High Efficiency and Enantioselectivity in the Rh-Catalyzed Conjugate Addition of Arylboronic Acids Using Monodentate Phosphoramidites

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Abstract: A very fast reaction and enantioselectivities >98% have been reached in the rhodium-catalyzed arylboronic acid addition to enones using a monodentate phosphoramidite ligand. Temperature-dependent studies show that monodentate phosphoramidites form stable complexes with metals and can induce high enantioselectivities even at high temperatures in polar solvents.

Enantioselective 1,4-additions of organometallic reagents to enones hold a prominent position in our repertoire to assemble carbon−carbon bonds in organic chemistry.[1] Following the introduction of chiral phosphoramidite ligands for the copper-catalyzed conjugate addition of dialkylzinc reagents,[2] which showed excellent enantioselectivities, numerous chiral catalysts have been introduced in recent years for this asymmetric reaction.[3]

These methods are, however, limited to aliphatic dialkylzinc reagents although a variety of functional groups are tolerated. A prominent example is the copper-catalyzed conjugate addition of an ester-functionalized organozinc reagent to a cyclopentenone as applied in the short asymmetric synthesis of prostaglandin PGE₁.[4] So far, the use of aryl- or alkenylzinc reagents in the copper-catalyzed conjugate addition has met with limited success.[5]

Hayashi and Miyaura have reported the rhodium-catalyzed conjugate addition of boronic acids as the method of choice to introduce aryl or alkenyl moieties to enones,[6] and high enantioselectivities with a broad scope

SCHEME 1. Rhodium-Catalyzed Conjugate Addition of Phenylboronic Acid to Cyclohexenone
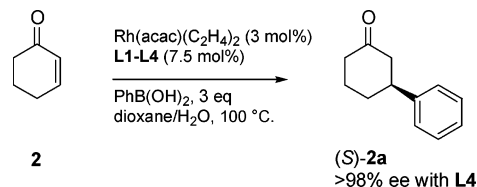
of substrates have been obtained. The chiral ligands employed in this reaction are bidentate in nature; most frequently, BINAP is used although binol-based diphosphonites,[7] and amidomonophosphines,[8] are also successful.[9]

Recently, we showed that simple monodentate phosphoramidites can be used as ligands in the rhodium-catalyzed asymmetric conjugate addition of boronic acids.[10] This was confirmed in a communication by Miyaura and co-workers.[11] Compared to bis-phosphines, phosphoramidites are simple, readily accessible, and easily tunable ligands. The amine part as well as the diol part can be extensively modified due to the molecular structure of these ligands. Despite the rather drastic conditions (dioxane, water, 100 °C for 5 h), the rhodium-bound phosphoramidite is remarkably stable.[10] In an attempt to improve the observed enantioselectivity, we examined phosphoramidites **L1**−**L4** in the rhodium-catalyzed conjugate addition of phenylboronic acid **1a** to cyclohexenone **2** (Scheme 1 and Table 1, entries 1−4).

We were pleased to find that ligand **L4** showed very high enantioselectivity, and (*S*)-3-phenylcyclohexanone (*S*)-**2a** was obtained quantitatively with an ee > 98%! To extend the scope of this reaction, we tested phosphoramidite **L4** using several substrates and arylboronic acids (Table 1, Scheme 2, entries 5−11). In most cases, full conversion was achieved within 5 h at 100 °C, and high levels of enantioselectivity (85 to >98% ee) were reached.[12] These results clearly show that the catalyst based on phosphoramidite **L4** is more enantioselective than the catalysts based on phosphoramidites **L1**−**L3** used in the screening.[13]

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(1) Tomioka, K. Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 1999; Vol. 3; Chapter 31.1.

(2) (a) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374. (b) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 927. (c) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999,** *121*, 1104. (d) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2001**, 735. (e) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 930.

(3) For reviews, see: (a) Krause N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186. (b) Krause N. *Angew. Chem., Int. Ed.* **1998**, *37*, 283. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Leggy, A. L. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; Chapter 7, p 224. (d) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.

(4) (a) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841. (b) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2002**, *67*, 7244.

(5) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259.

(6) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Hayashi, T. *Synlett* **2001**, 879. (c) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (d) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. (e) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (f) Sakuma, S.; Sakai, M.; Itooka, R.; Hayashi, T. *J. Org. Chem.* **2000**, *65*, 5951. (g) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852. (h) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716. (i) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052. (J) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944−8946.

