Tropos Organocatalyst

DOI: 10.1002/anie.201402293

Selector-Induced Dynamic Deracemization of a Selectand-Modified Tropos BIPHEPO-Ligand: Application in the Organocatalyzed Asymmetric Double-Aldol-Reaction**

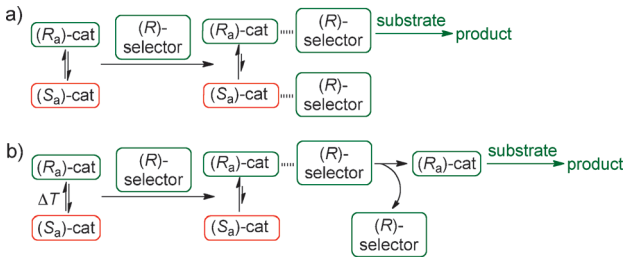
*Frank Maier and Oliver Trapp**

Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *Stereolabile interconverting catalysts open up the possibility of directing enantioselectivity in asymmetric synthesis by formation of diastereomeric complexes with chiral auxiliaries and deracemization. However, the stoichiometrically used auxilliaries can significantly limit the potential applications of such systems. We synthesized a new BIPHEPO tropos ligand containing achiral selectands in the backbone, which forms transient diastereomeric associates with amylose-tris-3,5-dimethylphenyl carbamate as a selector and thus deracemizes. The enantiomerically enriched BIPHEPO obtained was successfully used in the organocatalytic asymmetric double aldol addition of substituted methyl ketones to form benzaldehyde. This strategy combines an on-column deracemization with the high stereoinduction of chiral biarylphosphineoxides and opens up new possibilities in the field of self-amplified asymmetric syntheses.*

Dynamic stereoisomers constitute an interesting and important alternative to classical stereochemically stable ligands.[1] Among these the fluxional axially chiral 2,2′-bis(diphenylphosphino)biphenyl (BIPHEP) species have a prominent position as ligands for asymmetric catalysis. In contrast to the related BINAP ligands[2] the *o*,*o*′-disubstituted biphenyl enantiomers[3] convert dynamically into each other by rotation around the σ bond even at room temperature.[4]

Mikami and Noyori et al. took advantage of this dynamic property and used the unsubstituted BIPHEP as a ligand for asymmetric catalysis.[5] To deracemize the catalyst complex Mikami et al. employed stoichiometric amounts of chiral counterligands (selectors) to selectively align the BIPHEP tropos ligands in the corresponding diastereomeric complexes (Scheme 1). By coordination to transition-metal centers the interconversion barrier may increase, whereby the BIPHEP ligands show an atropisomeric behavior.[6,7]



Scheme 1. Asymmetric reactions using interconverting racemic catalysts. a) Chirality control and activation by the selector and b) chirality control by the selector.

After aligning the tropos ligands by chiral auxiliary ligands at elevated temperatures, the enantiomerically enriched catalysts can be used directly or be split off again at lower temperatures.[6]

Mikami et al. as well as other groups could apply these concepts to a number of metal complexes with tropos BIPHEP ligands and to a variety of asymmetric transformations.[5b,c,6b,e,f,8]

Another strategy for the deracemization of stereo labile compounds by means of stopped-flow HPLC (sfHPLC) on chiral stationary-phases were demonstrated by Pirkle et al.[9] and Lindner et al.[10] Wolf, König, and Roussel obtained the (−)-2,2′-diiodobiphenyl enantiomer in 90% yield by multiple separations and re-racemizations by sfHPLC.[11] Cannazza et al. refined this approach by using a second achiral column next to the chiral separation column for recycling of the unwanted enantiomer.[12]

Kotani and Nakajima et al. used chiral biarylphosphineoxide successfully as organocatalysts in enantioselective aldol and double aldol additions,[13] allylations[14] as well as ring-opening reactions and epoxidations.[15]

