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One Step Synthesis of Chiral Olefins *via* Asymmetric Diamination and their Applications as Ligands for Rhodium(I)-Catalyzed 1,4-Additions

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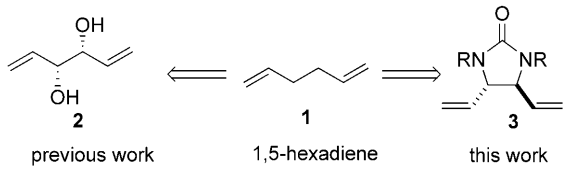
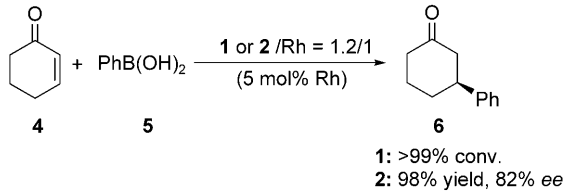
Abstract: A variety of acyclic chiral dienes were synthesized in a single step *via* palladium(0)-catalyzed asymmetric allylic and homoallylic C–H diamination of terminal olefins. The applications of such simple dienes as steering ligands for rhodium(I)-catalyzed asymmetric 1,4-additions afforded the corresponding adducts in excellent yields and up to 85% *ee*.

Keywords: acyclic chiral dienes; asymmetric catalysis; asymmetric diamination; conjugated addition; diene ligands



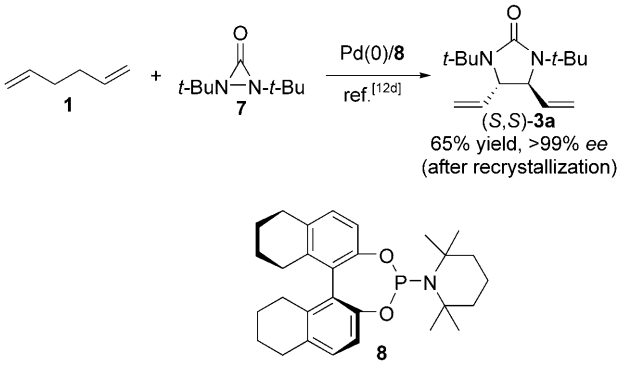
Scheme 1. Developing acyclic chiral diene ligands based on 1,5-hexadiene skeleton.



Scheme 2. Rh(I)-catalyzed asymmetric 1,4-additions with **1** or **2** as ligand.

Chiral olefins have proven to be excellent steering ligands for asymmetric catalysis, and some of them even exhibit a distinct advantage over other types of ligands to afford higher reactivities and/or enantioselectivities.[1,2] With lots of effort devoted to this lately emerging area, a few fantastic chiral chelating diene ligands bearing bicyclic frameworks have been successfully developed.[3–6] The bicyclic structures of these ligands play a crucial role in the asymmetric reactions, but also partially result in some difficulties in ligand synthesis. Hence, exploring novel, effective, and accessible chiral dienes is still one of the most important subjects in this field.[2b] Inspired by the fact that 1,5-hexadiene (**1**) has an ability to act as a steering ligand, very recently, we reported that a simple chiral acyclic diene **2** (Scheme 1) can be employed as an effective ligand for promoting Rh(I)-catalyzed asymmetric 1,4-additons with encouraging yields and *ee*s (Scheme 2),[7,8] which demonstrates that the complexes formed between Rh and a flexible diene are stable enough to ensure asymmetric induction.[9] Because of the convenient synthesis, chiral acyclic dienes have the potential to become a class of promising ligands in the future. Herein, we wish to report our efforts on this subject.