(7) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083.

(8) (a) Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921. (b) Kuriyama, M.; Nagai, K.; Yamada, K.-I.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932.

(9) For a review on rhodium-catalyzed carbon−carbon bond-forming reactions of organometallic compounds, see: Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(10) Boiteau, J. G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681 and 1385.

(11) Iguchi, Y.; Itooka, R.; Miyaura N. *Synlett* **2003**, *7*, 1040.

(12) The reaction time of 5 h as well as the use of 3 equiv of boronic acid was chosen as a standard protocol.

TABLE 1. Asymmetric Conjugate Addition of Boronic Acids to Enones[a]

entry	enone	R(BOH)$_2$	L	conv[b] (%)	ee[c] (%)
1	**2**	**1a**	**L1**	100	84
2	**2**	**1a**	**L2**	100	94
3	**2**	**1a**	**L3**	100	89
4	**2**	**1a**	**L4**	100	>98
5	**3**	**1a**	**L4**	100	85
6	**4**	**1a**	**L4**	95	96
7	**5**	**1a**	**L4**	100	87
8	**2**	**1b**	**L4**	60	95
9	**2**	**1c**	**L4**	100	98
10	**2**	**1d**	**L4**	100	96
11	**2**	**1e**	**L4**	100	98

[a] Reactions performed in dioxane/water at 100 °C, with 3 equiv of boronic acid on 0.4 mmol scale and a loading of 3 mol % catalyst. Ratio Rh/**L**: 1/2.5. [b] Conversions are determined by ^{1}H NMR. [c] Ee's are determined by chiral HPLC, on a DAICEL AD column.

SCHEME 2. Structure of the Substrates, Ligands, and Boronic Acids Used in the Rh-Catalyzed Conjugate Addition
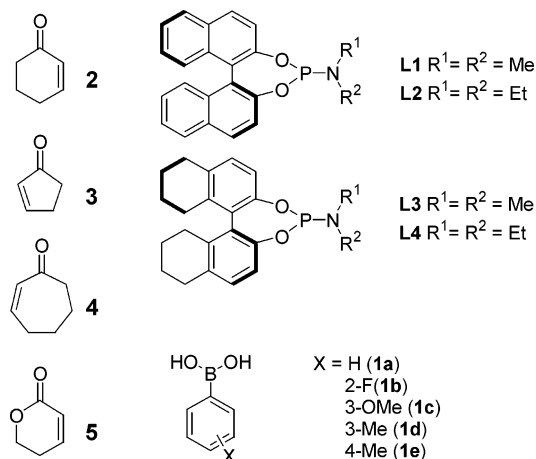
To investigate the activity and robustness of our new catalytic system, the addition of phenylboronic acid **1a** to cyclohexenone **2** was performed with a loading of 0.05 mol % of rhodium (ratio Rh/**L**: 1/2.5), which resulted in full conversion and ee of >98% within 2 h at 80 °C. This means a turnover number (TON) for this catalyst of 2000 which is remarkable for an asymmetric carbon−carbon bond-forming reaction. In addition, a comparison of phosphoramidite **L4** versus BINAP under the same conditions was made. With **L4** as a ligand using 1 mol % of catalyst, >99% conversion was reached within 5 min at 100 °C which corresponds to an initial turnover frequency (TOF) of 2500 h^{-1} (initial TOF = 110 h^{-1} for BINAP).[14] The conversion against time for the two ligands is depicted in Figure 1. In both cases, high levels of enantioselectivity (97−98%) are obtained but the rate of the reaction using phosphoramidite **L4** as a ligand is dramatically larger.

(13) Using different reaction conditions, Miyaura et al. obtained the highest ee using **L2** as the ligand; see ref 11.

