DOI: 10.1002/adsc.200800209

Asymmetric Synthesis of the Roche Ester and its Derivatives by Rhodium-INDOLPHOS-Catalyzed Hydrogenation

Jeroen Wassenaar,[a] Mark Kuil,[b] and Joost N. H. Reek[a,*]

[a] Van't Hoff Institute for Molecular Sciences, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands
Fax: (+31)-20-525-6422; phone: (+31)-20-525-6437; e-mail: reek@science.uva.nl
[b] BASF Nederland B.V. Catalysts, Strijkviertel 67, 3454 PK De Meern, The Netherlands

Received: April 4, 2008; Revised: April 24, 2008; Published online: June 13, 2008

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

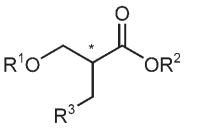
Abstract: (*S*)-3-Hydroxy-2-methylpropionate, known as the Roche ester, and several of its derivatives were successfully synthesized through asymmetric rhodium-catalyzed hydrogenation, using INDOLPHOS (diisopropyl{1-[(*S*)-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl]-3-methyl-2-indolyl}phosphine) as the chiral ligand, in excellent yield and the highest *ee* reported up to now (TOF over 5500 h^{-1} at 25 °C; up to 98% *ee* at −40 °C).

Keywords: asymmetric catalysis; hydrogenation; P ligands; rhodium; Roche ester

Introduction

Transition metal-catalyzed asymmetric hydrogenation has evolved in recent years as a practical and economical strategy in the preparation of fine chemical intermediates for the pharmaceutical industry.[1] In this course, a broad range of chiral hydrogenation catalysts have been developed, most of which rely on chiral mono- or bidentate phosphorus ligands.[2] The continuous development of new ligands has been shown to be vital in order to discover good catalysts. Two successful strategies in catalyst development have been reported that aim at catalysts for a broad substrate scope; the privileged ligand approach and combinatorial ligand approach. Privileged ligands, as defined by Jacobsen, usually consist of a rigid chiral backbone and give high selectivities for a broad range of substrates requiring only minor or no changes in the ligand structure.[3] In ultimate examples the ligands provide selective catalysts for several transition metal-catalyzed conversions. Alternatively, the combinatorial ligand approach utilizes the facile preparation of ligands enabling the construction of large and diverse libraries that, in conjunction with automated screening methods, allows the identification of the optimum catalyst for each individual substrate.[4] Our group has contributed to this field by developing both combinatorial[5,6] as well as privileged ligands.[7,8] To illustrate the potential of these ligands though, it is essential to employ them in the synthesis of relevant and challenging chiral targets.[6]

In the past decade, only a few reports appeared on the asymmetric synthesis of methyl 3-hydroxy-2-methylpropionate **1a**, known as the Roche ester, by means



1a R^1 = H, R^2 = Me, R^3 = H
1b R^1 = H, R^2 = Bn, R^3 = H
1c R^1 = Ac, R^2 = Me, R^3 = H
1d R^1 = H, R^2 = Me, R^3 = Ph

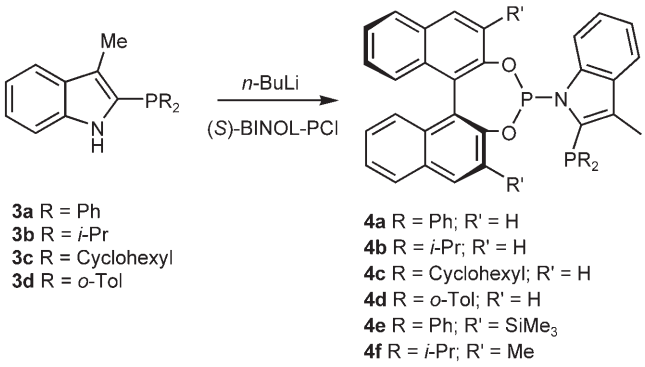
of enantioselective hydrogenation.[9–11] The Roche ester is a very important chiral starting material for the total synthesis of pharmaceutical compounds, e.g., in the synthesis of the anti-tumor agents tedanolide and discodermolide.[12] Importantly, as the Roche ester is a liquid the optical purity cannot be increased by crystallization and therefore asymmetric synthesis of this building block is only interesting if the *ee* of the product is very high (more than 95%). Jeulin et al. reported the synthesis of Roche ester derivatives with bulky ester groups in high enantioselectivity using an Ru-SYNPHOS catalyst.[9] However, the parent Roche ester containing a methyl ester (**1a**) was obtained in only 88% *ee*. Saito and co-workers reported 90% *ee* using an Rh-DuPHOS catalyst.[10] These examples represent the leads in the asymmetric synthesis of **1a** by enantioselective hydrogenation, but routes that provide over 90% enantiomeric purity remain a challenge.

