DOI: 10.1002/adsc.200600632

Asymmetric 1,4-Addition of Organoboron Reagents to Quinone Monoketals Catalyzed by a Chiral Diene/Rhodium Complex: A New Synthetic Route to Enantioenriched 2-Aryltetralones

Norihito Tokunaga[a] and Tamio Hayashi[a,*]

[a] Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan
Fax: (+81)-75-753-3988; e-mail: thayashi@kuchem.kyoto-u.ac.jp

Received: December 11, 2006

Dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A novel synthetic approach to 2-aryltetralones with high *ee* has been developed through asymmetric 1,4-addition of arylboronic acids to naphthoquinone monoketals catalyzed by a rhodium complex with the (*R,R*)-Ph-bod* ligand. The asymmetric addition proceeded in high yields with excellent enantioselectivity.

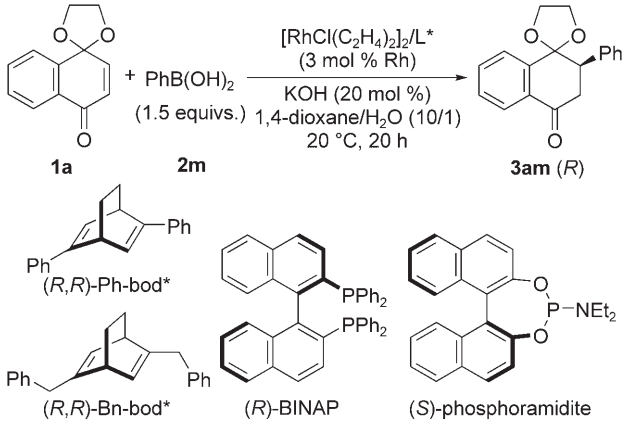
Keywords: asymmetric catalysis; boron; chiral diene ligands; conjugate addition; quinone monoketals; rhodium

Enantiomerically pure carbonyl compounds bearing aryl or alkenyl groups at the α position to the carbonyl moiety, which are represented by the 2-aryltetralones, constitute key intermediates to biologically important compounds.[1] Although their preparation using a stoichiometric amount of chiral reagents has been reported,[1,2] their catalytic asymmetric synthesis has not been well developed. The palladium- or nickel-catalyzed asymmetric α-arylation[3] and α-alkenylation[4] of carbonyl compounds provides an efficient method for the synthesis of chiral ketones substituted with quaternary stereogenic centers, but their application to the asymmetric synthesis of products containing hydrogen at the chiral carbon should present a problem due to the difficulty in keeping the stereogenic character of the chiral carbon center bound to an acidic hydrogen under basic conditions at a high reaction temperature. Another important method of providing α-chiral ketones is the catalytic asymmetric protonation of enolates,[5–7] but the asymmetric synthesis at the stage of carbon-carbon bond formation is more desirable. Our approach is to apply the rhodium-catalyzed asymmetric 1,4-addition[8,9] to the asymmetric synthesis of α-aryl ketones. Herein we report that the asymmetric 1,4-addition of aryl- and alkenylboron reagents to quinone monoketals[10] is efficiently catalyzed by a chiral diene/rhodium complex[11–14] and one of the enantioenriched addition products (96–99% *ee*) is readily converted into a 2-aryltetralone without loss of enantiomeric purity.