In our previous work, when two hydroxy groups were introduced into the achiral 1,5-hexadiene skeleton, a simple chiral chain diene ligand **2** was successfully achieved, which suggests that other types of chiral dienes containing 1,5-hexadiene skeletons are also candidate ligands. We envisioned that introduction of imidazolidin-2-one backbones to 1,5-hexadiene may provide a good opportunity to develop novel diene ligands (**3**) for asymmetric catalysis (Scheme 1).[10] The combination of flexible terminal olefins and rigid imidazolidin-2-one frameworks in ligand **3** and how it might affect asymmetric induction is interesting. Therefore, building the chiral imidazolidin-2-one frameworks became one of the key points.



Scheme 3. One-step synthesis of acyclic chiral diene *via* Pd(0)-catalyzed asymmetric diamination of 1,5-hexadiene.

Recently, Shi's group successfully developed a novel diamination methodology,[11–13] which provides an efficient and powerful protocol for us to construct the chiral imidazolidin-2-one backones of diene ligands. As shown in Scheme 3, chiral diene (*S*,*S*)-**3a** can be synthesized in one step *via* Pd(0)-catalyzed asymmetric allylic and homoallylic C–H diamination of 1,5-hexadiene with di-*tert*-butyldiaziridinone (**7**) as the nitrogen source,[12d] and its X-ray structure is shown in Figure 1.[14] The *ee* of **3a** can be further improved to >99% after recrystallization from *n*-hexane. Chiral diene **3a** was then used as a ligand in the reaction of 2-cyclohexenone (**4**) and phenylboronic acid (**5**) with $[RhCl(C_2H_4)_2]_2$ (5 mol% Rh) as a catalyst precursor in dioxane/MeOH (v/v = 10/1), we were pleased to find that quantitative conversion and up to 85% *ee* can be achieved (Figure 2).

Encouraged by this result, further studies on modifications of **3a** were undertaken to look for more effective ligands. The *tert*-butyl groups of **3a** can be easily and cleanly removed by treating with trifluoroacetic acid (TFA) at 80 °C according to literature methods to afford **3b**,[12] subsequently, other substituents were introduced conveniently to give chiral dienes **3c–f** (Figure 2). When using different 1,5-dienes as starting materials, ligands **3g–i** containing one di- or tri-substituted double bond can also be prepared *via* asymmetric diamination.[12] Ligands **3a–i** were then investigated by subjecting them to Rh(I)-catalyzed 1,4-addition of phenylboronic acid (**5**) to 2-cyclohexenone (**4**) in dioxane/MeOH (v/v = 10/1) at 50 °C for 3 h, and all the results are summarized in Figure 2. It was found that most of chiral diene-modified Rh(I) catalysts can promote this reaction well to afford the desired products in 16 to >99% conversions and 6–85% *ee*s. Our studies showed that the substituents on nitrogen (**3a–f**) have an obvious impact on both reactivity and enantioselectivity. Ligands containing one disubstituted double bond led to poor conversions and *ee*s, while ligands bearing a trisubstituted double bond gave no desired product, presumably because of the steric bulkiness.[16] Overall, **3a** was found to be the best ligand to give both the highest conversion and enantioselectivity.

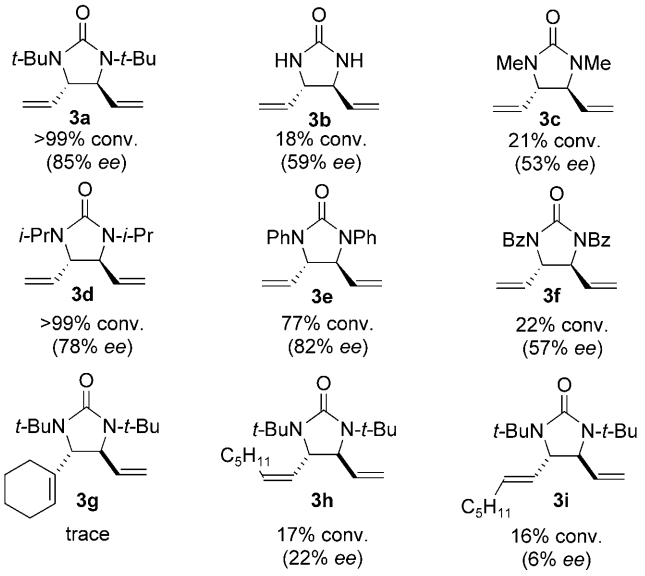


Figure 2. Rh(I)-catalyzed asymmetric 1,4-additions of phenylboronic acid (**5**) to 2-cyclohexenone (**4**) with selected chiral diene ligands **3**.[15]