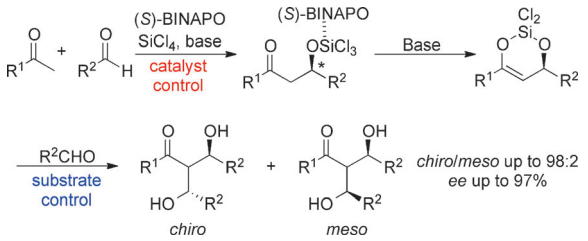
The active catalyst is formed by a hypervalent BINAPO-$SiCl_3$ species. Mechanistic studies on the double-aldol-additions demonstrate the need and the stereoselective influence of the employed chiral BINAPO ligands for the formation of the silyl enol ether (Scheme 2).[13e]

Herein we report on a new strategy for the catalytic transfer of chiral information, which combines the excellent stereo-inducing properties of BIPHEP tropos ligands with on-column deracemization (Scheme 3). Recently, we have studied in detail the stereo dynamics of tropos 5,5′-disubstituted BIPHEPO ligands.[16] These compounds show an ideal

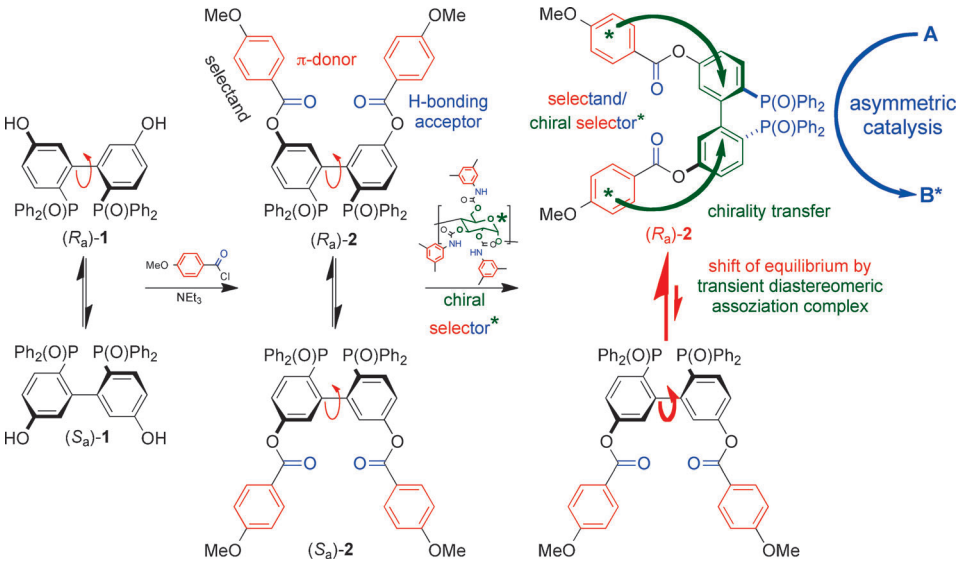
[*] Dr. F. Maier, Prof. Dr. O. Trapp
Ruprecht-Karls-Universität Heidelberg
Organisch-Chemisches Institut
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
E-mail: trapp@oci.uni-heidelberg.de
Homepage: http://www.trapp.uni-hd.de

[**] We thank the European Research Council (ERC) for financial support in the form of a Starting Grant (Nr. 258740, AMPCAT).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201402293.



Scheme 2. Enantioselective double-aldol-addition with (*S*)-BINAPO/$SiCl_4$ as an organocatalyst.[13e]



Scheme 3. Modification of BIPHEPO derivative **1** with selectands for targeted chirality transfer of a selector. By forming transient diastereomeric association complexes, the equilibrium is shifted in favor of the BIPHEPO (R_a)-**2**, which can be used for asymmetric catalysis.

behavior with respect to their barriers in the range of about 87–96 kJ mol^{-1},[16] that is, the enantiomerization rate is sufficiently high for rapid conversion at room temperature and the stereoisomers can be stabilized at lower temperatures.