Naphthoquinone monoketal **1a**, which is readily accessible from 1-naphthol by oxidation with $PhI(OAc)_2$ in ethylene glycol,[15] was allowed to react with $PhB(OH)_2$ (**2m**) in the presence of rhodium catalysts coordinated with some of the chiral ligands which have been reported to be effective for rhodium-catalyzed asymmetric 1,4-addition reactions[8,9] (Table 1). The best result was obtained with chiral diene ligand (*R,R*)-2,5-diphenylbicyclo[2.2.2]bicycloocta-2,5-diene (Ph-bod*).[11] Thus, a rhodium complex generated from $[RhCl(C_2H_4)_2]_2$ (3 mol% Rh) and (*R,R*)-Ph-bod* (1.1 equivs. to Rh) catalyzed the reaction in 1,4-dioxane/H_2O (10/1) at 20°C to give a 98% yield of the phenylation product **3am** which is 98% enantiomerically pure (entry 1). Another chiral diene ligand, (*R,R*)-Bn-bod*,[12] which is the dibenzyl analogue of (*R,R*)-Ph-bod*, was not as effective (entry 2). The chemical yield and enantioselectivity were lower in the reaction with phosphine-based ligands, (*R*)-BINAP[16] and (*S*)-phosphoramidite[17] (entries 3 and 4).

Under similar reaction conditions using (*R,R*)-Ph-bod* as a ligand, various aryl groups were introduced onto naphthoquinone monoketal **1a** in high yields with excellent enantioselectivity (96–99% *ee*) (Table 2). The presence of electron-withdrawing or -donating groups on the aryl group (**2n–s**) did not disturb the high efficiency of the present asymmetric 1,4-addition (entries 2–7). The enantioselectivity was kept high in the addition of sterically demanding *o*-tolyl (**2t**), 2-naphthyl (**2u**), and 3-thienyl (**2v**) groups (en-

Table 1. Rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acid (**2m**) to monoketal **1a**.[a]



Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	(*R*,*R*)-Ph-bod*	98	98 (*R*)
2	(*R*,*R*)-Bn-bod*	91	87 (*R*)
3	(*R*)-BINAP	68	92 (*R*)
4	(*S*)-phosphoramidite	35	33 (*S*)

[a] The reaction was carried out with 0.10 mmol of **1a** and 0.15 mmol of **2m** in 1,4-dioxane/H_2O (10/1) at 20 °C for 20 h in the presence of $[RhCl(C_2H_4)_2]_2$ (3 mol % Rh), ligand [3.3 mol % of chiral diene ligands and (*R*)-BINAP; 6.6 mol % of (*S*)-phosphoramidite], and KOH (20 mol %).

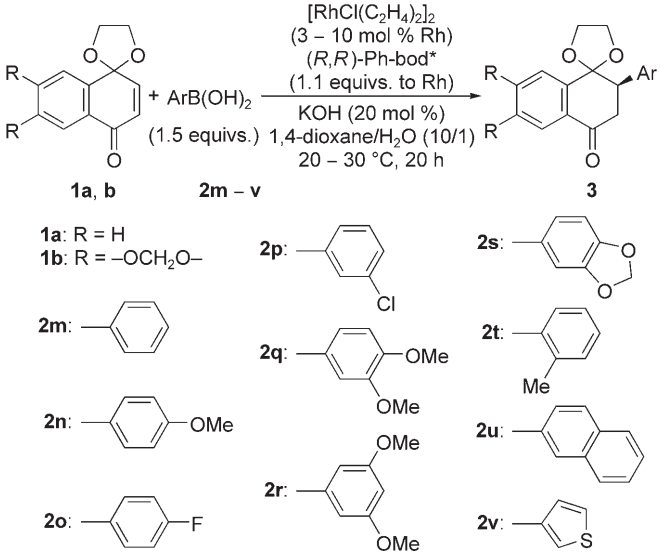
[b] Isolated yields purified by preparative thin-layer chromatography on silica gel (eluent: *n*-hexane/ethyl acetate = 2/1).

[c] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD-H, eluent: *n*-hexane/2-propanol = 90/10).

tries 8–10). The addition to monoketal **1b** which is substituted with a methylenedioxy group on naphthoquinone is slower, but the reaction was completed within 20 h by use of 10 mol % of the rhodium catalyst (entry 11). It is remarkable that the addition to monoketals **1** containing the bulky ethylene ketal moiety in close proximity to the reacting β-position of the enone takes place in high yields under mild conditions by use of the chiral diene/rhodium catalyst. The absolute configurations of these arylation products were assigned as (*R*) by correlation of compound **3bq** with a 2-aryltetralone derivative (*vide infra*).