(14) With BINAP, the rhodium-catalyzed conjugate addition requires 5 h to achieve complete conversion under these conditions. After completion of this study, it was published that using modified conditions, the reaction can be performed using the BINAP-based Rh catalyst in 6 h at 25 °C; see: Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.
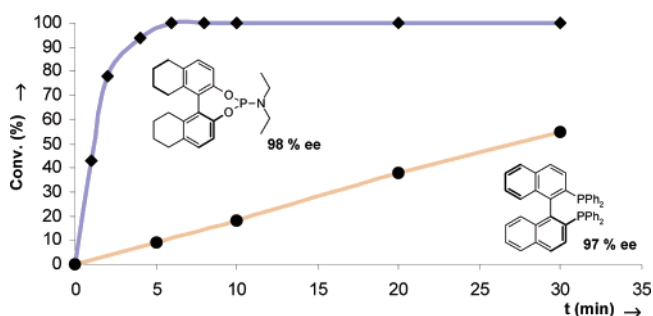
FIGURE 1. Comparison of ligands L4 and BINAP. Reactions performed in 1,4-dioxane/water = 10/1 at 100 °C, on 2 mmol scale with a loading of 1 mol % of catalyst.

TABLE 2. Effect of the Temperature on the Asymmetric Addition of Phenylboronic Acid to Cyclohexenone 2 Using L4 as ligand[a]

entry	T (°C)	conv[b] (%)	ee[c] (%)	ln k_S/k_R
1	45	100	99.1	5.39
2	60	100	98.7	5.04
3	70	100	98.8	5.17
4	80	100	98.5	4.93
5	100	100	98.3	4.71
6	110	100	98.2	4.68
7	120	100	98.4	4.81
8	130	100	96.1	3.93
9	140	100	94.2	3.51

[a] All reactions were performed on 0.4 mmol scale, using 3 mol % of rhodium catalyst and 1,4-dioxane as a solvent. [b] Conversions are determined by ^{1}H NMR. [c] Ee's are determined by chiral HPLC on a DAICEL AD column. Ee's and ln k_S/k_R values are the average of two runs. See the Supporting Information.

These exciting results showing fast catalytic conversion at 100 °C initiated several experiments at lower temperatures. Surprisingly, the ee found for (*S*)-**2a** was only improved marginally when the reaction was performed at 45 °C (Table 2).

This intriguing insensitivity of the ee toward the temperature incited us to run some reactions at higher temperatures.[15] Much to our surprise, the ee of (*S*)-**2a** was still exceeding 94% at 140 °C, which is remarkable in an asymmetric catalytic reaction using monodentate ligands. A similar trend with a BINAP-based catalyst has also been observed by Hayashi,[6i] as the same enantioselectivity at 120 °C and at 40 °C was reported, although the conversion obtained at 40 °C was less than 2%.[16]

In asymmetric catalysis, the observed enantioselectivity for a reaction is usually temperature dependent. Therefore, reactions are often performed at low temperature to allow an enhanced stereocontrol, though at the expence of reaction rate. In our particular case, we observed that the stereocontrol was hardly temperature-dependent, although obviously the conversion was slower at 45 °C than at 100 °C (16 h vs 5 min).[17]
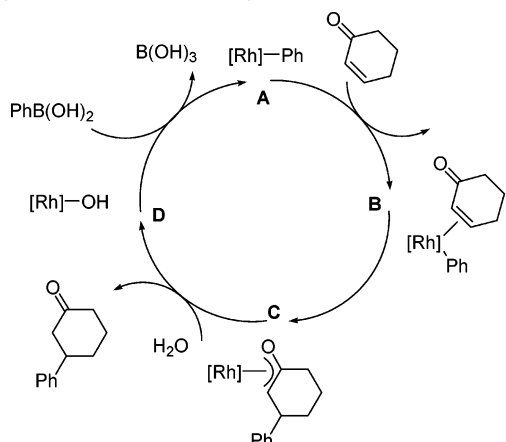
It is also interesting to note that the enantioselectivity of this reaction was found to be largely solvent-independent. When toluene and 2-propanol were used as solvent,

(15) Reactions were performed in a pressure-resistant flask on 0.4 mmol scale with 3 mol % of catalyst.

(16) For the BINAP-based catalyst, the rate of the transmetalation from phenylboronic acid to the hydroxorhodium species is very slow at temperatures lower than 80 °C; see ref 6i.

(17) Reactions at room temperature were difficult to reproduce.

