Radically Initiated Asymmetric Cyclizations as Model Reactions for Asymmetric Cyclocopolymerizations†

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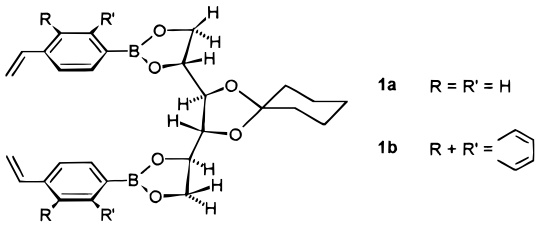
The two divinyl compounds 3,4-*O*-cyclohexylidene-D-mannitol 1,2;5,6-bis-*O*-[(4-vinylphenyl)boronate] (**1a**) and 3,4-*O*-cyclohexylidene-D-mannitol 1,2;5,6-bis-*O*-[(4-vinylnaphthyl-1)boronate] (**1b**) were cyclized by radical initiation either with an excess of 2,2′-azobis(isobutyronitrile) (AIBN) or with tributyltin hydride under radical-generating conditions. The cyclization products contained a 19-membered ring and were obtained in yields of around 60%. During this cyclization, two new stereogenic centers are formed and four stereoisomers are therefore possible. The composition could be determined quantitatively after removing the template, 3,4-*O*-cyclohexylidene-D-mannitol, and deboronation, thus furnishing **5**−**8**. In this way the stereochemical course of the cyclization could be investigated in detail. The reaction is a good model for the stereochemical course of the cyclocopolymerization of monomers **1a** or **1b** with other comonomers such as methyl methacrylate. It was shown that with both monomers the first step shows low stereoselectivity, whereas the second step is highly stereoselective, which is the cause of the strong optical activity of the copolymers from **1a** or **1b** after removal of the template.

Introduction

Previously, we have reported investigations concerning the preparation of optically active polymers from 1-substituted or 1,1-disubstituted olefins in which the chirality of the polymers is dependent on the configuration of the main chain (main-chain chirality).[1−3] It was possible to obtain copolymers, e.g. **P1**, with high optical activity by copolymerization of the bifunctional monomer **1** with



other common comonomers (e.g. methyl methacrylate), followed by removal of the chiral template, 3,4-*O*-cyclohexylidene-D-mannitol. Studies of the mechanism of the copolymerization of **1a** showed[2,3] that a cyclocopolymerization (see Scheme 1) occurs, leading to linear copolymers and inducing chirality in the (4-vinylphenyl)boronic acid diads. Further investigations, using suitable low molecular weight model compounds, showed that both (*S*,*S*)- and (*R*,*S*)- configurated diads are present in comparable amounts.[2]

Over the past few years a number of new examples of induced chirality in cyclopolymerization using threitol derivatives as template molecules have been reported.[4] Recently, a further example was published.[5] An asymmetric cyclopolymerization without a chiral template has also been described; in this case, the asymmetric induction was brought about by an optically active catalytic system.[6]

More information on the mechanism of the asymmetric cyclopolymerization in the presence of templates and especially on the stereochemical course of the cyclization was needed, and the radical cyclization of **1a** and **1b** forming monomeric products has now been examined.[7] This allowed the reaction products to be analyzed and their composition to be determined quantitatively. In this way it should also be possible to compare the stereochemical course of the cyclization of the styrene derivative **1a** and the 1-vinylnaphthalene derivative **1b**. The radically initiated copolymerization of **1b** with methyl methacrylate and subsequent removal of the template also results in the formation of optically active copolymers **P1b** with main-chain chirality.[8,9] These polymers show extremely strong exciton couplets upon circular dichroism analysis. The reaction mechanism seems to be similar to the cyclocopolymerization of **1a**. There is, however, a difference since, due to the strong interaction of the dioxaborolane ring system with the peri position of the naphthalene ring system, the naphthalene rings are rotated out of the dioxaborolane plane. Furthermore, the position of the vinyl groups of the naphthalene system will be anti to the naphthalene rings, and

† This paper is dedicated to Hans Paulsen on the occasion of his 75th birthday.

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(1) Wulff, G.; Zabrocki, K.; Hohn, J. *Angew. Chem.* **1978**, *90*, 567; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 535.

(2) Wulff, G.; Kemmerer, R.; Vogt, B. *J. Am. Chem. Soc.* **1987**, *109*, 7449.

(3) For a review, see: Wulff, G. *Angew. Chem.* **1989**, *101*, 22; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 21.

(4) Kakuchi, T.; Kawai, H.; Katoh, S.; Haba, O.; Yokota, K. *Macromolecules* **1992**, *25*, 5545. Yokota, K.; Haba, O.; Satoh, T.; Kakuchi, T. *Macromol. Chem. Phys.* **1995**, *196*, 2383.

(5) Nakano, T.; Okamoto, Y.; Sogah, D. Y.; Zheng, S. *Macromolecules* **1995**, *28*, 8705.

(6) Coates, G. W.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6270.

(7) These results have first been reported at the 5th International Polymer Conference (IPC 94), Osaka, Japan, 1994. See: Wulff, G.; Gladow, S.; Kühneweg, B.; Krieger, S. *Macromol. Symp.* **1996**, *101*, 355.

(8) Wulff, G.; Gladow, S.; Krieger, S. *Macromolecules* **1995**, *28*, 7434.

(9) The 1-vinylnaphthalene diads in **P1b** possess the (*S*,*S*)-configuration in copolymers with methyl methacrylate. This has been shown in ref 8; unfortunately Figure 2 of this paper is a misdrawing, showing opposite configurations in the Fischer projection, as in Figure 2 of ref 10.

(10) Wulff, G.; Gladow, S. *Macromol. Chem. Phys.* **1995**, *196*, 3341.