Recently, we reported the synthesis of a new hybrid bidentate phosphine-phosphoramidite ligand INDOL-

PHOS (**4**) and its application in asymmetric rhodium-catalyzed hydrogenation and hydroformylation.[8] In terms of bite angle and rigidity, the ligand shows similarities with DuPHOS, up to now the most successful ligand for the preparation of **1a**, which therefore prompted our interest in applying INDOLPHOS in the synthesis of Roche ester derivatives. We here report the asymmetric synthesis of the Roche ester and its derivatives through rhodium-INDOLPHOS-catalyzed hydrogenation.

Results and Discussion

INDOLPHOS ligands **4a–f** are prepared in one step from the corresponding indolylphosphines **3a–d** by condensation with a bisnaphthol phosphorochloridite (Scheme 1).[13] It was observed previously that bulky



3a R = Ph
3b R = *i*-Pr
3c R = Cyclohexyl
3d R = *o*-Tol

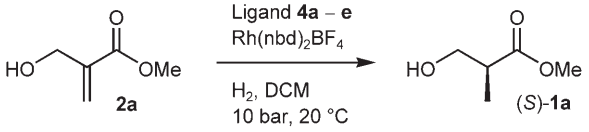
4a R = Ph; R' = H
4b R = *i*-Pr; R' = H
4c R = Cyclohexyl; R' = H
4d R = *o*-Tol; R' = H
4e R = Ph; R' = $SiMe_3$
4f R = *i*-Pr; R' = Me

Scheme 1. Synthesis of INDOLPHOS ligands.

phosphines were important in order to achieve high selectivity in asymmetric hydrogenation.[8] Therefore, we expanded the INDOLPHOS library with a cyclohexylphosphine (**4c**) and an *o*-tolylphosphine (**4d**) donor group.

Ligands **4a–f** were studied in the rhodium-catalyzed hydrogenation of methyl 2-hydroxymethylacrylate **2a**, which is available in one step *via* Baylis–Hillman reaction of methyl acrylate and formaldehyde, giving Roche ester **1a**. The catalysts were generated *in situ* from $[Rh(nbd)_2]BF_4$ and the corresponding INDOLPHOS ligand in dichloromethane (Table 1). All ligands give rhodium catalysts that display high activity as all reactions are (almost) complete after 20 h at 10 bar H_2 and room temperature, providing **1a** as the only product. On the other hand, large variations are observed with regard to the enantioselectivity of the catalysts based on the various ligands. The catalyst generated from the parent INDOLPHOS ligand **4a** gives an almost racemic product, whereas the introduction of bulky groups on the bisnaphthol moiety or the use of bulky phosphines results in moderate to ex-

Table 1. Ligand screening in the rhodium-catalyzed asymmetric hydrogenation of methyl 2-hydroxymethylacrylate.[a]



Entry	Ligand	% Conv.	% *ee*[b]
1	**4a**	100	7
2	**4b**	100	91
3	**4c**	100	85
4	**4d**	100	66
5	**4e**	80	62
6	**4f**	100	74
7	**(*S*)-Monophos**[c]	100	43

[a] Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, [Rh] = 1.0 mM, 10 bar of H_2, at 20 °C for 20 h using $[Rh(nbd)_2]BF_4$ as metal precursor.
[b] The (*S*)-enantiomer was obtained in all cases.
[c] (*S*)-(+)-(3,5-Dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a'*]dinaphthalen-4-yl)dimethylamine.

cellent enantioselectivities of up to 91% *ee* (Table 1, entries 1–6). This large dependence of the enantioselectivity on the steric properties of the ligand may be rationalized by the formation of the bis-ligated species $[Rh(\mathbf{4a})_2]BF_4$. In previous studies we detected this species by NMR when mixing equimolar amounts of **4a** with $[Rh(nbd)_2]BF_4$.[8] Importantly, when changing the steric properties of the ligand to more bulky substituents on either the phosphine (**4b–d**) or bisnaphthol (**4e**), only mono-ligated species [Rh(**4**)(nbd)]BF_4 were observed. Additional factors disfavouring bis-ligated species in the case of **4b**, **4c** and **4f** are the lack of π-stacking interactions and the stronger *trans*-effect of alkylphosphines.