Starting from 5,5′-dihydroxy-2,2′-bis(diphenylphosphinyl)-1,1′-biphenyl (**1**), reaction with 4-methoxybenzoyl chloride gave the corresponding tropos 5,5′-disubstituted BIPHEPO 2,2′-bis(diphenylphosphinyl)-5,5′-bis(4-methoxybenzoyloxy)-1,1′-biphenyl (**2**). This molecular design with the benzoyl selectands in the backbone showed excellent interaction properties with the chiral stationary phases Chiralpak IA and (*R*,*R*)-Whelk-O1 (Scheme 3). Interactions with an electron-rich π system and an H-bonding acceptor favor the chiral recognition of one of the atropisomers and thereby make an efficient chiral resolution by the formation of transient diastereomeric association complexes feasible. Moreover the interconversion barrier $\Delta G^{\ddagger}$ should be in the range of about 90 to 95 kJ mol^{-1}, so that a sufficiently high interconversion speed can be achieved at room temperature. First, the dynamic properties of **2** were determined by enantioselective dynamic HPLC (DHPLC).[17] As expected, the enantiomer separations are characterized by extremely high separation selectivities α between 1.7 and 3.9, which are favored by the selectand groups. The elution profiles exhibited the characteristic plateau formations arising from the mutual dynamic interconversion of the enantiomers. They were evaluated with the "Unified Equation"[18] and the enantiomerization barrier $\Delta G^{\ddagger}$ as well as the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were directly determined. Representative elution profiles of the DHPLC experiments of BIPHEPO **2** are shown in Figure 1 and the corresponding Eyring plot in Figure 2.

By evaluation of the elution profiles the interconversion barrier of BIPHEPO **2** was determined to be $\Delta G^{\ddagger} = 91.2$ kJ mol^{-1} and the activation parameters $\Delta H^{\ddagger} = (72.0 \pm 0.2)$ kJ mol^{-1} and $\Delta S^{\ddagger} = -(64 \pm 1)$ kJ mol^{-1} K^{-1}. This corresponds to a rate constant at room temperature of $k = 3.16 \times 10^{-4}$ s^{-1}.

For the targeted deracemization of **2** the chromatographic HPLC separation conditions were optimized and the racemic mixture of **2** was kept on the respective stationary phase under stopped-flow conditions for 24 h. By the formation of transient diastereomeric association complexes between BIPHEPO enantiomers and the chiral selectors (Chiralpak IA and (*R*,*R*)-Whelk-O1) of the stationary phase, the stereolabile ligands are aligned. The enantiomeric excesses

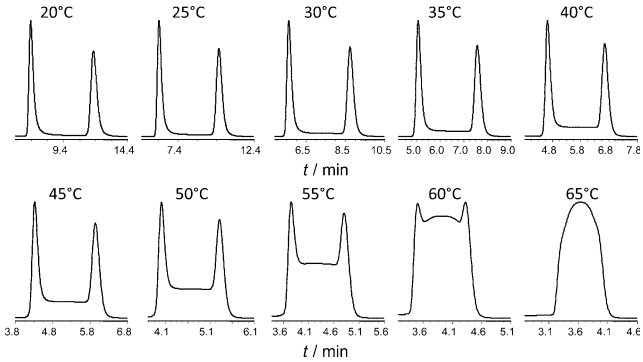


Figure 1. Experimental interconversion profiles of **2**, obtained by enantioselective DHPLC between 20 °C and 65 °C.

obtained were determined by diode array detection after decreasing the column temperature to 10 °C, and subsequent elution of the enantiomers. Deracemizations with high enantiomeric ratios of 77:23 in the presence of the selector amylose-tris-3,5-dimethyl-phenyl-carbamate[19] (Chiralpak IA) and 71:29 in the presence of the (*R*,*R*)-Whelk-O1 selector could be achieved.

Advantages over the use of chiral auxiliaries are the chromatographic separation of the desired deracemized

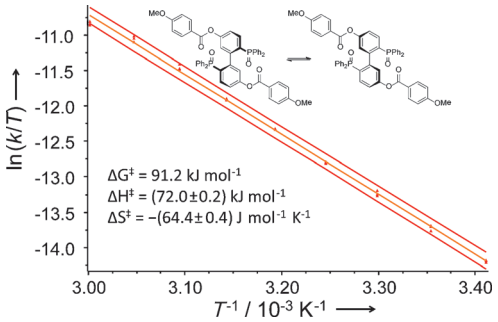


Figure 2. Eyring plot analysis and interconversion parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ for **2**.

enantiomer and the intrinsic recyclability of the immobilized selector. The experimental setup and the corresponding chromatograms as well as the enantiomeric ratios are depicted in Figure 3.

