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Electronic and steric tuning of chiral diene ligands for rhodium-catalyzed asymmetric arylation of imines

Electronic and steric tuning of chiral diene ligands for rhodium-catalyzed asymmetric arylation of imines†‡

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Rhodium-catalyzed asymmetric arylation of imines using electronically and sterically-modified chiral diene ligands gave the corresponding diarylmethylamines in high yield and with high enantioselectivity using just 0.3 mol% of catalyst.

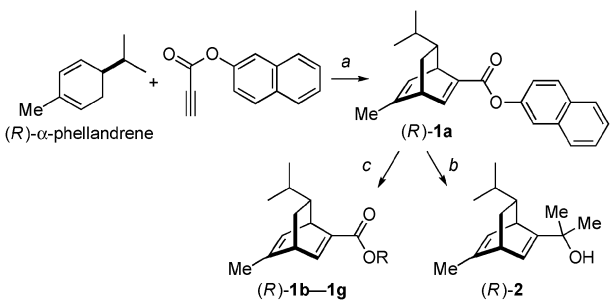
The advent of chiral diene ligands represents an important new development in asymmetric catalysis. Such ligands confer higher activities and enantioselectivities than phosphorus ligands in rhodium-catalyzed asymmetric addition reactions.[1–7] The high efficiency of chiral diene ligands has been investigated through mechanistic and kinetic studies,[8] and there have been limited studies aimed at the steric[9] and electronic modification[10,11] of these ligands. Very recently, we reported a simple synthesis of a highly effective chiral diene ligand possessing a bicyclo[2.2.2]octadiene framework, which was assembled through the [4 + 2] cycloaddition of α-phellandrene.[2] We have probed the steric and electronic requirements of these ligands and report here the development of simple, sterically-bulky ester substituted dienes that provide high catalytic activity and enantioselectivity in the rhodium-catalyzed asymmetric arylation of *N*-sulfonylimines.

The synthetic route to the bicyclo[2.2.2]octadiene framework through the cycloaddition of (*R*)-α-phellandrene was greatly improved by use of 2-naphthyl propiolate as the dienophile (Scheme 1). A high yield of the chemically and enantiomerically pure cycloaddition product **1a** was isolated by simple recrystallization of the crude reaction mixture (See ESI‡). The 2-naphthyl ester was readily converted into other esters **1b–1g** by direct transesterification or by hydrolysis and successive esterification of the carboxylic acid. Treatment of ester **1a** with methyllithium gave tertiary alcohol **2**, which has been reported to be an efficient chiral ligand for rhodium-catalyzed asymmetric 1,4-addition reactions.[2]

The chiral dienes, **1**, obtained here were examined for the rhodium-catalyzed asymmetric addition of arylboronic acids to *N*-nosylimines of aromatic aldehydes.[12,13] The results obtained for the addition of phenylboroxine **8m** to the nosylimine of 4-chlorobenzaldehyde **7a** are summarized in Table 1, which also contains the data reported with some other chiral diene ligands **3–6**.[3–6] In the presence of 3 mol% of the diene–rhodium catalyst, the reaction at 60 °C for 6 h gave high yields of the nosylated diarylmethylamine **9am**. In general, the ester group substituted bicyclo[2.2.2]octadienes were more enantioselective than those substituted with alkyl or aryl groups (entries 1–7 *vs.* 8–10).[14] Among the ester groups, aryl esters induced higher enantioselectivities than alkyl esters, with sterically more bulky aryl esters (entries 1, 6, and 7) exhibiting higher enantioselectivity than less bulky esters, the highest being 98% ee for 2,6-dimethylphenyl ester **1g** (entry 7).

