For a reference on the synthesis of (*S*)-diisopropyl-3,3′-dibromo-1,1′-binaphthyl-2,2′-dicarboxylate, see: Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576.

Scheme 2. Synthesis of Binaphthyl-Based Chiral Diene Ligands



results are summarized in Table 1.[16] It was found that all the ligand-modified rhodium(I) catalysts can promote this reaction efficiently to afford the desired product **7a** in 34−87% conversions with 57−86% ee's (Table 1, entries 1−11). Studies showed that the aryl substituents on the 3,3′-positons have obvious impacts on both reactivity and enantioselectivity for the arylation. Chiral dienes **4b** and **4c** gave better conversions and ee's in comparison with **4a** (Table 1, entries 1 vs 2 and 3). Ligand **4k** bearing an ortho-substituted phenyl largely decreased the reactivity (Table 1, entry 11). Considering both reactivity and enantioselectivity, chiral diene **4c** proved to be the best ligand for the arylation. The temperature and solvent for **4c**/Rh(I)-catalyzed reactions were further investigated. Increasing the temperature to 60 °C led to a decrease for both conversion and ee (Table 1, entry 12). When the temperature was dropped to 15 °C, a slightly higher ee (86%) and lower conversion (76%) were afforded. The enantioselectivity can be improved to 88% with dioxane as solvent, but the conversion was very low (Table 1, entry 18).

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

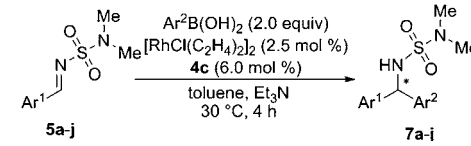
entry	ligand, Ar =	solvent	temp (°C)	convn[b] (%)	ee[c,d] (%)
1	Ph (**4a**)	toluene	30	76	77
2	4-MeC_6H_4 (**4b**)	toluene	30	81	85
3	**4-$MeOC_6H_4$ (4c)**	**toluene**	**30**	**87**	**84**
4	4-^{i}PrOC_6H_4 (**4d**)	toluene	30	76	71
5	4-FC_6H_4 (**4e**)	toluene	30	71	75
6	biphenyl (**4f**)	toluene	30	71	82
7	3,5-$Me_2C_6H_3$ (**4g**)	toluene	30	61	86
8	3,5-$F_2C_6H_3$ (**4h**)	toluene	30	60	72
9	3-MeC_6H_4 (**4i**)	toluene	30	76	79
10	2-Np (**4j**)	toluene	30	34	85
11	2-$MeOC_6H_4$ (**4k**)	toluene	30	35	57
12	4-$MeOC_6H_4$ (**4c**)	toluene	60	67	73
13	4-$MeOC_6H_4$ (**4c**)	toluene	45	80	81
14	4-$MeOC_6H_4$ (**4c**)	toluene	15	76	86
15	4-$MeOC_6H_4$ (**4c**)	acetone	30	21	84
16	4-$MeOC_6H_4$ (**4c**)	DCM	30	52	84
17	4-$MeOC_6H_4$ (**4c**)	THF	30	43	86
18	4-$MeOC_6H_4$ (**4c**)	dioxane	30	40	88

[a] All of the reactions were carried out with aldimine **5a** (0.2 mmol), arylboronic acid **6a** (0.4 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol, 5 mol % Rh), ligand (0.012 mmol, 6 mol %), and Et_3N (0.4 mmol) in solvent (0.8 mL) at the indicated temperature under argon for 4 h. [b] The conversion was determined by crude ^1H NMR. [c] The ee was determined by chiral HPLC (Chiralpak OD-H column). [d] The configuration was determined to be *S* by comparing the optical rotation with the reported one.

(16) One binaphthyl-based chiral diene containing non-terminal olefins has also been investigated, but no desired product was observed judged by the crude ^1H NMR.

4c/Rh(I)-catalyzed asymmetric arylations of various *N*,*N*-dimethylsulfamoyl-protected aldimines (**5a**−**j**) with arylboronic acids were subsequently investigated. As shown in Table 2, all the arylations went smoothly to give the corresponding diarylmethylamines in 48−82% yields and 70−84% ee's. Deprotection of **7a** was then conducted in a sealed tube for 30 min assisted by microwave (750 W) based on literature methods[10c] with slight modifications. The reaction with ethylenediamine as solvent (1,3-diaminopropane was used in the literature[10c]) proceeded cleanly and efficiently to give the free amine **11** in quantitative yield with retention of configuration (Scheme 3).

Table 2. 4c/Rh(I)-Catalyzed Asymmetric Arylation of Aldimines with Arylboronic Acids[a]

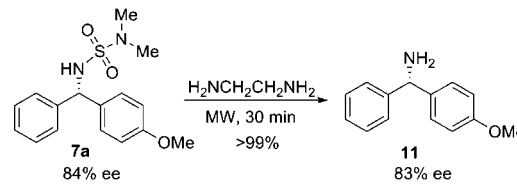


entry	product	Ar^1	Ar^2	yield[b] (%)	ee[c] (%)
1	**7a**	Ph	4-$MeOC_6H_4$	82	84
2	**7b**	4-ClC_6H_4	4-$MeOC_6H_4$	64	76
3	**7c**	4-$CF_3C_6H_4$	4-$MeOC_6H_4$	71	74
4	**7d**	4-MeC_6H_4	4-$MeOC_6H_4$	68	79
5	**7e**	3-ClC_6H_4	4-$MeOC_6H_4$	71	79
6	**7f**	2-ClC_6H_4	4-$MeOC_6H_4$	55	83
7	**7g**	2-$MeOC_6H_4$	4-$MeOC_6H_4$	53	79
8	**7h**	2-Np	4-$MeOC_6H_4$	81	78
9	**7i**	Ph	4-$EtOC_6H_4$	80	79
10	**7j**	4-$CF_3C_6H_4$	4-MeC_6H_4	48	70

[a] All of the reactions were carried out with aldimine **5** (0.4 mmol), arylboronic acid (0.8 mmol), $[RhCl(C_2H_4)_2]_2$ (0.01 mmol, 5 mol % Rh), **4c** (0.024 mmol, 6 mol %), and Et_3N (0.8 mmol) in toluene (1.6 mL) at 30 °C under argon for 4 h. [b] Isolated yield. [c] The ee was determined by chiral HPLC (Chiralpak AD-H column) unless other stated; a Chiralpak OD-H column was used for entries 1 and 7.

In summary, various binaphthyl-based chiral dienes were synthesized and used as steering ligands for the first time

Scheme 3. Removal of the *N*,*N*-Dimethylsulfamoyl Protecting Group Assisted by Microwave[10c,17]



for rhodium-catalyzed asymmetric arylations of *N*,*N*-dimethylsulfamoyl-protected aldimines with arylboronic acids. A variety of optically active diarylmethylamines were obtained in reasonable yields and good ee's. Although the efficiency, enantioselectivity, as well as substrate scope are still not satisfactory and await further improvements, the current studies expand the scope of chiral olefins as ligands which may be helpful for the design of novel ligands in the future. Searching for more efficient chiral acyclic olefin ligands and exploring their applications in other metal-catalyzed asymmetric reactions are currently underway in our laboratory.

(17) The enantiomeric excess of **11** was determined by chiral HPLC after protecting with *p*-tolylsulfonyl (Ts) group.

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Supporting Information Available: Procedure for the synthesis of binaphthyl-based chiral dienes, rhodium-catalyzed arylations, and deprotection of **7a**, characterization of **4a**−**k** and **7a**−**j**, and data for the determination of enantiomeric excesses of **7a**−**j** along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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