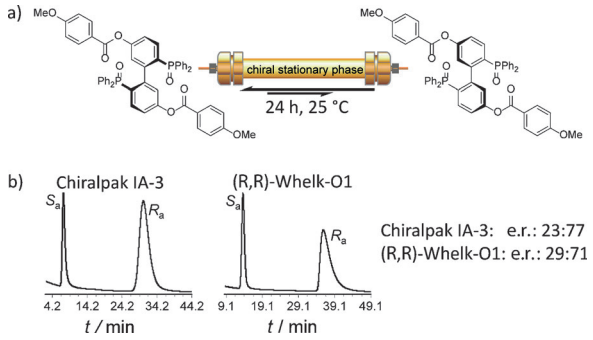


Figure 3. Deracemization of BIPHEPO **2** by chiral HPLC stationary phases. a) Schematic representation of the deracemization in presence of a chiral stationary phase and b) chromatograms obtained after 24 h residence time of the selectand modified BIPHEPO derivative **2** in presence of the chiral stationary phase Chiralpak IA-3 and (*R*,*R*)-Whelk-O1.

From the peak-area ratio of the enantiomers the thermodynamic equilibrium constant K and directly from this the difference of the Gibbs free energies $\Delta\Delta G°$ of the diastereomeric association complexes[20] on the respective stationary phase can be calculated by using Equation (1).

$$\Delta\Delta G^{\circ} = -R\,T\ln(\Delta K_{R,S}) \qquad (1)$$

This results in the following values $\Delta\Delta G° = 3.0\ \mathrm{kJ\,mol^{-1}}$ in the presence of Chiralpak IA-3 and $\Delta\Delta G° = 2.2\ \mathrm{kJ\,mol^{-1}}$ in presence of the (*R*,*R*)-Whelk-O1 selector.[21]

For complete on-column deracemization of BIPHEPO (**2**), a new two-column multi-stopped-flow HPLC technique (two-column msfHPLC) was developed, which is based on a gradual separation of the faster eluting enantiomer and re-racemization of the faster eluted enantiomer, which shows a decreased interaction with the chiral stationary phase. This feature makes it possible, to convert the racemate into the enantiomer (S_a)-**2**. As a result of the high separation factors of $\alpha > 3$ for **2** on the chiral stationary phase Chiralpak IA-3 and, at the same time low peak widths, three separation cycles were performed on each of the HPLC columns. For this purpose, the racemic mixture of enantiomers of **2** was injected onto the chiral stationary phase at low temperature (−5 °C). After the faster eluted (S_a)-enantiomer passed the column outlet of the first column, the solvent flow was stopped and the column was heated for 60 min to 70 °C resulting in re-racemization of the (R_a)-enantiomer. After cooling to −5 °C, the (S_a)-enantiomer was separated again. After three separation and re-racemization cycles the second column with a chiral stationary phase was connected by a six-port valve, and the enrichment process was repeated three additional times before the (R_a)-enantiomer was eluted (cf. Figure 4).

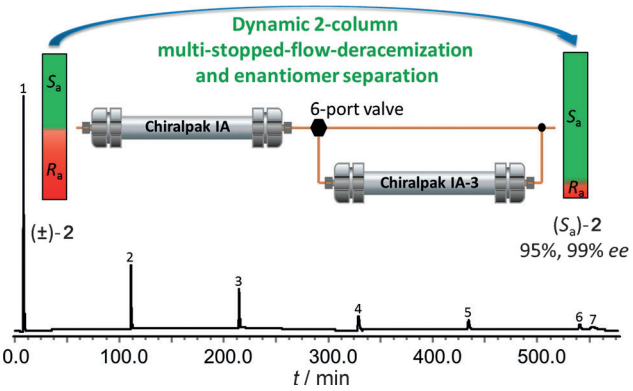


Figure 4. Two-column multi-stopped-flow experiment for the chiral resolution of the tropos BIPHEPO ligand **2**.