Asymmetric alkenylation of the monoketal **1a** also proceeded with high enantioselectivity by use of alkenylboron reagents and the Rh/(*R*,*R*)-Ph-bod* as a catalyst to give the corresponding 1,4-adducts **5** of 96–99 % *ee* (Scheme 1). For the introduction of the unsubstituted vinyl group, potassium vinyltrifluoroborate[18](**4n**) was used conveniently. Dihydroquinone monoketal **1c**[19] is another good substrate which undergoes the asymmetric 1,4-addition of arylboronic acids **2m–o** with high enantioselectivity (96–98 % *ee*),

Table 2. Asymmetric 1,4-addition of arylboronic acids **2** to naphthoquinone monoketals **1** catalyzed by Rh/(*R*,*R*)-Ph-bod*.[a]



Entry	1	2	Yield [%][b]	*ee* [%][c]
1[d]	**1a**	**2m**	98 (**3am**)	98 (*R*)
2[d]	**1a**	**2n**	94 (**3an**)	99 (*R*)
3[e]	**1a**	**2o**	93 (**3ao**)	98 (*R*)
4[f]	**1a**	**2p**	95 (**3ap**)	99 (*R*)
5[e]	**1a**	**2q**	94 (**3aq**)	98 (*R*)
6[e]	**1a**	**2r**	86 (**3ar**)	97 (*R*)
7[e]	**1a**	**2s**	95 (**3as**)	96 (*R*)
8[g]	**1a**	**2t**	96 (**3at**)	99 (*R*)
9[f]	**1a**	**2u**	97 (**3au**)	98 (*R*)
10[e]	**1a**	**2v**	87 (**3av**)	98 (*R*)
11[h]	**1b**	**2q**	95 (**3bq**)	98 (*R*)

[a] The reaction was carried out with 0.30 mmol of **1** and 0.45 mmol of **2** in 1,4-dioxane/H_2O (10/1) for 20 h in the presence of $[RhCl(C_2H_4)_2]_2$/(*R*,*R*)-Ph-bod* (1.1 equivs. of Rh) complex and KOH (20 mol %).

[b] Isolated yields purified by preparative thin-layer chromatography on silica gel (eluent: *n*-hexane/ethyl acetate).

[c] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD-H).

[d] With 3 mol % Rh at 20 °C.

[e] With 6 mol % Rh at 30 °C.

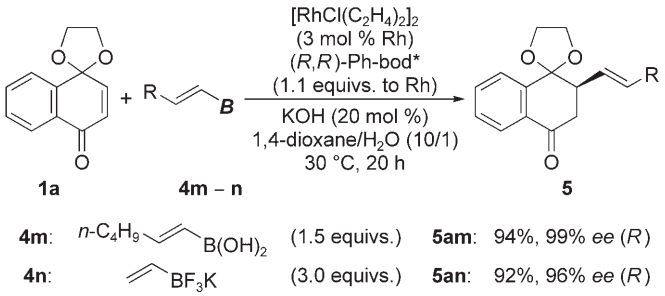
[f] With 6 mol % Rh at 20 °C.

[g] With 3 mol % Rh at 30 °C.

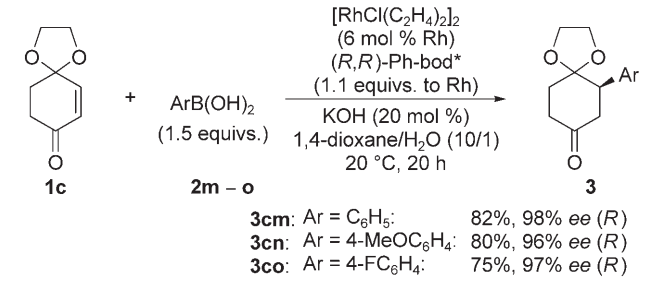
[h] With 10 mol % Rh at 20 °C.

although the chemical yields are a little lower (Scheme 2).