SCHEME 3. Proposed Mechanism for the Rh-Catalyzed Conjugate Addition of Phenylboronic Acid to Cyclohexenone
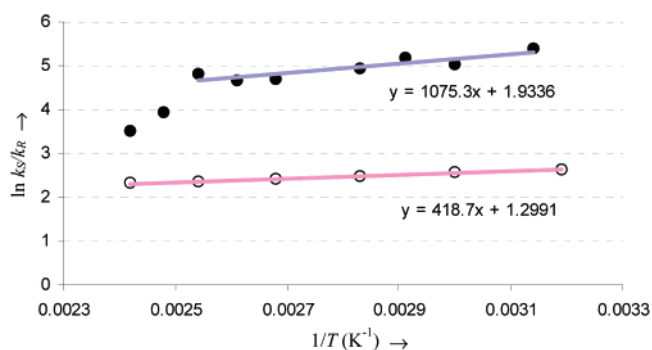

FIGURE 2. Eyring plots of $\ln(k_S/k_R)$ as a function of $1/T$ for the catalytic asymmetric addition of phenylboronic acid to cyclohexenone: (○) MonoPhos **L1**, (●) phosphoramidite **L4**. For **L1** at 373 K, $\Delta\Delta H^{\ddagger} = -0.83 \pm 0.06$ kcal·mol^{-1} (45%), $T\Delta\Delta S^{\ddagger} = 0.96 \pm 0.07$ kcal·mol^{-1} (55%); for **L4** at 373 K, $\Delta\Delta H^{\ddagger} = -2.1 \pm 0.2$ kcal·mol^{-1} (60%), $T\Delta\Delta S^{\ddagger} = 1.4 \pm 0.2$ kcal·mol^{-1} (40%).

the ee for (*S*)-**2a** remained >98%, although complete conversion required 3 h at 80 °C compared to 20 min in dioxane. In addition, the small amount of water (10%) present in these reactions could be replaced by methanol without a change in ee, although the rate of the reaction again decreased.

The catalytic cycle of the rhodium catalyzed conjugate addition of boronic acids has been studied by Hayashi and several of the intermediates have been characterized by NMR[6i] (Scheme 3). The enantiodiscrimination is attributed to the addition of the phenyl bound to rhodium to one of the π-faces of the α,β-unsaturated ketone (step **B → C**).

Encouraged by the high enantioselectivities obtained, we were interested in determining the contributions of enthalpy and entropy to the ee of this reaction. The temperature independence allowed us to consider an entropy-driven or largely entropy-driven enantioselection.[18] In asymmetric catalysis, the effect of temperature on enantioselectivity has been studied in the asymmetric hydrosilylation by Scharf et al.[19] A partially entropy-controlled enantioselectivity has been reported for a Mn-catalyzed oxidation by Katsuki et al.[20]

In a chemical reaction, when enantiomers or diastereoisomers are produced, the ee or de is determined by the difference in $\Delta G^{\ddagger}$ between the two transition states ($\Delta\Delta G^{\ddagger}$). To determine the terms $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, and their contribution to the enantioselectivity, a modified Eyring equation[21] is usually employed (eq 1).

$$\ln\frac{k_S}{k_R} = \frac{-\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R} \qquad (1)$$

Figure 2 shows the values of $\ln(k_S/k_R)$ with ligand **L1** and **L4** plotted against $1/T$.[22] As the reaction is es-

sentially irreversible and the products do not racemize, k_S/k_R is identical to the enantiomeric product ratio.

The Eyring plots for the rhodium-catalyzed addition of boronic acid to cyclohexenone show a straight curve with a small slope whereas a fully entropy controlled enantioselection should give a horizontal curve. Calculations of $\Delta\Delta H^{\ddagger}$, derived from the slope, and $\Delta\Delta S^{\ddagger}$, derived from the intercept (eq 1), reveals that in both cases the entropy contribution to the ee roughly equals the enthalpy contribution. Both $\Delta\Delta H^{\ddagger}$ (<0) and $\Delta\Delta S^{\ddagger}$ (>0) favor the major enantiomer, which gives a kind of rationale for the high ee's observed. This large entropy contribution to the enantioselectivity probably originates from the catalytic complex and is not due to differences in solvation between the two diastereomeric complexes as various solvents give the same ee.[23]

The interpretation of the large entropy contribution to the enantioselectivity is not straightforward, and cannot be related directly to a characteristic of monodentate ligands, since temperature independence of the ee has also been reported using the bidentate ligand BINAP.[6b] It is usually accepted that rigid and bulky bidentate ligands, like BINAP, create a well-defined chiral environment around the metal center where the substrate can access the metal almost exclusively in one orientation.[1] For this reason, the bidentate nature of ligands is generally assumed to be very important in order to obtain a high enantioselectivity. Here, we show that small monodentate phosphoramidite ligands, like **L4**, create probably a similar well defined asymmetric surrounding around the rhodium even at high temperatures. Compared to BINAP where the two phosphorus atoms are linked by covalent bonds, the preferred orientation of the phosphoramidites is probably only maintained by strong steric interactions. The similar performance of BINAP and **L4**, in terms of enantioselectivity, can be explained by a pseudo-bidentate behavior of two phosphoramidites