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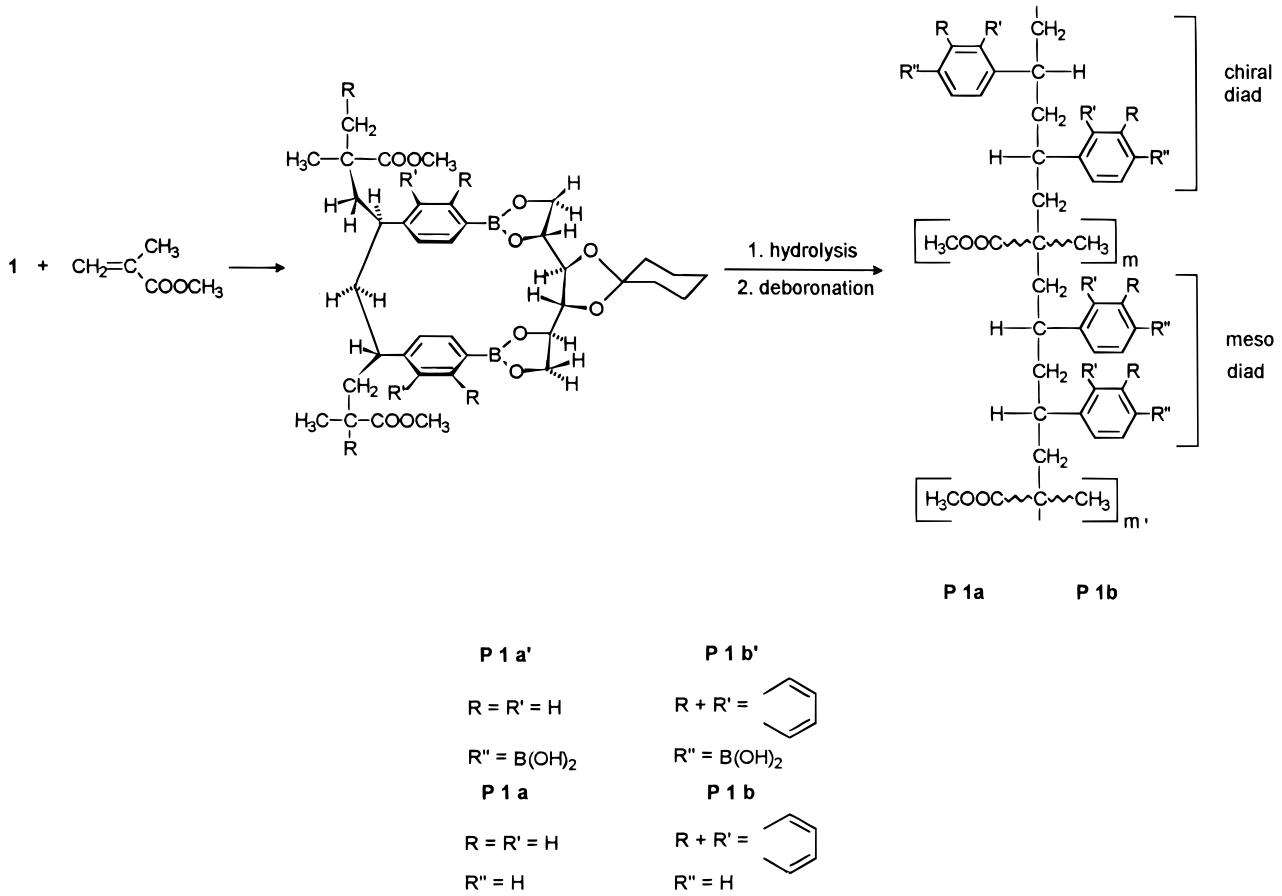
Scheme 1. Schematic Representation of the Asymmetric Cyclocopolymerization of 1 with Methyl Methacrylate[a]



[a] In the formula of the initial cyclization product only one stereoisomer is presented. The formula of the open-chain polymer shows the two main diads (meso diad and (*S*,*S*)-diad) in the chain.

the naphthalene rings will no longer possess rotational symmetry, as was the case for **1a**. Rotamers are hence expected, as was previously evidenced during a photochemical intramolecular [2 + 2] cycloaddition of **1b**.[11] In the latter case the activated complex for the reaction must be completely different compared to that for the cyclopolymerization. Further details on the mechanism of the cyclopolymerization of **1b** are therefore desirable.

Results

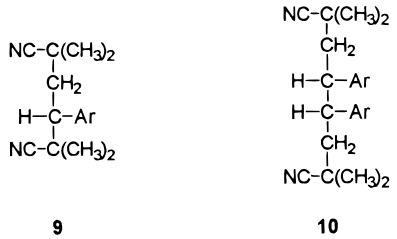
The radically initiated cyclizations of **1a** and **1b** to monomeric cyclic structures were attempted by two different synthetic pathways. The first method was patterned on a previously reported procedure for the intramolecular cyclization of achiral divinyl compounds induced by radicals obtained from the thermolysis of an excess of azobis(isobutyronitrile) (AIBN).[12] The other method was also first described for an intramolecular cyclization of achiral divinyl compounds but involved the use of tributyltin hydride under radical-generating conditions.[13]

Cyclizations with AIBN. A toluene solution of monomer **1a** or **1b** and a toluene solution containing a 3-fold molar excess of AIBN were dropped simultaneously during 12 h into a large volume of toluene heated to 80 °C. Under these conditions a large excess of isobutyronitrile radicals is formed while the monomers **1a** or **1b** are present in low concentrations. The isobutyronitrile radical attacks a double bond of the monomers **1a** and **1b**. Since both **1a** and **1b** possess time-averaged C_2-symmetry, it does not matter which of their two double bonds is attacked. The intermediate radical **2** predominantly causes a cyclization when the primary monomer radical attacks the second double bond and furnishes radical **3** (see Scheme 2). This is in accordance with the observation that **1a** as well as **1b** undergo nearly exclusively cyclopolymerization, which involves the same cyclization step. In contrast to cyclopolymerization, an excess of highly reactive isobutyronitrile radicals now leads to a preferred recombination of the radical **3** with an isobutyronitrile radical and yields **4**. Side reactions, which diminish the yield of **4**, include polymerization, when the radical **3** attacks another monomer **1**. Another side reaction could be the recombination of the radical **2** with an isobutyronitrile radical. After hydrolysis and deboronation, this should furnish an enantiomeric mixture of **9**. Less probable is a nearly simultaneous attack of an isobutyronitrile radical at both double bonds of **1** and a subsequent intramolecular recombination. This would yield meso compound **10** and an enantiomeric mixture of **11** after splitting off the template and deboronation.