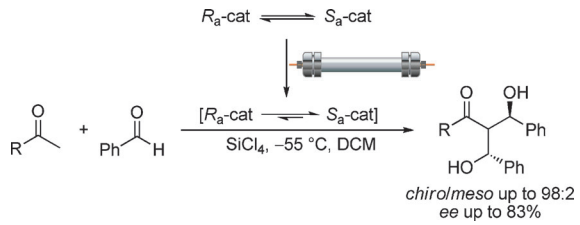
Peaks 1–6 correspond to the faster eluted (S_a)-enantiomer **2** and peak 7 corresponds to the slower eluting (R_a)-enantiomer **2**. BIPHEPO derivative (S_a)-**2** was obtained with a yield of 94.5 % and (R_a)-**2** with a yield of 5.5 % with an enantiomeric purity of greater than 99 %. Enriched BIPHEPO enantiomers show atropisomeric behavior at temperatures of −50 °C.

Because of that behavior, the chiral information of chiral HPLC stationary phases can be transferred to **2** at elevated temperatures and stored at reduced temperatures, and subsequently transferred to other chiral systems.

As a model reaction for the catalytic transfer of the stored stereochemical information the organocatalyzed double-aldol-addition of substituted methyl ketones to benzaldehyde developed by Kotani and Nakajima et al.[13–15] was studied (cf. Scheme 2). For this purpose the BIPHEPO-enantiomers were enriched on a preparative scale by the newly developed two-column-msfHPLC technique under on-column deracemization. To prevent subsequent racemization of enantiomerically enriched **2** the HPLC solvent was removed at −20 °C in a high vacuum, a stock solution of **2** was then prepared in CH_2Cl_2 and cooled to −55 °C. The enantiomeric excesses of the resulting stock solutions were determined for the on-column deracemization by HPLC to 27 % (in favor of the (R_a) enantiomer) and to 91 % (in favor of (S_a) enantiomer) for the two-column-msfHPLC technique.

The double-aldol-addition of methyl ketones to benzaldehyde was then performed with the enriched BIPHEPO

enantiomers in DCM at −55 °C. For the formation of the active catalyst complex 4.0 equivalents tetrachlorosilane and 10 mol% **2** were used (Scheme 4). The newly developed concept for the deracemization of chiral tropos BIPHEP-oxides and their direct use as ligands in organocatalysts for double-aldol-additions is shown in Scheme 4.



Scheme 4. Asymmetric double-aldol-reaction of substituted methyl ketones with benzaldehyde catalyzed by dynamically deracemized BIPHEPO ligand **2** and $SiCl_4$.

As nucleophilic reaction components, cyclopropyl methyl ketone and methyl-2-thienyl ketone were used. After workup of the reactions, the enantiomeric excesses were determined directly without chromatographic purification using enantioselective HPLC. The yields of isolated products, the enantiomeric- and diastereomeric selectivities of the double-aldol-addition are summarized in Table 1.

Table 1: Stereoselective double-aldol-addition.

Entry	R	Ligand	Yield [%]	d.r. *chiro/meso*	*ee* [%]
1	cyclopropyl	(S_a)-**2**[a]	89	91:9	83
		(R_a)-**2**[b]	93	79:21	25
		(S_a)-BINAPO[c]	95	88:12	90
2	2-thienyl	(S_a)-**2**[a]	84	98:2	80
		(S_a)-BINAPO[c]	84	91:9	84

[a] 91% *ee*. [b] 27% *ee*. [c] > 99% *ee*.

The enantioselectivities obtained using the (S_a)-enantiomer **2** are 83% *ee* for the cyclopropyl methyl ketone and 80% *ee* for the methyl-2-thienyl ketone. The high stereoinduction is comparable to that of BINAPO, because ligand **2** was only used with an enantiomeric excess of 91%. It is noteworthy that the diastereoselectivity of (S_a)-BIPHEPO derivative **2** exceeds the observed selectivity of the (S_a)-BINAPO ligand.