(18) (a) Sugimura, T.; Tei, T.; Mori, A.; Okuyama, T.; Tai, A. *J. Am. Chem. Soc.* **2000**, *122*, 2128. (b) Sugimura, T.; Hagiya, K.; Sato, Y.; Tei, T.; Tai, A.; Okuyama, T. *Org. Lett.* **2001**, *3*, 37. (c) Tei, T.; Sato, Y.; Hagiya, K.; Tai, A.; Okuyama, T.; Sugimura, T. *J. Org. Chem.* **2002**, *67*, 6593.

(19) Haag, D.; Runsink, J.; Scharf, H−D. *Organometallics* **1998**, *17*, 398.

(20) Nishida, T.; Miyafuji, A.; Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 7053.

(21) (a) Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107. (b) Bushmann, H.; Scharf, H−D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477. See also ref 18a.

(22) The same behavior was observed for the two phosphoramidites although the ee values are lower in the case of **L1**. In the case of **L4**, the ln k_S/k_R values at 130 °C and 140 °C were not included in the curve because in this range, a decrease of 4% ee induces an important drop in the ratio value.

(23) Strictly spoken, the difference in $\Delta S^{\ddagger}_{\text{solvation}}$ between both diastereomeric complexes is the same in various solvents.
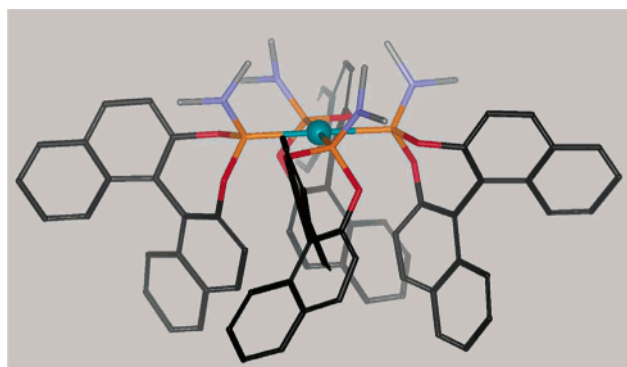
FIGURE 3. Crystal structure of Rh(**L1**)$_4$BF$_4$.

at the metal center as these ligands might bind to the rhodium in a locked configuration, thereby mimicking a bidentate ligand. The high enantioselectivity obtained at 140 °C (entry 9, Table 2) indicates that the rotation of the ligands around the P–Rh bond should be difficult. An equilibrium of the rhodium–phosphoramidite complex with the free ligand has to be excluded because free **L1** rapidly hydrolyses in dioxane/H$_2$O = 10/1 at 100 °C.[10] Additional support for the hypothesis that the two monodentate ligands restrict each other in their conformational flexibility is obtained from the crystal structure of Rh(**L1**)$_4$BF$_4$ depicted in Figure 3,[24] although the complex differs from the actual catalytic species (which contains two ligands **L1** at the Rh in a cis coordination). Based on this crystal structure, a computational simulated rotation of the phosphoramidites around the rhodium–phosphorus bond using molecular mechanics showed that such a rotation is strongly disfavored by the steric hindrance of the bis-β-naphthol moieties. The concept that monodentate ligands can act in a similar way as bidentate ligands is of great interest in the search for new catalysts using simple monodentate chiral ligands.[25]

In conclusion, monodentate phosphoramidites are extremely effective ligands in the rhodium-catalyzed conjugate addition of boronic acids to enones. A very fast reaction and enantioselectivities >98% have been reached, which clearly confirms that monodentate ligands and especially monodentate phosphoramidites can be as efficient as the bidentate diphosphines used so far. Temperature-dependent studies show that in contrast to the common notion, monodentate ligands can form stable complexes with metals and can induce high enantioselectivities even at high temperatures in polar solvents.

Supporting Information Available: Experimental details describing the synthesis, characterization, and analysis of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308.

(25) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197.