During the experiments shown in Table 1, it was observed that the catalytic activity of rhodium catalysts coordinated with the ester-substituted dienes **1** was particularly high. Indeed, the phenylation of imine **7a** to afford **9am** was completed in 1.5 h in the presence of just 0.3 mol% of the rhodium catalyst when coordinated with **1a** (Fig. 1). With other types of diene ligand at the same loadings, the phenylation reaction did not go to completion, even after a longer reaction time (6 h). The rhodium catalyst with the bicyclo[3.3.1]diene **5** provided high enantioselectivity, but lost its catalytic activity at a low conversion.[5a]

Table 2 summarizes the results obtained with 0.3 mol% loading of the rhodium catalyst coordinated with the ester-substituted diene ligand **1g**. The *N*-nosylimines substituted with 4-MeO (**7b**) and 2-Me (**7c**) on the phenyl underwent the asymmetric addition of phenylboroxine as smoothly as **7a** to give high yields of the corresponding arylphenylmethylamines with high (98% ee) enantioselectivity (entries 2 and 3).



Scheme 1 Synthesis of chiral diene ligands: (a) Me_2AlCl (1.0 equiv.), CH_2Cl_2, −78 °C to rt, 67%; (b) MeLi (2.4 equiv.), Et_2O–THF, 0 °C, 87%; (c) method A (R = Me, Et, *i*Pr, *t*Bu): NaOR or LiOR, THF, rt, 93–99%; method B (R = 1-naphthyl or 2,6-$Me_2C_6H_3$): (i) NaOMe, THF, rt, 98%; (ii) LiOH (aq.), MeOH, 50 °C, then HCl (aq.); (iii) DMAP, DCC, ROH, CH_2Cl_2, rt, 2 h, 94–95% (in 2 steps). DMAP = 4-dimethylaminopyridine, DCC = dicyclohexylcarbodiimide.

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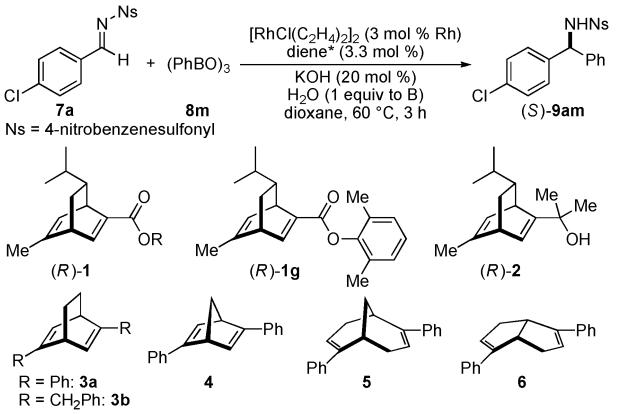
‡ Electronic Supplementary Information (ESI) available: Experimental procedures, compound characterization data, and X-ray crystallographic data of Rh(acac)((*R*)-**1a**) (CCDC 718052). See DOI: 10.1039/b904624k/

Table 1 Asymmetric phenylation of nosylimine **7a** catalyzed by rhodium–diene complexes[a]



Entry	Diene* (R)	Yield (%)[b]	ee (%)[c]	ref.
1	**1a** (2-naphthyl)	95	95	—
2	**1b** (Me)	98	92	—
3	**1c** (Et)	94	90	—
4	**1d** (*i*-Pr)	99	92	—
5	**1e** (*t*-Bu)	95	94	—
6	**1f** (1-naphthyl)	93	96	—
7	**1g** (2,6-$Me_2C_6H_3$)	94[d]	98[d]	—
8	**2**	93	56	—
9	**3a** [(*R*,*R*)-Ph-bod*]	96	89	5*a*
10	**3b** [(*R*,*R*)-Bn-bod*]	99	70	5*a*
11	**4** [(*R*,*R*)-Ph-nbd*]	92	98	4
12	**5** [(*S*,*S*)-Ph-bnd*]	96	98	5*a*
13[e]	**6**	35	98.5	6*a*

[a] The reaction was carried out with imine **7a** (0.10 mmol), $(PhBO)_3$ (0.12 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol% Rh), diene* (3.3 mol%), and 3.1 M aq KOH (6.5 μL) in dioxane (0.80 mL). [b] Isolated yield. [c] Determined by HPLC analysis with chiral stationary phase columns. [d] Average values of three experiments. [e] With Et_3N in toluene.