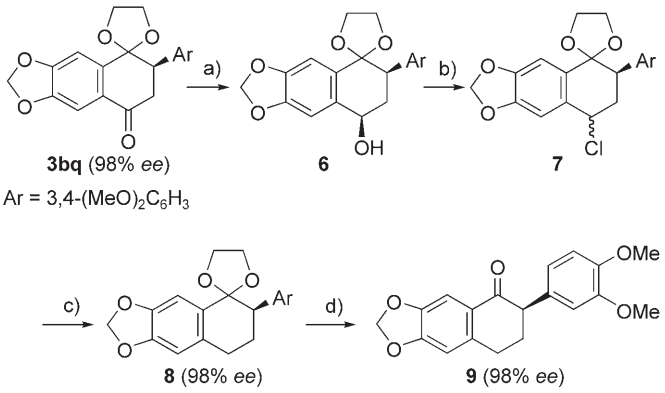
The asymmetric arylation products obtained here from naphthoquinone monoketals by the rhodium-catalyzed asymmetric 1,4-addition can be converted into 2-aryltetralones without loss of the enantiomeric purity. As an example, the synthesis of chiral ketone **9**,[1] which is a key intermediate to hexahydrobenzo[*c*]benzophenanthridine alkaloids, is shown in Scheme 3. Reduction of ketone **3bq** (98 % *ee*, Table 2,



Scheme 1. Asymmetric 1,4-addition of alkenylborons **4** to monoketal **1a** catalyzed by Rh/(*R*,*R*)-Ph-bod*.



Scheme 2. Asymmetric 1,4-addition of arylboronic acids **2** to dihydrobenzoquinone monoketal **1c**.



Scheme 3. Transformation of **3bq** to 2-aryltetralone **9**. a) $LiAlH_4$, THF, 0 °C, 1 h, 94 %; b) *n*-BuLi, THF, 0 °C, 0.5 h; then TsCl, 0 °C to room temperature, 12 h; c) $NaBHEt_3$, toluene, 0 °C to room temperature, 2.5 h, 61 % (2 steps), 98 % *ee*; d) 10 % aqueous HCl, MeOH, −15 °C, 1 h, 81 %, 98 % *ee*.

entry 11) with $LiAlH_4$ in THF at 0 °C gave the *cis*-hydroxy ketal **6** (94 % yield) as a single isomer. A crude mixture of chloride **7**, which was obtained by treatment of **6** with *n*-BuLi in THF at 0 °C followed by addition of *p*-toluenesulfonyl chloride, was subjected to the reduction with $NaBHEt_3$ in toluene to give a 61 % yield of ketal **8**. Deprotection of the ketal in **8** with 10 % HCl in methanol at −15 °C for 1 h provided an 81 % yield of the α-aryl ketone **9** which is 98 % *ee*. In this acidic deprotection, the low reaction temperature

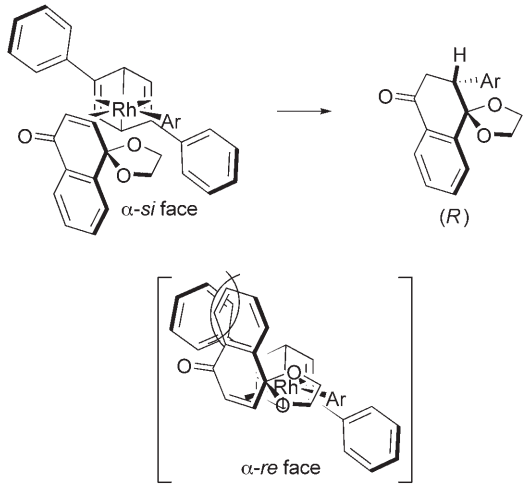


Figure 1. Enantioselection in the rhodium-catalyzed asymmetric 1,4-addition.

is important to prevent the reaction from racemization (85 % *ee* at 28 °C and 92 % *ee* at 0 °C). The absolute configuration of **9** was determined to be (*R*) by correlation with (*S*)-**9**,[1] indicating that the 1,4-addition product **3bq** obtained with (*R*,*R*)-Ph-bod* has the (*R*) configuration.