We have synthesized a novel tropos BIPHEPO ligand with selectands in the backbone, which has excellent separation properties on chiral stationary phases. This allowed an on-column deracemization by stopped-flow HPLC experiments, and by using a newly developed two-column-multi-stopped-flow HPLC method. The enantiomerically enriched BIPHEPO **2** was then successfully used as a ligand in the organocatalytic double-aldol-addition of methyl ketones to benzaldehyde, with good enantio- and diastereoselectivity. This strategy combines a catalytic on-column deracemization with the high stereoinduction of chiral biarylphosphineoxide. This process allows the selective use of stereochemically labile compounds as dynamic storage medium for stereochemical information and their amplified transmission to target compounds.

Received: February 11, 2014
Published online: June 25, 2014

Keywords: deracemization · dynamic HPLC · ligand design · organocatalysis · tropos biaryls

[1] M. T. Reetz, X. Li, *Angew. Chem.* **2005**, *117*, 3019 – 3021; *Angew. Chem. Int. Ed.* **2005**, *44*, 2959 – 2962; D. Selent, W. Baumann, K.-D. Wiese, A. Börner, *Chem. Commun.* **2008**, 6203 – 6205.
[2] R. Noyori, *Angew. Chem.* **2002**, *114*, 2108 – 2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008 – 2022.
[3] a) O. Trapp, G. Schoetz, V. Schurig, *Chirality* **2001**, *13*, 403 – 414; b) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518 – 5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384 – 5427; c) C. Wolf, *Chem. Soc. Rev.* **2005**, *34*, 595 – 608; d) C. Wolf, *Dynamic Stereochemistry of Chiral Compounds—Principles and Applications*, RSC, Cambridge, **2008**; e) O. Trapp, *Electrophoresis* **2010**, *31*, 786 – 813.
[4] F. Maier, O. Trapp, *Angew. Chem.* **2012**, *124*, 3039 – 3043; *Angew. Chem. Int. Ed.* **2012**, *51*, 2985 – 2988.
[5] a) T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 1086 – 1087; b) K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem.* **1999**, *111*, 517 – 519; *Angew. Chem. Int. Ed.* **1999**, *38*, 495 – 497.
[6] a) T. Korenaga, K. Aikawa, M. Terada, S. Kawauchi, K. Mikami, *Adv. Synth. Catal.* **2001**, *343*, 284 – 288; b) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369 – 3400; c) K. Mikami, S. Kataoka, Y. Yusa, K. Aikawa, *Org. Lett.* **2004**, *6*, 3699 – 3701; d) K. Mikami, H. Kakuno, K. Aikawa, *Angew. Chem.* **2005**, *117*, 7423 – 7426; *Angew. Chem. Int. Ed.* **2005**, *44*, 7257 – 7260; e) K. Aikawa, M. Kojima, K. Mikami, *Angew. Chem.* **2009**, *121*, 6189 – 6193; *Angew. Chem. Int. Ed.* **2009**, *48*, 6073 – 6077; f) K. Aikawa, K. Mikami, *Chem. Commun.* **2012**, *48*, 11050 – 11069.
[7] a) T. Punniyamurthy, M. Mayr, A. S. Dorofeev, C. J. R. Bataille, S. Gosiewska, B. Nguyen, A. R. Cowley, J. M. Brown, *Chem. Commun.* **2008**, 5092 – 5094; b) M. D. Tudor, J. J. Becker, P. S. White, M. R. Gagné, *Organometallics* **2000**, *19*, 4376 – 4384.
[8] a) J. J. Becker, P. S. White, M. R. Gagné, *J. Am. Chem. Soc.* **2001**, *123*, 9478 – 9479; b) M. Schmitkamp, D. Chen, W. Leitner, J. Klankermayer, G. Franciò, *Chem. Commun.* **2007**, 4012 – 4014.
[9] W. H. Pirkle, D. S. Reno, *J. Am. Chem. Soc.* **1987**, *109*, 7189 – 7190.
[10] E. Tobler, M. Lämmerhofer, G. Mancini, W. Lindner, *Chirality* **2001**, *13*, 641 – 647.
[11] C. Wolf, A. König, C. Roussel, *Chirality* **1995**, *7*, 610 – 611.
[12] G. Cannazza, M. M. Carrozzo, U. Battisti, D. Braghiroli, C. Parenti, *J. Chromatogr. A* **2009**, *1216*, 5655 – 5659.
[13] a) S. Kotani, S. Hashimoto, M. Nakajima, *Synlett* **2006**, *7*, 1116 – 1118; b) M. Sugiura, N. Sato, S. Kotani, M. Nakajima, *Chem. Commun.* **2008**, 4309 – 4311; c) Y. Shimoda, T. Tando, S. Kotani, M. Sugiura, M. Nakajima, *Tetrahedron: Asymmetry* **2009**, *20*, 1369 – 1370; d) M. Sugiura, N. Sato, Y. Sonoda, S. Kotani, M. Nakajima, *Chem. Asian J.* **2010**, *5*, 478 – 481; e) Y. Shimoda, S. Kotani, M. Sugiura, M. Nakajima, *Chem. Eur. J.* **2011**, *17*, 7992 – 7995; f) S. Aoki, S. Kotani, M. Sugiura, M. Nakajima, *Chem. Commun.* **2012**, *48*, 5524 – 5526; g) K. Osakama, M. Sugiura, M. Nakajima, S. Kotani, *Tetrahedron Lett.* **2012**, *53*, 4199 – 4201.