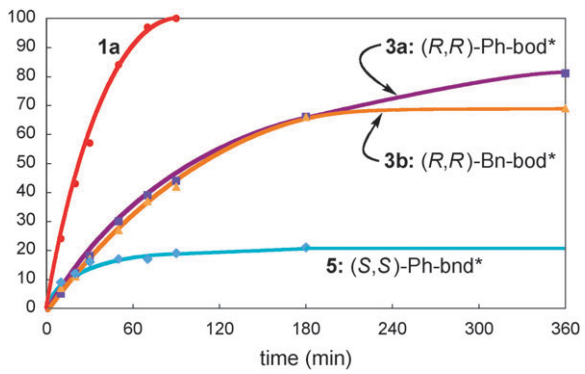
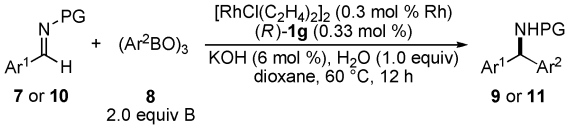


Fig. 1 Kinetic experiments. The reaction was carried out with imine **7a** (1.5 mmol), $(PhBO)_3$ (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (0.3 mol% Rh), diene* (0.33 mol%), and 3.3 M KOH (aq.) (27 μL) in dioxane (4.0 mL). In the case of diene **5**, $[RhCl((S,S)$-Ph-bnd* (**5**))$]_2$ was used. The yields were determined by ^1H NMR (using hexamethylbenzene as an internal standard).

Addition of arylboroxines substituted with electron-donating or -withdrawing groups also proceeded well with 0.3 mol% of the **1g**–rhodium catalyst (entries 4–9). Asymmetric phenylation of *N*-tosylimine **10** is another successful example, which

Table 2 Asymmetric arylation of imines **7** and **10** catalyzed by the rhodium–(*R*)-**1g** complex[a]



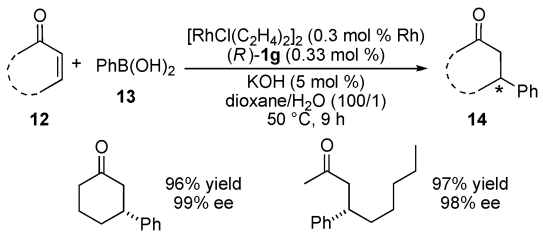
Entry	PG	Ar^1	Ar^2	Yield[b] (%)	ee[c] (%)
1	Ns	**7a**: 4-ClC_6H_4	**8m**: Ph	98 (**9am**)	98 (*S*)
2	Ns	**7b**: 4-$MeOC_6H_4$	**8m**: Ph	97 (**9bm**)	98 (*S*)
3	Ns	**7c**: 2-MeC_6H_4	**8m**: Ph	91 (**9cm**)	98 (*S*)
4	Ns	**7d**: Ph	**8n**: 4-$MeOC_6H_4$	98 (**9dn**)[d]	>99.5 (*R*)
5	Ns	**7d**: Ph	**8o**: 4-ClC_6H_4	95 (**9do**)[d]	98.5 (*R*)
6	Ns	**7d**: Ph	**8p**: 3-$MeOC_6H_4$	90 (**9dp**)	97 (*R*)
7	Ns	**7d**: Ph	**8q**: 2-MeC_6H_4	95 (**9dq**)[d]	>99.5 (*R*)
8	Ns	**7b**: 4-$MeOC_6H_4$	**8o**: 4-ClC_6H_4	90 (**9bo**)	99.1 (*R*)
9	Ns	**7c**: 2-MeC_6H_4	**8n**: 4-$MeOC_6H_4$	98 (**9cn**)	98 (*S*)
10[e]	Ts	**10a**: 4-ClC_6H_4	**8m**: Ph	96 (**11am**)	99.0 (*S*)

[a] The reaction was carried out with an imine (1.5 mmol), $(Ar^2BO)_3$ (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (0.3 mol% Rh), **1g** (0.33 mol%), and 3.3 M KOH (aq.) (27 μL) in dioxane (4.0 mL). [b] Isolated yield. [c] Determined by HPLC analysis with chiral stationary phase columns. [d] Products **9dn**, **9do**, and **9dq** are enantiomers of **9bm**, **9am**, and **9cm**, respectively. [e] $(PhBO)_3$ (3.0 equiv. B) was used. Ts = *p*-toluenesulfonyl.

gave a quantitative yield of the corresponding tosylamine **11** with 99% enantioselectivity (entry 10).