The (*R*) configuration of the 1,4-addition product **3** obtained with (*R*,*R*)-Ph-bod* is consistent with the steric features of the Rh/(*R*,*R*)-Ph-bod* complex (Figure 1).[20] The coordination of the carbon-carbon double bond on monoketal **1** with its α-*si* face is much more favorable than that with its α-*re* face due to the steric repulsions caused by one of the phenyl rings of the chiral diene ligand.

In summary, we found that the asymmetric 1,4-addition of arylboronic acids to naphthoquinone monoketals proceeds with high enantioselectivity by use of a Rh/(*R*,*R*)-Ph-bod* complex as a catalyst. The reaction provides a new efficient synthetic route to enantiomerically enriched α-arylated tetralones, which are valuable chiral building blocks for the synthesis of biologically active compounds.

Experimental Section

Typical Procedure

To a solution of $[RhCl(C_2H_4)_2]_2$ (1.8 mg, 0.0045 mmol, 3 mol % Rh) and (*R*,*R*)-Ph-bod* (2.6 mg, 0.0099 mmol, 1.1 equivs. to Rh) in 1,4-dioxane (0.60 mL) was added aqueous KOH (30 μL, 2.0 M, 20 mol % KOH) at room temperature and the mixture was stirred for 5 min. Monoketal **1a** (60.2 mg, 0.30 mmol) and $PhB(OH)_2$ (**2m**) (55.3 mg, 0.45 mmol, 1.5 equivs. to **1a**) were added to this catalyst solution with 1,4-dioxane (1.5 mL) and H_2O (0.18 mL) at room temperature. After 20 h stirring at 20 °C, water was added, the mixture was extracted with Et_2O, and the ex-

tracts were dried over $MgSO_4$. Evaporation of the solvent followed by preparative thin-layer chromatography on silica gel (eluent: *n*-hexane/ethyl acetate = 2/1) gave **3am** as a white solid; yield: 79.9 mg (0.29 mmol, 96%). The enantiomeric excess of **3am** was determined to be 98% *ee* on a Chiralpak AD-H column (eluent: *n*-hexane/2-propanol = 90/10).

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science, and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry). N.T. thanks the Japan Society for Promotion of Science for the award a fellowship for graduate students.