(11) Wulff, G.; Krieger, S.; Kühneweg, B.; Steigel, A. *J. Am. Chem. Soc.* **1994**, *116*, 409.
(12) Kämmerer, H.; Jung, A.; Shukla, J. S. *Makromol. Chem.* **1967**, *107*, 259. Kämmerer, H.; Shukla, J. S. *Makromol. Chem.* **1968**, *116*, 62.
(13) Shea, K. J.; O`Dell, R.; Sasaki, D. Y. *Tetrahedron Lett.* **1992**, *33*, 4699.

With the experimental procedure mentioned before, a mixture of stereoisomers for the cyclization product **4** is formed in high yield. It was our main goal to determine the stereochemistry of **4**. As two new stereogenic centers are generated, four stereoisomers have to be expected. Owing to the lability of the boronate esters **4**, a purification was not feasible at this stage. Therefore, compounds **4a** and **4b** were hydrolyzed, and the template 3,4-*O*-cyclohexylidene-D-mannitol was removed. In order to facilitate separation of the dimerization products, the crude mixture was directly deboronated, thus yielding a mixture of **5**−**8** as well as the byproducts **9**−**11** and some oligomers. Purification involved Kugelrohr distillation and chromatography on silica. The pure diastereoisomers **5a**/**6a** and **7a**/**8a** were obtained in the case of **1a**, and **5b**/**6b** and **7b**/**8b** in the case of **1b**. Since the yield of purified diastereomers is 49% (for **1a**) and 55% (for **1b**), the yield of the corresponding cyclization product **4** should be in the range of at least 60%, which is fairly good for such a cyclization involving a 19-membered ring.

The ratio of the diastereomers **5**/**6**:**7**/**8** was determined by gas chromatography from the original mixture obtained after deboronation. In both cases, for the phenyl (**a**) as well as for the naphthyl derivatives (**b**), the ratio is 1.0:1.1, corresponding to a de of 4.8%. After distillation of the crude deboronation reaction mixture, the ratio of the enantiomers was determined by HPLC using a chiral cellulose−tris(3,5-dimethylphenylcarbamate) (Daicel) column, which achieves baseline separation of all four



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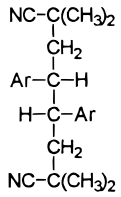

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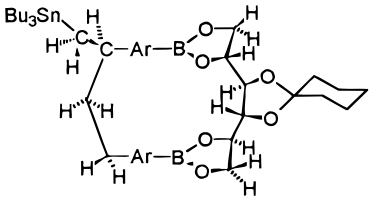

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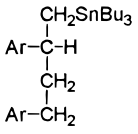

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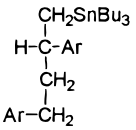

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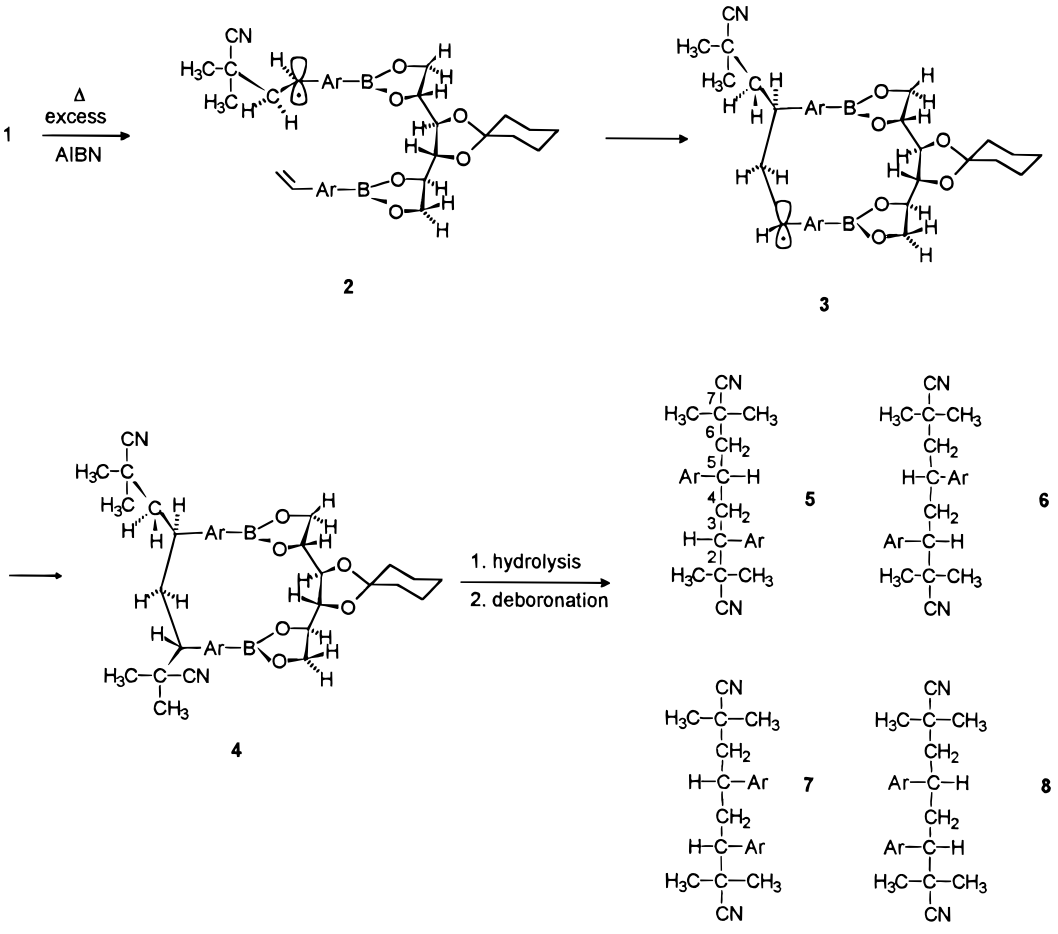
Scheme 2. Schematic Representation of the Radical Cyclization of 1 and the Preparation of the Dimers 5−8[a]