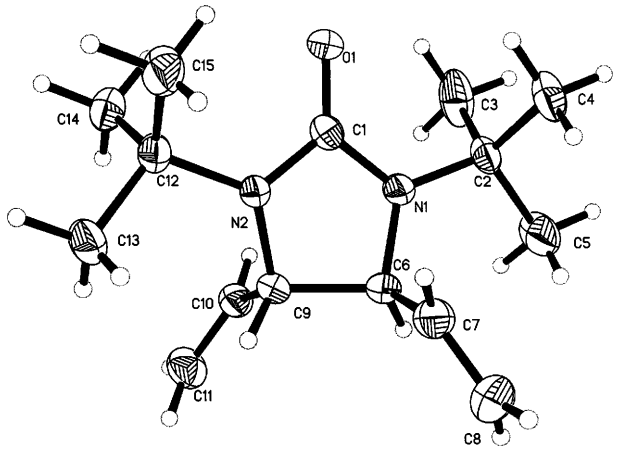
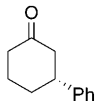
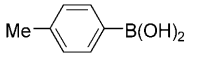
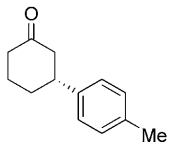
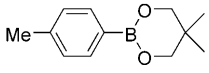
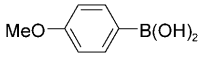
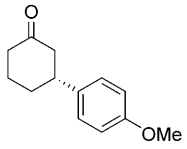
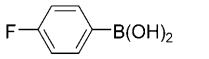
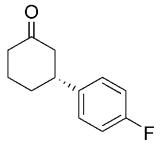
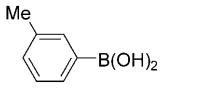
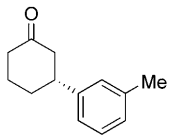
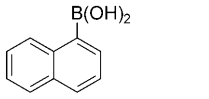
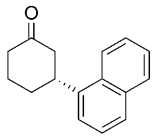
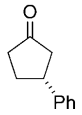
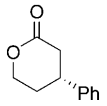


Figure 1. The X-ray structure of **3a**.

The substrate scope was further studied, and some of the results are summarized in Table 1. It was found that chiral diene **3a**-modified Rh catalysts can promote these reactions with moderate to excellent reactivities (51–99% yields) and moderate to good enantioselectivities (55–85% *ee*s) (Table 1, entries 1–9, 11). Addition of *meta*- or *para*-substituted arylboronic acids to 2-cyclohexenone (**4**) under the catalysis of Rh(I)/**3a** gave excellent yields and good *ee*s, and boronic acids with electron-donating groups displayed higher activities (Table 1, entries 4, 6, 8). 1-Naphthylboronic acid was also an effective substrate for this

Table 1. Rh(I)/**3a**-catalyzed asymmetric 1,4-additions.[a]

Entry	Substrate	Product[c]	Yield [%][d]	*ee* [%][e]
1	$PhB(OH)_2$		99	85
2	$(PhBO)_3$		93	75
3	$PhBF_3K$		51	80
4			96	80
5			87	76
6			98	85
7			56	84
8			96	78
9			88	55
10[b]	$PhB(OH)_2$		81	43
11	$PhB(OH)_2$		77	61

[a] All the reactions were carried out with organoboron reagent (0.30 mmol), unsaturated carbonyl compound (0.20 mmol), KOH (0.015 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol), **3a** (0.012 mmol) in dioxane/MeOH) (10/1, v/v, 0.66 mL) at 50 °C under argon for 3 h unless otherwise noted; for entry 2, the reaction was carried out with organoboron reagent (0.10 mmol).