The ligand screening experiments indicate that especially bulky, electron-rich alkylphosphines are required for catalysts that provide the product in *ee* values over 80%. Comparison with Monophos confirms this necessity and demonstrates the added value of hybrid ligands in this transformation (Table 1, entry 7).[14]

After the encouraging screening results, conditions were optimized for the most selective catalyst based on ligand **4b**. These optimization experiments were carried out in the AMTEC SPR16 consisting of 16 parallel reactors equipped with temperature and pressure sensors, and a mass flow controller, allowing the reaction rates to be determined from gas-uptake profiles. The rate measurements revealed turnover frequencies of over 5500 $mol_{\mathbf{1a}} \cdot mol_{Rh}^{-1} \, h^{-1}$ (Table 2, entry 2). Lowering the hydrogen pressure does not affect the *ee* but leads to an almost linear decrease of the rate suggesting a first order dependency on the partial hydrogen pressure (Table 2, entries 1 and 2).

Table 2. Variation of conditions in the rhodium-catalyzed asymmetric hydrogenation of methyl 2-hydroxymethylacrylate using ligand **4b**.[a]

Entry	S/C	*P* [bar]	*T* [°C]	% Conv.	TOF[b]	% *ee*[c]
1	100	5	25	100	3.2×10^3	93
2	100	10	25	100	5.7×10^3	93
3	400	10	25	95	1.1×10^3	93
4	1000	10	25	46	2.5×10^3	92
5[d]	100	10	−15	100	n.d.	95
6[d]	100	10	−40	100	n.d.	98
7[d,e]	100	20	−40	100 (87)[f]	n.d.	98

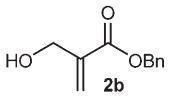
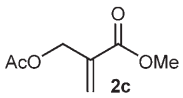
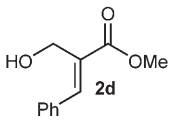
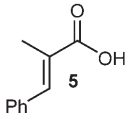
[a] Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1 for 1.5 h using $[Rh(nbd)_2]BF_4$ as metal precursor.
[b] Turnover frequency determined at 10% conversion ($mol_{\mathbf{1a}}\cdot mol_{Rh}^{-1}\cdot h^{-1}$)
[c] The (*S*)-enantiomer was obtained in all cases.
[d] 15 h of reaction time.
[e] Reaction performed on a 50-mmol scale.
[f] Isolated yield after flash chromatography.

When the catalyst loading was reduced to 0.25–0.1 mol%, activity dropped and full conversion was no longer reached (Table 2, entry 2–4). The gas-uptake profiles (Supporting Information) for entries 3 and 4 level off at 95% and 46% conversion, respectively, indicating catalyst deactivation at lower catalyst loading, which is most probably caused by small, undetectable, impurities in the substrate. In order to increase the enantioselectivity we conducted the hydrogenation at −15 °C and −40 °C which results in an unprecedented *ee* of 98% and full conversion (Table 2, entries 5 and 6). Following these optimized reaction conditions (−40 °C), Roche ester **1a** was obtained on a 50-mmol scale in high isolated yield (87%) and excellent *ee* up to 98% (Table 2. entry 7).

The scope of the Rh-INDOLPHOS-catalyzed hydrogenation towards Roche ester derivatives **1b–d** was studied to explore the limits of the approach and to identify structural motifs in the substrate governing the stereoselective outcome. First, the methyl ester was replaced with a benzyl ester (**2b**), and also this substrate was fully converted in high stereoselectivity (Table 3, entries 1 and 2). The substrate that is protected with an acyl group at the primary alcohol functionality (**2c**) seems less reactive as it is not fully converted under these conditions and the *ee* of the product reaches only 35%, indicating the importance of the alcohol group in the enantiodiscriminating step (Table 3, entries 3 and 4). Introduction of a phenyl group on the double bond (**2d**) also reduces the reactivity of the substrate (35% conversion), and the product formed is racemic (Table 3, entries 5 and 6).

The asymmetric hydrogenation of the structurally related α-methylcinnamic acid **5** results in moderate yield and an enantioselectivity of 78% *ee* (Table 3, entries 7 and 8). Considering the structural similarity of

Table 3. Scope of the rhodium-INDOLPHOS-catalyzed hydrogenation.[a]

Entry	Substrate	Ligand	% Conv.	% *ee* (config.)
1	 **2b**	**4b**	100	89 (*S*)
2		**(*S*)-Monophos**[b]	90	48 (*S*)
3	 **2c**	**4b**	34	35 (*S*)
4		**(*S*)-Monophos**[b]	50	0
5	 **2d**	**4a**	33	0
6		**(*S*)-Monophos**[b]	23	0
7	 **5**	**4e**	45	78 (*R*)
8[c]		**4e**	46	73 (*R*)
9[d]		**(*R*)-Monophos**[b]	43	8 (*S*)

[a] Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, 10 bar of H_2, at 20 °C for 20 h using $[Rh(nbd)_2]BF_4$ as metal precursor. Additional catalytic results are available in the supporting information.
[b] (*S*)-(+)-(3,5-Dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl)dimethylamine.
[c] 20 bar H_2.
[d] Literature value.[15]

2d and **5**, the difference in reactivity and selectivity towards asymmetric hydrogenation is remarkable.