[a] For the cyclization only one stereoisomer is represented, whereas all four possible stereoisomers of the dimers are shown. Ar stands for phenyl in the case of **a** and 1-naphthyl in case of **b**.

Table 1. Quantitative composition (in %) of the Stereoisomers Formed after Hydrolysis of 4 and Deboronation of the Reaction Products

type of compound	**5**	**5/6**	**6**	%ee (**5**:**6**)	**7**	**7/8**	**8**	%ee (**7**:**8**)	%de (**5**/**6**:**7**/**8**)
phenyl **a**		47.6				52.4			4.8
naphthyl **b**		47.6				52.4			4.8
phenyl **a**	44.2		3.4	85.7	48.4		4.0	84.7	
naphthyl **b**	42.9		4.7	80.3	46.7		5.7	78.2	

Table 2. Optical Rotation of the Diastereomers and the Copolymers

compd	*c* (g/100 mL)	$[\alpha]^{20}_{365}$	compd	*c* (g/100 mL)	$[\alpha]^{20}_{435}$
7a/**8a**	1.0	+13.2°	**7b**/**8b**	0.5	−28.5°
5a/**6a**	0.5	−259.6°	**5b**/**6b**	0.5	+275°
polymer **P1a**	1.2	−30°	polymer **P1b**	1.0	+73.5°

stereoisomers **5a**−**8a** as well as of **5b**−**8b**. The results of the quantitative analysis of the two mixtures are given in Table 1.

The next step is the assignment of structures **5**−**8** to the four stereoisomers formed since these compounds are new both for the phenyl as well as the naphthyl derivatives. In both cases, starting with **1a** or with **1b**, the diastereomers could be separated preparatively by chromatography on silica, and the faster migrating isomers **7a**/**8a** as well as **7b**/**8b** crystallized readily. The slower migrating isomer **5a**/**6a** could not be crystallized, and **5b**/**6b** crystallized rather slowly. This gives some indication of the similarity of their structures.

The investigation of the chiroptical properties presents another possibility for characterization, since all four diastereomers are not racemic mixtures but contain one enantiomer strongly enriched. The sign of optical rotation of the slower moving diastereomers is identical with that of the corresponding polymers **P1a** and **P1b**, respectively, prepared from **1a** or **1b** (see Table 2). The sign of the optical rotation as well as of the circular dichroism of **5a**/**6a** is also identical with those of the model compounds prepared for the assignment of the absolute configuration of **P1a**.[2] Therefore, the main enantiomer of **5a**/**6a** is **5a** and has (3*R*,5*S*)-configuration. This corresponds to an (*S*,*S*) diad in **P1a**. Since the ring closure and the subsequent recombination to **4** is similar for both diastereomers, the formation of the other diastereomer **7a**/**8a** also should be very stereoselective and the main enantiomer must therefore be **7a** with a (3*R*,5*R*)-configuration.

The assignment of the stereoisomers in the naphthyl series (**5b**−**8b**) is a little more complicated. A similar assignment can be proposed by analogy with the phenyl derivatives and by comparison of the optical rotations with the polymer **P1b**. The assignment of the diastereomeric structure can be more accurately based on comparison of the NMR data with those of similar compounds. Diastereomeric 2,4-bis(1-pyrenyl)pentanes have been synthesized and investigated spectroscopically.[14,15] The preferred conformation of the two diastereomers was determined. Only the (*S*,*S*)/(*R*,*R*)-diastereomer showed a strong interaction between the two pyrenyl ring systems, evidenced by a strong shielding of the 9 and 10 protons of the aromatic rings. The same phenomenon was observed in the diastereomer **5b**/**6b**, in

(14) Vandendriesche, J.; Palmans, P.; Toppet, S.; Boens, N.; De Schryver, F. C.; Masuhara, H. *J. Am. Chem. Soc.* **1984**, *106*, 8057.
(15) De Schryver, F. C.; Collart, P.; Vandendriesche, J.; Goedeweeck, R.; Swinnen, A.; Van der Auweraer, M. *Acc. Chem. Res.* **1987**, *20*, 159.

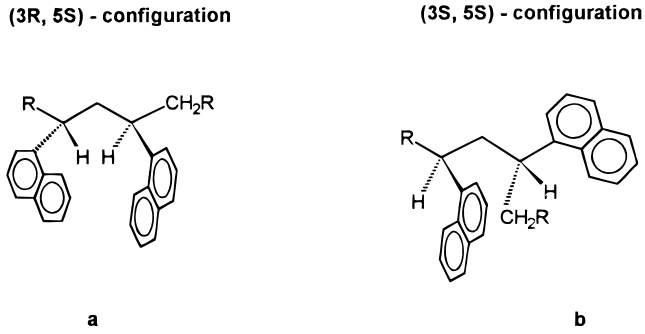


Figure 1. The preferred conformation of **5b**/**6b** is shown in part a, that of **7b**/**8b** in part b. The data are in accord with those previously reported for 2,4-bis(1-pyrenyl) pentanes.[14,15]