[b] **3d** was used instead of **3a**.

[c] The absolute configuration was determined by comparing the optical rotation with the reported one.

[d] Isolated yield.

[e] The *ee* was determined by chiral HPLC (Chiralpak AD-H column) unless otherwise stated, Chiralcel OJ-H column for entry 9, Chiralcel OB-H column for entry 10, and Chiralcel AS-H column for entry 11.

reaction, but only resulted in relatively lower *ee* (Table 1, entry 9). The reactions between potassium phenyltrifluoroborate or boronate ester and 2-cyclohexenone (**4**) can proceed smoothly to afford the desired products in good yields and *ee*s (Table 1, entries 3 and 5). However, the reaction between 2-cyclopentenone and phenylboronic acid (**5**) under the catalysis of Rh(I)/**3d** only gave a moderate enantioselectivity (Table 1, entry 10).

In conclusion, an acyclic chiral diene **3a** prepared in only one step *via* Pd(0)-catalyzed asymmetric diamination was found to be highly effective for the Rh(I)-catalyzed asymmetric conjugated 1,4-additions, and encouraging results (up to 99% yield and 85% *ee*) have been successfully achieved. Although the efficiency, enantioselectivity, and substrate scope still await further improvement, the facile processes for synthesis and modification make acyclic chiral dienes a class of potentially intriguing ligands. Studies searching for more effective acyclic chiral dienes, elucidating detailed structures of diene-Rh complexes, and expanding the applications of acyclic chiral diene ligands in other types of metal-catalyzed asymmetric reactions are currently underway in our laboratory.

Experimental Section

Preparation of Chiral Diene 3a (Scheme 3)

Diene **3a** was prepared according to the literature method with slight modifications.[12d] Into a 10-mL round-bottom flask were charged with $Pd_2(dba)_3$ (0.4575 g, 0.5 mmol) and ligand **8** (1.02 g, 2.2 mmol). The flask was evacuated and then filled with argon before addition of benzene (1.5 mL, distilled from sodium). The resulting solution was then immersed into an oil bath (65 °C), and stirred for 10 min, followed by removal of solvents under vacuum at room temperature. To the resulting solid, 1,5-hexadiene (0.82 g, 1.19 mL, 10 mmol) was added, and the reaction mixture was immersed into an oil bath (65 °C) with stirring. Then di-*tert*-butyldiaziridinone (**7**) (4.25 g, 25 mmol) was added by syringe pump at a rate of 5.0 mmol h^{-1} for 5 h, and the mixture was stirred for additional 1 h. After being cooled to room temperature, the mixture was diluted with diethyl ether, and sequentially washed with 5% aqueous HCl, water, saturated brine, and dried over anhydrous Na_2SO_4. Then the solvent was removed and the residue was purified by flash chromatography (silica gel, hexanes: ethyl acetate = 20:1) to give the diamination product; further crystallization from *n*-hexane gave **3a** as a colorless crystal; yield: 1.625 g (65%); >99% *ee*; mp 51–52 °C; $[\alpha]_D^{20}$: −62.1 (*c* 0.72, $CHCl_3$). IR (film): $\nu = 1691\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.97$ (ddd, $J = 16.8$, 10.0, 8.4 Hz, 2H), 5.22 (d, $J = 16.8$ Hz, 2H), 5.13 (d, $J = 10.0$ Hz, 2H), 3.61 (d, $J = 8.4$ Hz, 2H), 1.34 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.4$, 139.7, 115.9 , 62.8, 53.3, 28.8.