As control experiments we also studied Monophos-based rhodium catalysts in these hydrogenation reactions. As is clear from the results, in none of the examples did this catalyst give better results than the INDOLPHOS-based catalysts (Table 1, entry 6, and Table 3, entries 2, 4, 6 and 9). This superiority of INDOLPHOS over Monophos in the hydrogenation of Roche ester derivatives shows the importance for chelating ligands in this reaction.

Conclusions

In conclusion, Roche ester **1a** is successfully synthesized through asymmetric rhodium-catalyzed hydrogenation using INDOLPHOS in high yield and unprecedented enantioselectivity (up to 98% *ee*) on a preparative scale. The bidentate character of INDOLPHOS is of importance as all experiments with monodentate Monophos ligands resulted in poor *ee* of the product. A short study of the substrate scope revealed little sensitivity of the catalyst with regard to the ester group present in the substrate; both methyl as benzyl esters were converted in high selectivity. However, the primary alcohol function seems to have an important function as the acyl-protected substrate could not

be hydrogenated in high selectivity. The trisubstituted substrate with an additional phenyl group at the 3-position, is less reactive and forms the product as a racemate. Hydrogenation of the structurally related α-methylcinnamic acid **5** results in moderate activity and high enantioselectivity up to 78% *ee*.

Experimental Section

General Procedure for the Synthesis of Indolylphosphines 3a–d

To a solution of 3-methylindole (1.78 g, 13.6 mmol) in THF (40 mL) was added dropwise 5.7 mL of *n*-BuLi (2.5 M in hexanes) at −70 °C. The resulting suspension was stirred at −70 °C for 20 min. Carbon dioxide was bubbled through the suspension for 10 min to give a clear pale yellow solution which was allowed to warm to room temperature after which the solvent was removed under vacuum. The resulting white residue was dissolved in THF (40 mL) to give a clear pale yellow solution which was cooled to −70 °C. To this solution, 8.4 mL of *t*-BuLi (1.7 M in pentanes) was added and the resulting orange solution was stirred at −70 °C for 1 h. The appropriate chlorophosphine (13.6 mmol) was added and the reaction mixture was stirred for 16 h while being allowed to warm to room temperature. The resulting yellow solution was washed with 40 mL degassed saturated aqueous NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude, pale yellow solid was recrystallized from hot MeOH to yield the product as colourless crystals.

Dicyclohexyl(3-methyl-2-indolyl)phosphine (3c): Yield: 2.84 g (64%).

Di-(*o*-Tolyl)-(3-methyl-2-indolyl)phosphine (3d): Yield: 3.88 g (83%).

General Procedure for the Synthesis of INDOLPHOS Ligands 4a–f

To a solution of the corresponding indolylphosphine **3** (1.46 mmol) in THF (5 mL) was added dropwise 0.58 mL of *n*-BuLi (2.5 M in hexanes) at −70 °C. The resulting pale yellow solution was stirred for 0.5 h at −70 °C. To this solution, a solution of (*S*)-(−)-2,2′-bisnaphthol phosphorochloridite (0.51 g, 1.46 mmol) in THF (4 mL) was added at −70 °C. The reaction mixture was stirred for 1 h at −70 °C and then allowed to warm to room temperature. The resulting pale yellow solution was concentrated under vacuum. Toluene (5 mL) was added and the suspension was filtered over Celite after which the solvent was removed under vacuum to obtain a white powder. In selected cases the crude product was further purified by SiO_2 chromatography.

Dicyclohexyl{1-[(*S*)-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl]-3-methyl-2-indolyl}phosphine (4c): Yield: 553 mg (59%).

Di-(*o*-Tolyl)-{1-[(*S*)-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl]-3-methyl-2-indolyl}phosphine (4d): Yield: 749 mg (78%).