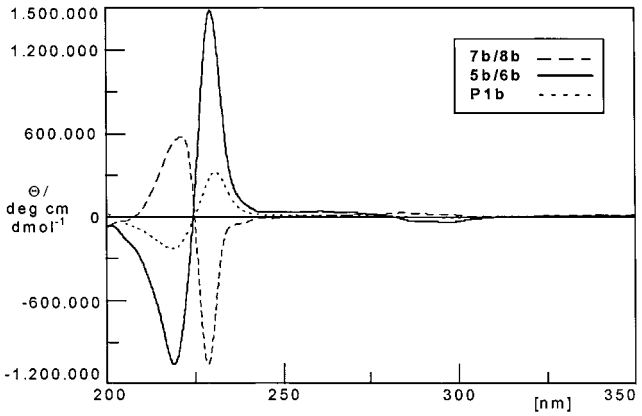


Figure 2. CD spectra (in THF) of the enantiomerically enriched **5b**/**6b** and **7b**/**8b** as well as that of the corresponding polymer **P1b**.

which four protons (6,7,6′,7′-H) of the naphthalene rings are strongly shifted upfield to $\delta = 6.43-6.63$, whereas the other naphthalene protons show their resonances at $\delta = 7.01-7.90$. The interaction of the four protons can be explained by a similar conformation, as in the case of the pyrenyl derivatives. This is shown in Figures 1a and 3.

The naphthalene protons of the second diastereomer show all resonances at $\delta = 7.23-7.98$, and in this case, no ring current influence from the second ring system is observed, as would be expected from the preferred conformation shown in Figure 1b. Therefore, by analogy with the previously reported observations for the diastereomeric 2,4-bis(1-pyrenyl)pentanes, **5b**/**6b** represent the (3*S*,5*R*)/(3*R*,5*S*)-configuration, which corresponds to (*S*,*S*)/(*R*,*R*) in the 2,4-bis(1-pyrenyl)pentanes and in the corresponding polymer **P1b**. Accordingly, **7b**/**8b** have the (3*S*,5*S*)/(3*R*,5*R*)-configuration, corresponding to (*S*,*R*)/(*R*,*S*) in polymer **P1b**.

The prevailing enantiomer in the diastereomers can be determined by circular dichroism. Figure 2 shows the CD spectra of the enantiomerically enriched **5b**/**6b** and **7b**/**8b** as well as that of the corresponding polymer **P1b**.

The prevailing enantiomer of **5b**/**6b** exhibits a strong positive exciton couplet at 226 nm (zero crossing) with [A] = 1008.0 L mol^{-1} cm^{-1} (calculated for 100% ee) corresponding to the ^1B_b transition of naphthalene. This exciton couplet is caused by the dipole−dipole interaction of the electric transition moments of the ^1B_b transition of the neighboring naphthalene rings. The ^1B_b transition is polarized along the long axis of the naphthalene chromophore.

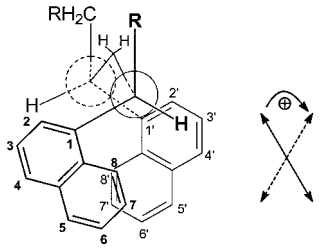


Figure 3. Application of the exciton couplet rules[16,17] to **5b**/**6b** which proves a positive chirality of the main enantiomer **5b**.

Since the conformation of the two diastereomers can be deduced from the investigation of 2,4-bis(1-pyrenyl)-pentanes[14,15] as well as from a comparison of the NMR data, the exciton couplet rules of Nakanishi and Harada[16,17] can be applied.

A structure like **5b** should possess naphthalene rings positioned relative to each other as represented in Figure 3. From this, a positive exciton couplet is expected. This suggests that in **5b**/**6b** the **5b** isomer with (3*R*,5*S*)-configuration is the prevailing enantiomer. A similar conformational analysis of **7b**/**8b** resulted in a preferred conformation from which a negative exciton couplet is expected for **7b**. With these considerations all structures for **5b**−**8b** have been assigned.

As already pointed out, the yields of the ring closure products **4** from **1a** as well as from **1b** range around 60%. The main byproduct (with 20−25% yield) stems from the recombination of the isobutyronitrile radical with radical **2**, which after workup leads to **9a** and **9b**, respectively. The compounds can be isolated from the reaction mixtures by distillation and chromatography. They consist of a mixture of enantiomers for which the ratio has not been determined. For comparison, **9a** (a known compound[18]) could be obtained in 65% yield and as a racemic mixture by heating styrene with AIBN under conditions similar to those used for **1a**. Similarly, the new naphthyl derivative **9b** can be synthesized as a racemic mixture from 1-vinylnaphthalene.

Another side product (formed in only 0.5−1.0% yield) consisted of diastereomeric mixtures of **10a**/**11a** and **10b**/**11b**, respectively. These compounds were also synthesized independently to prove their structures. The mixture **10a**/**11a** can be obtained by heating styrene with AIBN but using a lower amount of AIBN than required for the synthesis of **9a**. The mixture of diastereomers is obtained in 45% yield and can be separated into pure **10a** and **11a** (as a racemic mixture). Similarly, a mixture of **10b**/**11b** arises from 1-vinylnaphthalene, from which **10b** crystallized easily in pure form.

Oligomers were only formed in low amounts during this radical cyclization and were not investigated further.

Cyclization with Tributyltin Hydride. Isobutyronitrile radicals are highly reactive. A less reactive radical with strong sterical demand should show a higher stereoselectivity. To prove this, cyclizations are performed with tributyltin hydride in the presence of AIBN.[13] Tributyltin radicals generated from isobutyronitrile radicals and tributyltin hydride attack **1**. Similarly to radical **2**, cyclization furnishes an analog of **3** and this radical abstracts a hydrogen from tributyltin hydride to generate the ring system **12** and a new stannyl radical. In contrast to **4**, the cycle **12** contains only one new stereogenic center. The workup to isolate **12** was similar to that reported for **4**; the deboronation was performed with BuLi and gave two enantiomers, **13** and **14**. An excess of one enantiomer is formed as shown by the optical rotations of **13a**/**14a** of $[\alpha]^{20}_{365} = -39.6°$ and **13b**/**14b** of $[\alpha]^{20}_{365} = -37.0°$. Enantiomeric excesses could again be determined by HPLC using cellulose−tris(3,5-dimethylphenylcarbamate) as stationary phase (Table 3).