The high performance of the **1g**–rhodium catalyst was also observed in the asymmetric 1,4-addition to α,β-unsaturated ketones **12**[15,16] (Scheme 2). With 0.3 mol% loading of the catalyst, both cyclic and linear enones were efficiently converted to the corresponding β-aryl ketones with 98–99% ee, the enantioselectivity being among the highest so far reported with chiral diene ligands.[1,2] The dienes currently described, possessing a bulky ester group on the coordinating double bond, are anticipated to have a broad range of substrate scope in addition to the standard type enones shown here.

The X-ray crystal structure of Rh(acac)((*R*)–**1a**) is shown in Fig. 2. The two carbon–carbon double bonds coordinate to the rhodium center to form a pseudo-symmetric structure, its bicyclo[2.2.2]octadiene framework being similar to that of $[RhCl(Ph\text{-}bod^*)]_2$.[5b,17] The bond distances between rhodium and the four carbons of the two double bonds are slightly shorter for the ester-substituted olefin (2.10 and 2.11 Å) than the methyl-substituted olefin (2.11 and 2.13 Å). The length of the ester-substituted double bond is slightly longer than the other double bond (1.41 *vs.* 1.39 Å). The ester carbonyl carbon–oxygen bond is close to parallel to the olefinic double



Scheme 2 Rhodium–chiral diene-catalyzed 1,4-addition of arylboronic acids to enones.

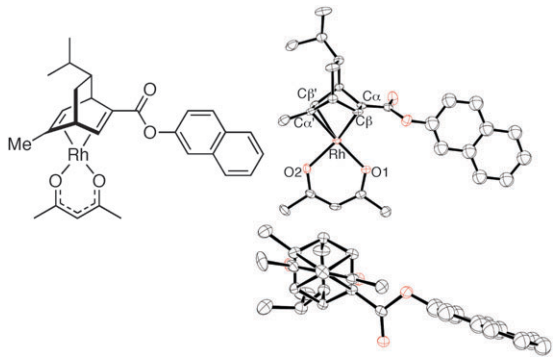


Fig. 2 ORTEP illustration of Rh(acac)((*R*)–**1a**) with thermal ellipsoids drawn at 50% probability level. Hydrogen atoms and the disorder are not shown (See ESI‡). Selected bond lengths: Rh–Cα = 2.11 Å, Rh–Cβ = 2.10 Å, Rh–Cα′ = 2.13 Å, Rh–Cβ′ = 2.11 Å, Cα–Cβ = 1.41 Å, Cα′–Cβ′ = 1.39 Å.

bond with an *s-trans* conformation. As a result, the aryloxy group becomes located close to the coordination site, *cis* to the double bond attached to this ester. The high catalytic activity of the rhodium complex is believed to arise from the presence of the double bond conjugated with the ester group. This electron-deficient double bond is expected to accelerate the transmetalation forming the rhodium–aryl bond *trans* to the ester-substituted double bond.[18,19]

The absolute configuration of the products, (*S*) for **9am** with a (*R*)-**1** ligand, is consistent with the stereochemical pathway that has been proposed for the reactions using C_2-symmetric diene ligands[3a,5a] (Fig. 3). The present rhodium complex with ligand **1**, which is unsymmetrically substituted with a methyl and an ester group, will form an aryl–rhodium bond on the site *trans* to the more electron-withdrawing double bond, leaving the remaining site available for coordination of the imine. The sterically more bulky aryl ester will recognize the enantioface of the imine more efficiently.[9]

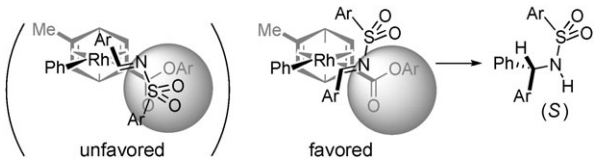


Fig. 3 Stereochemical pathway with Rh–(*R*)-**1** catalyst.

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