Representative Procedure for 3a/Rh(I)-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid (5) to 2-Cyclohexenone (4) (Table 1, entry 1)

To a Schlenk flask charged with phenylboronic acid (**5**) (0.0366 g, 0.30 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0019 g, 0.005 mmol, 2.5 mol%), and chiral diene ligand **3a** (0.0030 g, 0.012 mmol, 6.0 mol%) was added degassed dioxane (0.60 mL) under argon. The resulting mixture was heated to 50 °C and stirred for 15 min, followed by addition of 2-cyclohexenone (**4**) (0.0192 g, 0.20 mmol) and KOH in MeOH (0.015 mmol, 0.25 M, 0.060 mL). The reaction mixture was stirred at 50 °C for 3 h, solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexanes: ethyl acetate = 5:1, v/v) to give the desired product *ent*-**6** as a pale yellow oil; yield: 0.0345 g (99%); 85% *ee*; $[\alpha]_D^{20}$: +16.8 (*c* 0.90, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ (t, $J = 7.8$ Hz, 2H), 7.21–7.26 (m, 3H), 2.98–3.04 (m, 1H), 2.35–2.63 (m, 4H), 2.07–2.18 (m, 2H), 1.75–1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.0$, 144.4, 128.7, 126.7, 126.6, 49.0, 44.8, 41.2, 32.8, 25.5.

Acknowledgements

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References

[1] a) *Asymmetric Catalysis in Organic Synthesis*, (Ed.: R. Noyori), Wiley, New York, **1994**; b) *Comprehensive Asymmetric Catalysis*, Vols 1–3, (Eds: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; c) *Catalytic Asymmetric Synthesis*, (Ed.: I. Ojima), Wiley-VCH, New York, **2000**.

[2] For reviews on chiral diene ligands, see: a) F. Glorius, *Angew. Chem.* **2004**, *116*, 3444; *Angew. Chem. Int. Ed.* **2004**, *43*, 3364; b) C. Defieber, H. Grützmacher, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4558; *Angew. Chem. Int. Ed.* **2008**, *47*, 4482.

[3] For leading references on diene ligands developed by Hayashi's group, see: a) T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508; b) R. Shintani, K. Ueyama, I. Yamada, T. Hayashi, *Org. Lett.* **2004**, *6*, 3425; c) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13584; d) R. Shintani, K. Okamoto, Y. Otomaru, K. Ueyama, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 54; e) Y. Otomaru, N. Tokunaga, R. Shintani, T. Hayashi, *Org. Lett.* **2005**, *7*, 307; f) R. Shintani, Y. Sannohe, T. Tsuji, T. Hayashi, *Angew. Chem.* **2007**, *119*, 7415; *Angew. Chem. Int. Ed.* **2007**, *46*, 7277; g) R. Shintani, Y. Ichikawa, K. Takatsu, F.-X. Chen, T. Hayashi, *J. Org. Chem.* **2009**, *74*, 869; h) R. Shintani, Y. Tsutsumi, M. Nagaosa, T. Nishimura, T. Hayashi, *J. Am. Chem. Soc.* **2009**, *131*, 13588.

[4] For leading references on diene ligands developed by Carreira's group, see: a) C. Fisher, C. Defieber, T. Suzuki, E. M. Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 1628; b) C. Defieber, J.-F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.* **2004**, *6*, 3873; c) J.-F. Paquin, C. R. J. Steptenson, C. Defieber, E. M. Carreira, *Org. Lett.* **2005**, *7*, 381.

[5] For leading references on diene ligands developed by Lin's group, see: a) Z.-Q. Wang, C.-G. Feng, M.-H. Xu, G.-Q. Lin, *J. Am. Chem. Soc.* **2007**, *129*, 5336; b) C.-G. Feng, Z.-Q. Wang, C. Shao, M.-H. Xu, G.-Q. Lin, *Org. Lett.* **2008**, *10*, 4101; c) C.-G. Feng, Z.-Q. Wang, P. Tian, M.-H. Xu, G.-Q. Lin, *Chem. Asian J.* **2008**, *3*, 1511.