Table 3. Percentage of Enantiomers in 13/14 Determined by HPLC with Cellulose−tris(3,5-dimethylphenyl carbamate)

compd	(*R*)	(*S*)	%ee	(*R*):(*S*)
13a/**14a**	57.5	42.5	15	1.35
13b/**14b**	68	32	36	2.13

It can be seen that with a more selective radical the enantiomeric excess is higher for the first stereogenic center. This is especially true for the naphthyl derivatives, which show an ee of 36% (in contrast to 4.6% ee for isobutyronitrile radicals).

The absolute configuration of the prevailing enantiomer can again be determined by CD. In the case of **13b**/**14b**, a strong negative exciton coupling is observed at 227 nm (zero crossing). In accordance with the discussion of the CD of **5b** (see also Figure 3) and previous investigations for compounds with two interacting chromophores but only one stereogenic center,[19] the main enantiomer **14b** should possess (*R*)-configuration. Since the same mechanism applies for **1a**, the phenyl derivative **14a** is the main enantiomer with an (*R*)-configuration.

Discussion

Radically induced cyclization of **1a** and **1b** in the presence of an excess of radicals provides the monomeric cycles **4** and **12** in relatively good yields. The facile formation of macrocycles is in accordance with the cyclocopolymerization of these monomers shown in Scheme 1. Nearly exclusive cyclopolymerization occurs during polymerization, whereas some side reactions take place during cyclizations in the presence of an excess of radicals.

The cyclization with an excess of isobutyronitrile radicals (to **4**) offers some advantages for the investigation of the stereochemical course of the reaction. After splitting off the template and deboronation, four stereoisomers, **5**−**8** are formed, as expected for the generation of two new stereogenic centers. Since the $^{\bullet}C(CH_3)_2CN$ radical nearly exclusively attacks the less substituted methylene group of the double bond and forms the more stable radical (e.g. **2**), the stereochemistry at the initially attacked double bond can be distinguished from that of the second. The stereochemistry at the stereogenic center adjacent to the $CH_2C(CH_3)_2CN$ group (i.e. C-5) is therefore indicative of the selectivity of the primary radical attack.

A further advantage of this model system is the formation of chiral compounds **7** and **8**, which are models for the meso-diad in the polymer. The meso-diad of the polymer, is, in principle, achiral, and therefore the (*R*,*S*)-

(16) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in OrganicStereochemistry; University Science Books: Mill Valley, CA, 1983.*

(17) Nakanishi, K.; Berova, N. In *Circular Dichroism—Principles and Application*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH: Weinheim, 1994.

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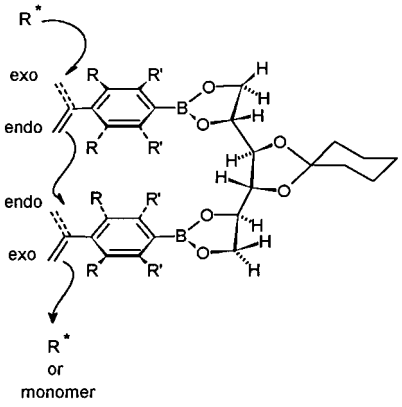
Scheme 3. Schematic representation of the Different Steps of the Radical Cyclization of 1[a]



[a] Leads to the stereoisomers of the cyclization products as shown in Schemes 1 and 2. Only the last step differs in the radical cyclization and the asymmetric cyclocopolymerization.

and (*S*,*R*)-configurations cannot be distinguished in the polymer. The origin of the meso-diads in the polymer could either be a low selectivity in the step generating the first stereogenic center or a low selectivity in the second step. This question can now be answered for model system **4**. The chiral diads ["racemo"], which are observed in the cyclopolymerization of **1a** and **1b**, possess the (*S*,*S*)-configuration, which corresponds to (3*R*,5*S*) in the dimers.

The initial attack at the monomers **1a** or **1b** can occur at both double bonds of the monomer, resulting in identical products since **1a** and **1b** possess time-averaged C_2-symmetry. X-ray crystallography of a mannitol derivative with 1,2;5,6-di-*O*-(phenylboronate) groups (a model for **1a**) showed[3] that the dioxaborolane rings and phenyl rings are in the plane and that the two phenyl rings show only a small deviation from a parallel orientation. Thus, in the crystal there is a terraced arrangement of the ring systems, which should also be one of the preferred conformations in solution. There are two stabilized conformations of the double bond in **1a** (shown in Scheme 3) which are designated *exo* and *endo* with respect to the second ring system. The radical can either attack the double bond in the *endo* or *exo* conformation. Assuming an attack at the first double bond from the *endo* site (see Scheme 3), a benzyl radical **2** is formed, which in principle could attack the second double bond in its *endo* or in its *exo* configuration to form e.g. **3**. In either case, this benzyl radical reacts at the *Si* face. The steric requirements are better fulfilled for an attack of radical **2** (in a preferred conformation in conjugation with the aromatic ring) at the second double bond in its *endo* position. On the other hand, an attack at an *exo*-positioned second double bond requires an unfavorable rotation around the benzyl radical bond, as well as an out-of-plane rotation of the second double bond, resulting in a destabilized new benzyl radical (isomer of **3**). This ring formation from **2** to **3** should be the decisive step in the formation of the second new stereogenic center since the radical **3** should only react from beneath from the *Re* face with another radical (or with a monomer in the case of polymerization). If an attack takes place at the first stereogenic center, the (*S*)-configuration is expected at the *endo* position and the (*R*)-configuration at the *exo* position. As can be seen from Table 4, an attack at the less hindered *exo* position is slightly favored, with an ee of 3.6−2.8%, and signifies that the attack is possible in both ways with nearly the same probability. Surprisingly, this is true both for the phenyl as well as for the naphthyl derivative. In the case of the naphthyl derivative **1b** (Scheme 3) there is only one preferred conformation of the double bond due to an unfavorable interaction with the periproton of the naphthalene. Therefore an interconversion from *endo* to *exo* can only be achieved by rotation of the whole ring system (for this reason the naphthalene ring system was indicated with dotted lines in the case of the *exo* double bond).