[14] M. Nakajima, S. Kotani, T. Ishizuka, S. Hashimoto, *Tetrahedron Lett.* **2005**, *46*, 157 – 159.
[15] E. Tokuoka, S. Kotani, H. Matsunaga, T. Ishizuka, S. Hashimoto, M. Nakajima, *Tetrahedron: Asymmetry* **2005**, *16*, 2391 – 2392.
[16] F. Maier, O. Trapp, *Chirality* **2013**, *25*, 126 – 132.
[17] a) J. Veciana, M. I. Crespo, *Angew. Chem.* **1991**, *103*, 85 – 88; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 74 – 76; b) F. Gasparrini, L. Lunazzi, S. Alcaro, C. Villani, *J. Org. Chem.* **1995**, *60*, 5515 – 5519; c) O. Trapp, V. Schurig, *J. Am. Chem. Soc.* **2000**, *122*, 1424 – 1430; d) O. Trapp, V. Schurig, *Comput. Chem.* **2001**, *25*, 187 – 195; e) O. Trapp, V. Schurig, *Chem. Eur. J.* **2001**, *7*, 1495 – 1502; f) O. Trapp, V. Schurig, *J. Chromatogr. A* **2001**, *911*, 167 – 175; g) I. D′Acquarica, F. Gasparrini, M. Pierini, C. Villani, G. Zappia, *J. Sep. Sci.* **2006**, *29*, 1508 – 1516.
[18] a) O. Trapp, *Anal. Chem.* **2006**, *78*, 189 – 198; b) O. Trapp, *Chirality* **2006**, *18*, 489 – 497; c) O. Trapp, *Electrophoresis* **2006**, *27*, 2999 – 3006; d) O. Trapp, *Electrophoresis* **2007**, *28*, 691 – 696; e) O. Trapp, S. K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447 – 7451; *Angew. Chem. Int. Ed.* **2007**, *46*, 7307 – 7310; f) O. Trapp, S. K. Weber, S. Bauch, T. Bäcker, W. Hofstadt, B. Spliethoff, *Chem. Eur. J.* **2008**, *14*, 4657 – 4666; g) O. Trapp, *Chem. Today* **2008**, *26*, 26 – 28; h) O. Trapp, *J. Chromatogr. B* **2008**, *875*, 42 – 47; i) O. Trapp, S. Bremer, S. K. Weber, *Anal. Bioanal. Chem.* **2009**, *395*, 1673 – 1679; j) J. Troendlin, J. Rehbein, M. Hiersemann, O. Trapp, *J. Am. Chem. Soc.* **2011**, *133*, 16444 – 16450.
[19] Y. Okamoto, E. Yashima, *Angew. Chem.* **1998**, *110*, 1072 – 1095; *Angew. Chem. Int. Ed.* **1998**, *37*, 1020 – 1043.
[20] L. Thunberg, S. Allenmark, *Tetrahedron: Asymmetry* **2004**, *15*, 1507 – 1511.
[21] W. H. Pirkle, C. J. Welch, B. Lamm, *J. Org. Chem.* **1992**, *57*, 3854 – 3580.