[6] For recent examples of chiral diene ligands, see: a) K. Alkawa, A. Akutagawa, K. Mikami, *J. Am. Chem. Soc.* **2006**, *128*, 12648; b) S. Helbig, S. Sauer, N. Cramer, S. Laschat, A. Baro, W. Frey, *Adv. Synth. Catal.* **2007**, *349*, 2331; c) T. Gendrineau, O. Chuzel, H. Eijsberg, J.-P. Genet, S. Darses, *Angew. Chem.* **2008**, *120*, 7783; *Angew. Chem. Int. Ed.* **2008**, *47*, 7669; d) T. Gendrineau, J.-P. Genet, S. Darses, *Org. Lett.* **2009**, *11*, 3486.

[7] For leading reviews on Rh-catalyzed asymmetric conjugated additions, see: a) T. Hayashi, K. Yamashaki, *Chem. Rev.* **2003**, *103*, 2829; b) C. Gennari, C. Monti, U. Piarulli, *Pure Appl. Chem.* **2006**, *78*, 303; c) J. Christoffers, G. Koripelly, A. Rosoak, M. Rössle, *Synthesis* **2007**, 1279.

[8] X. Hu, M. Zhuang, Z. Cao, H. Du, *Org. Lett.* **2009**, *11*, 4744.

[9] For references on the formation of metal complexes with natural chiral dienes (one terminal double bond involved), see: a) B. D. G. Johnson, J. Lewis, D. J. Yarrow, *J. Chem. Soc. Dalton Trans.* **1974**, 1054; b) W. Winter, B. Koppenhöfer, V. Schurig, *J. Organomet. Chem.* **1978**, *150*, 145; c) L. A. Oro, *J. Less-Common Met.* **1977**, *53*, 289.

[10] For leading references on chiral ligands bearing imidazolidin-2-one backbones, see: a) S. Lee, Y. Zhang, C. Song, J. Lee, J. Choi, *Angew. Chem.* **2002**, *114*, 875; *Angew. Chem. Int. Ed.* **2002**, *41*, 847; b) Y. Liu, K. Ding, *J. Am. Chem. Soc.* **2005**, *127*, 10488; c) Y. Liu, C. A. Sandoval, Y. Yamaguchi, X. Zhang, Z. Wang, K. Kato, K. Ding, *J. Am. Chem. Soc.* **2006**, *128*, 14212.

[11] For leading reviews on diamination, see: a) D. Lucet, T. L. Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580; b) M. S. Mortensen, G. A. O'Doherty, *Chemtracts: Org. Chem.* **2005**, *18*, 555; c) S. R. S. S. Kotti, C. Timmons, G. Li, *Chem. Biol. Drug Des.* **2006**, *67*, 101; d) R. M. de Figueiredo, *Angew. Chem.* **2009**, *121*, 1212; *Angew. Chem. Int. Ed.* **2009**, *48*, 1190; e) F. Cardona, A. Goti, *Nat. Chem.* **2009**, *1*, 269.

[12] For leading references on Pd(0)-catalyzed diaminations, see: a) H. Du, B. Zhao; Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 762; b) H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7496; c) H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 11688; d) H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 8590.

[13] For leading references on Cu(I)-catalyzed diaminations, see: a) W. Yuan, H. Du, B. Zhao, Y. Shi, *Org. Lett.* **2007**, *9*, 2589; b) H. Du, B. Zhao, W. Yuan, Y. Shi, *Org. Lett.* **2008**, *10*, 4231.

[14] For the crystal structures of **3a**, see Supporting Information. The absolute configuration of **3a** was determined to be *S*,*S* judged by its derivative containing one bromine atom. CCDC 749930 (**3a**) and CCDC 755622 (derivative of **3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[15] All the reactions were carried out with 2-cyclohexenone (**4**) (0.20 mmol), phenylboronic acid (**5**) (0.30 mmol), KOH (0.015 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol), diene ligand (0.012 mmol) in dioxane/MeOH (10/1, v/v, 0.66 mL) at 50 °C under argon for 3 h.

[16] Ligands **3g–i** were used directly as obtained *via* asymmetric diamination without recrystallization.