Preparative Scale Asymmetric Hydrogenation of Methyl 2-Hydroxymethylacrylate (2a)

INDOLPHOS ligand **4b** (309 mg, 0.55 mmol) and $[Rh(nbd)_2]BF_4$ (187 mg, 0.50 mmol) were dissolved in dry DCM (50 mL). Methyl 2-hydroxymethylacrylate **2a** (5.8 g, 50 mmol) was added and the mixture was transferred to a 150-mL stainless steel autoclave equipped with a glass insert and a mechanical stirrer. The autoclave was cooled to −40 °C and subsequently purged three times with 15 bar of dihydrogen and pressurized at 20 bar H_2. The reaction mixture was stirred for 15 h at −40 °C after which it was allowed to warm to room temperature. The pressure was reduced to 1.0 bar and the solvent was removed under reduced pressure. Et_2O (50 mL) was added to the residue and the resulting yellow suspension was filtered through a plug of SiO_2 which was rinsed twice with Et_2O (2×50 mL). Removal of the solvent under reduced pressure gave a colourless oil; yield: 5.16 g (87%); 98% *ee* (chiral GC); $[\alpha]_D^{20}$: +15.4 (*c* 3.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz, 298 K): $\delta = 3.72$ (m, 5H), 2.68 (m, 1H), 2.10 (br s, 1H), 1.18 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.5 MHz, 298 K): $\delta = 176.14$ (C_q), 64.57 (CH_2), 51.83 (CH_3), 41.62 (CH), 13.40 (CH_3).

Supporting Information

Spectroscopic and analytical data of ligands, additional experimental details for the AMTEC SPR16, catalytic results, and gas-uptake profiles are available in the Supporting Information.

Acknowledgements

We gratefully acknowledge NRSC-C and the European Union (RTN Revcat MRTN-CT-2006–035866) for financial support.

References

[1] a) J. G. de Vries, C. J. Elsevier, *The Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Weinheim, **2007**; b) N. B. Johnson, I. C. Lennon, P. H. Moran, J. A. Ramsden, *Acc. Chem. Res.* **2007**, *40*, 1291–1299.

[2] W. J. Tang, X. M. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3069.

[3] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691–1693.

[4] a) C. Jakel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912–2942; b) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071–3100.

[5] a) V. F. Slagt, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2003**, 2474–2475; b) V. F. Slagt, M. Röder, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2004**, *126*, 4056–4057; c) M. Kuil, P. E. Goudriaan, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2006**, 4679–4681; d) X. B. Jiang, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2007**, 2287–2289; e) M. Kuil, P. E. Goudriaan, A. W. Kleij, D. M. Tooke, A. L. Spek, P. W. N. M. van Leeuwen, J. N. H. Reek, *Dalton Trans.*

2007, 2311–2320; f) V. F. Slagt, P. W. N. M. van Leeuwen, J. N. H. Reek, *Dalton Trans.* **2007**, 2302–2310; g) A. J. Sandee, J. N. H. Reek, *Dalton Trans.* **2006**, 3385–3391; h) A. J. Sandee, A. M. van der Burg, J. N. H. Reek, *Chem. Commun.* **2007**, 864–866.

[6] X. B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245–1249; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223–1227.

[7] a) F. Doro, M. Lutz, J. N. H. Reek, A. L. Spek, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **2008**, 1309–1317; b) D. G. I. Petra, P. C. J. Kamer, A. L. Spek, H. E. Schoemaker, P. W. N. M. van Leeuwen, *J. Org. Chem.* **2000**, *65*, 3010–3017; c) D. G. I. Petra, J. N. H. Reek, J. W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. J. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2000**, *6*, 2818–2829; d) D. G. I. Petra, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, A. M. Van Loon, J. G. de Vries, H. E. Schoemaker, *Eur. J. Inorg. Chem.* **1999**, 2335–2341.

[8] J. Wassenaar, J. N. H. Reek, *Dalton Trans.* **2007**, 3750–3753.

[9] S. Jeulin, T. Ayad, V. Ratovelomanana-Vidal, J. P. Genêt, *Adv. Synth. Catal.* **2007**, *349*, 1592–1596.

[10] H. Shimizu, T. Saito, H. Kumobayashi, *Adv. Synth. Catal.* **2003**, *345*, 185–189.

[11] Y. Keiji, N. Koichi, (Nippon Shokubai Co. Ltd.), Japanese Patent 2000128832, **2000**.

[12] a) A. B. Smith, C. M. Adams, S. A. L. Barbosa, A. P. Degnan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12042–12047; b) S. J. Mickel, G. H. Sedelmeier, D. Niederer, R. Daeffler, A. Osmani, K. Schreiner, M. Seeger-Weibel, B. Bérod, K. Schaer, R. Gamboni, *Org. Process Res. Dev.* **2004**, *8*, 92–100.

[13] All INDOLPHOS ligands are based on (*S*)-BINOL.

[14] M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540.

[15] R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem.* **2005**, *117*, 4281–4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4209–4212.