Table 4. Stereoselectivity in the Formation of the First and the Second Stereogenic Center of 4

first step	**5a** + **8a** = 48.2%	**6a** + **7a** = 51.8%	3.6% ee
	5b + **8b** = 48.6%	**6b** + **7b** = 51.4%	2.8% ee
second step	**5a**:**8a** = 44.2:4.0	83.4% de	("racemo")
	7a:**6a** = 48.4:3.4	86.9% de	("meso")
	5b:**8b** = 42.9:5.7	76.5% de	("racemo")
	7b:**6b** = 46.7:4.7	81.7% de	("meso")

It was of interest to investigate whether or not the selectivity for the first step can be influenced by the reactivity and the steric demand of the radical. Therefore, in another experiment the cyclization was induced with the sterically demanding and less reactive tributyltin radical. The *exo* position was then favored with an ee of 15% for **1a** and 36% for **1b**. The selectivity consequently depends on the nature of the radical and is remarkably more pronounced in the case of the naphthyl derivative **1b**, which in itself is more crowded. An attacking polymeric radical should behave somewhere between the isobutyronitrile and the tributyltin radical, so that in this case a slight excess of the *exo* attack (resulting in an (*R*)-configuration) is expected.

The quantitative composition of the four products **5**−**8** allows the diastereoselectivity of the second step forming the second stereogenic center to be calculated (see Table 4).

The second stereogenic center C-3 is formed with much higher stereoselectivity, favoring the (3*R*)-configuration in 76−87% de, i.e. (*R*):(*S*) ratios are 88:12 to 93.5:6.5. Interestingly, the selectivity is somewhat higher starting from a (5*R*)-configuration, which is true both for the phenyl derivative **1a** as well as the naphthyl derivative **1b**. A (3*R*,5*R*)-configuration in these model compounds (**7a** and **7b**) corresponds to the (*R*,*S*)-configuration (meso diad) in a polymer. These diads are therefore nearly exclusively formed due to the low selectivity when the first stereogenic center C-5 is established. The question is whether the formation of the (3*S*)-isomer is mainly determined during the step from **2** to **3** (ring closure) or from **3** to **4** (recombination). Furthermore, it is of interest whether or not stereoselectivity remains the same during the polymerization. The ring closure step from **2** to **3** should be identical in the radical cyclization and during the cyclopolymerization since it involves similar radicals. The only difference is a large polymeric chain substituent at the radical instead of an isobutyronitrile group in **2**. This might increase the selectivity of the ring closure due to hindered rotation of the radical.

With regard to the last step it is unlikely that the higher reactivity of the isobutyronitrile radical compared to a monomer will cause another stereochemical outcome in this step. Inspection of the space-filling models of **3** reveals that the only attack, even of a radical, should come from beneath. It is therefore assumed that the 6.5−12% of (3*S*)-configurated stereogenic centers in the last step have been established during the ring closure step from **2** to **3**.

In contrast to a polymerization, the strong reactivity of the radicals and their high concentration causes considerable amounts of byproducts, especially **9**, which is formed in 20−25% yield. During polymerization a similar reaction with the monomer would cause either cross-linking, which is not observed, or insertion of the monomer, thus forming a 21-membered ring. Under usual conditions this is not observed, but can be impelled by copolymerization in the presence of aluminum sesquichloride.[20] Without addition of such reagents, more than 99% of cyclocopolymerization involving a 19-membered ring was found. It is not to be expected that the side-reaction of **2** with isobutyronitrile radicals is stereoselective, thus reacting preferably with one of the two isomers of **2** resulting from *endo*- or *exo*-attack at the first double bond. The ratio of (*R*):(*S*) at the first stereogenic center in **5**−**8** should therefore not be changed by this side reaction.

Conclusion

The asymmetric, radical-initiated cyclization of either **1a** or **1b** with an excess of azobis(isobutyronitrile) involved a 19-membered ring and led to the monomeric cyclization products **4a** and **4b**, respectively, in good yields. This reaction is a good model for the stereochemical course of the asymmetric cyclocopolymerization of **1a** or **1b** with a comonomer such as methyl methacylate. Unlike the situation for the polymer, the stereochemistry in the cyclization products **4a** and **4b** can easily be investigated. For this, the template molecules as well as the boron are removed, giving the stereoisomers **5**−**8**. Their ratio allows the stereoselectivity of the different steps of the cyclization to be deduced. There is a good analogy with the cyclocopolymerization so that these results can also be used in the interpretation of the stereoselectivity of the different steps of the cyclocopolymerization.

Furthermore, it was found that **1a** and **1b** gave very similar results in these investigations, showing that the stereochemical course is the same in both cases and that the reaction products have identical stereochemistry. This means that during cyclopolymerization the stereochemistry along the polymeric chain of copolymers obtained from **1a** and **1b** should be identical.

Experimental Section

General Procedures. Elemental analyses were performed in the microanalytical laboratory of the Faculty of Natural Sciences of the Heinrich-Heine-University Düsseldorf. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz with $CDCl_3$ as solvent and TMS as internal standard ($\delta = 0$). CD spectral measurements were carried out at 25 °C in a 0.1 mm cuvette. UV spectral measurements were carried out at 25 °C in a 1 mm cuvette. Melting points were measured with a Büchi 510 melting point apparatus.