References

[1] For example, see: J. L. Vicario, D. Badía, E. Domínguez, L. Carrillo, *Tetrahedron: Asymmetry* **2000**, *11*, 1227.
[2] V. K. Aggarwal, B. Olofsson, *Angew. Chem.* **2005**, *117*, 5652; *Angew. Chem. Int. Ed.* **2005**, *44*, 5516.
[3] For palladium-catalyzed reaction, see: a) J. Åhman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 1918; b) T. Hamada, A. Chieffi, J. Åhman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261; nickel-catalyzed reaction: c) D. J. Spielvogel, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 3500.
[4] A. Chieffi, K. Kamikawa, J. Åhman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897.
[5] For reviews, see: a) L. Duhamel, P. Duhamel, J.-C. Plaquevent, *Tetrahedron: Asymmetry* **2004**, *15*, 3653; b) J. Eames, N. Weerasooriya, *Tetrahedron: Asymmetry* **2001**, *12*, 1; c) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; d) C. Fehr, *Angew. Chem.* **1996**, *108*, 2726; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566; e) A. Yanagisawa, H. Yamamoto, in: *Comprehensive Asymmetric Catalysis*, Vol. III, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, p 1295; f) A. Yanagisawa, in: *Comprehensive Asymmetric Catalysis,* Suppl. 2, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **2004**, p. 125.
[6] For a recent example of catalytic asymmetric protonation of silyl enol ethers, see: A. Yanagisawa, T. Touge, T. Arai, *Angew. Chem.* **2005**, *111*, 3916; *Angew. Chem. Int. Ed.* **2005**, *44*, 1546.
[7] For a palladium-catalyzed asymmetric decarboxylative protonation: J. T. Mohr, T. Nishimata, D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 11348.
[8] For reviews, see: a) T. Hayashi, *Synlett* **2001**, 879; b) C. Bolm, J. P. Hildebrand, K. Muñiz, N. Hermanns, *Angew. Chem.* **2001**, *113*, 3382; *Angew. Chem. Int. Ed.* **2001**, *40*, 3284; c) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169; d) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; e) T. Hayashi, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13.
[9] a) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579; b) T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052.
[10] For examples of catalytic asymmetric 1,4-addition to quinone monoketals, see: by copper catalyst: a) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem.* **1997**, *109*, 2733; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620; b) R. Imbos, M. H. G. Brilman, M. Pineschi, B. L. Feringa, *Org. Lett.* **1999**, *1*, 623; by organocatalyst: c) T. Ooi, S. Takada, S. Fujioka, K. Maruoka, *Org. Lett.* **2005**, *7*, 5143.
[11] a) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13584; b) Y. Otomaru, K. Okamoto, R. Shintani, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 2503; c) R. Shintani, T. Kimura, T. Hayashi, *Chem. Commun.* **2005**, 3213; d) R. Shintani, K. Okamoto, T. Hayashi, *Chem. Lett.* **2005**, 1294; e) R. Shintani, K. Okamoto, T. Hayashi, *Org. Lett.* **2005**, *7*, 4757; f) T. Nishimura, Y. Yasuhara, T. Hayashi, *Org. Lett.* **2006**, *8*, 979.
[12] a) R. Shintani, K. Okamoto, Y. Otomaru, K. Ueyama, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 54; b) R. Shintani, A. Tsurusaki, K. Okamoto, T. Hayashi, *Angew. Chem.* **2005**, *117*, 3977; *Angew. Chem. Int. Ed.* **2005**, *44*, 3909; c) T. Hayashi, N. Tokunaga, K. Okamoto, R. Shintani, *Chem. Lett.* **2005**, 1480; d) F.-X. Chen, A. Kina, T. Hayashi, *Org. Lett.* **2006**, *8*, 341.
[13] a) T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508; b) Y. Otomaru, N. Tokunaga, R. Shintani, T. Hayashi, *Org. Lett.* **2005**, *7*, 307; c) Y. Otomaru, A. Kina, R. Shintani, T. Hayashi, *Tetrahedron: Asymmetry* **2005**, *16*, 1673; d) A. Kina, K. Ueyama, T. Hayashi, *Org. Lett.* **2005**, *7*, 5889; e) G. Berthon-Gelloz, T. Hayashi, *J. Org. Chem.* **2006**, *71*, 8957.
[14] a) C. Fischer, 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. Defieber, C. R. J. Stephenson, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 10850; d) J.-F. Paquin, C. R. J. Stephenson, C. Defieber, E. M. Carreira, *Org. Lett.* **2005**, *7*, 3821; e) F. Läng, F. Breher, D. Stein, H. Grützmacher, *Organometallics* **2005**, *24*, 2997; f) M. A. Grundl, J. J. Kennedy-Smith, D. Trauner, *Organometallics* **2005**, *24*, 2831.
[15] F. Farina, M. C. del Paredes, J. J. Soto, *An. Quim.* **1995**, *91*, 50.
[16] H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, R. Noyori, *J. Org. Chem.* **1986**, *51*, 629.
[17] J.-G. Boiteau, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2003**, *68*, 9481.
[18] G. A. Molander, M. R. Rivero, *Org. Lett.* **2002**, *4*, 107.
[19] R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn, D. Zheng, *Tetrahedron Lett.* **1995**, *36*, 2423.
[20] For the structure of a Rh/(*R*,*R*)-Ph-bod* complex: see Ref.[11b]