Analytical TLC was performed using precoated silica gel plates. Daicel Chiralcel OD columns were used for HPLC for racemic resolution (flow rate of 0.2 mL/min, hexane/*i*-PrOH = 9/1 as eluent; the separation of **13a**/**14a** required a flow rate of 0.1 mL/min and hexane as eluent).

Template Monomers. 3,4-*O*-Cyclohexylidene-D-mannitol 1,2;5,6-bis-*O*-[(4-vinylphenyl)boronate] (**1a**)[2] and 3,4-*O*-cyclohexylidene-D-mannitol 1,2;5,6-bis-*O*-[(4-vinylnaphthyl-1)boronate] (**1b**)[8] were prepared as described earlier.

2,2,7,7-Tetramethyl-3,5-diphenyloctane-1,8-dinitrile (5a−8a). Following a previously reported procedure,[12] a solution of 3.0 g (6 mmol) of **1a** in 200 mL of toluene and a second solution of 4.44 g (27 mmol) of AIBN in 200 mL of toluene were dropped simultaneously during 12 h into 1.5 L of toluene heated to 80 °C. After removal of the solvent, the residue was suspended in dilute aqueous NaOH and extracted with diethyl ether. The aqueous solution was then acidified with hydrochloric acid and the product was extracted with diethyl ether. After removal of the organic solvent, the colorless crude product was deboronated using $AgNO_3/NH_3$ as described before.[2] The syrupous residue was then distilled in a Kugelrohr distillation apparatus (180 °C at 2 Pa): UV (THF) λ_{max} (ϵ) 206 nm (11 400), 258 nm (530). The diastereomers were separated by column chromatography on silica, using CH_2Cl_2 as eluent.

5a/**6a** [(3*R*,5*S*)/(3*S*,5*R*)]: yield 23.9%; TLC with CH_2Cl_2, R_f 0.47; colorless resin; content of **5a**, 92.9%; $[\alpha]^{20}_{365} = -259.6$ (*c* 0.5, THF); CD (THF) $\lambda = 218.2$ nm; molar ellipticity $= -4.41 \times 10^4$; ^{1}H NMR ($CDCl_3$) $\delta = 0.99, 1.04, 1.20, 1.21$ (12 H, s), 1.86−1.88 (2H, m), 2.08 (1H, dd, $J = 12.0$; 2.8 Hz), 2.21−2.47 (2H, m), 2.40−2.50 (1H, m), 6.99−7.95 (10H, m); ^{13}C NMR ($CDCl_3$) $\delta = 24.80, 26.50, 26.92, 27.85$ (4C), 31.73, 36.38, 38.85, 40.39, 48.38, 50.97 (6C), 124.54, 124.63 (2C), 127.04, 127.75, 127.99, 128.53, 128.75, 129.29, 138.09, 143.10 (12C); MS *m*/*z* = 344 (M^+), 276, 198, 172, 91 (100); HPLC for **5a**, t_R 29.6 min, **6a**, t_R 32.5 min.

7a/**8a** [(3*R*,5*R*)/(3*S*,5*S*)]: yield 25.1%; TLC with CH_2Cl_2, R_f 0.56; white crystals after recrystallization from hexane/$CHCl_3$ (19:1); mp 126 °C; content of **7a**, 92.3%; $[\alpha]^{20}_{365} = +13.2$ (*c* 1.0, THF); CD (THF) $\lambda = 218.2$ nm; molar ellipticity $= +1.54 \times 10^4$; ^{1}H NMR ($CDCl_3$) $\delta = 0.95, 1.12, 1.14, 1.38$ (12H; s), 1.91 (1H, dd, $J = 14.2$; 2.7 Hz), 1.97 (1H, dd, $J = 14.2$; 10.6 Hz), 2.17−2.23 (2H, m), 2.51−2.59 (1H, m), 2.68 (1H, dd, $J = 4.8$; 9.9 Hz), 6.99−7.35 (10H, m); ^{13}C NMR ($CDCl_3$) $\delta = 24.55, 26.80, 27.06, 27.58$ (4C), 31.94, 36.83, 40.24, 40.74, 44.72, 52.10 (6C), 124.51, 124.65 (2C), 126.76, 127.43, 127.67, 128.50, 128.67, 129.24, 138.26, 144.73 (12C); HPLC for **7a**, t_R 32.0 min, for **8a**, t_R 29.1 min. Anal. Calcd for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.40; H, 8.08; N, 8.28.

2,2,7,7-Tetramethyl-3,5-bis(1-naphthyl)octane-1,8-dinitriles (5b−8b) were prepared as described for **5a**−**8a**. Kugelrohr distillation at 220 °C and 2 Pa afforded **5b**−**8b**; UV (THF) λ_{max} 224 nm (ϵ 104 000), 284 nm (ϵ 12 800). Separation of the diastereomers was accomplished by column chromatography on silica using CH_2Cl_2 as eluent.

5b/**6b** [(3*R*,5*S*)/(3*S*,5*R*)]: yield 27.0%; TLC with CH_2Cl_2, R_f 0.24; white crystals after recrystallization from hexane/$CHCl_3$ (19:1); mp 61 °C; content of **5b**, 90.1%; $[\alpha]^{20}_{435} = +275$ (*c* 0.5, THF); CD (THF) λ (nm) [molar ellipticity] 219.1 [-1.12×10^6], 224.6 [zero crossing], 229.0 [1.55×10^6]; ^{1}H NMR ($CDCl_3$) $\delta =$ 0.86, 0.99, 1.20, 1.25 (12H, s), 1.91 (1H, dd, $J = 14.3$; 7.7 Hz), 2.14 (1H, dd, $J = 14.3$; 5.1 Hz), 2.60−2.69 (1H, m), 2.86−2.96 (1H, m), 3.15 (1H, dd, $J = 12.0$; 2.9 Hz), 3.46−3.54 (1H, m), 6.43−6.63 (4H, m), 7.01−7.24 (2H, m), 7.53-7.90 (8H, m); ^{13}C NMR ($CDCl_3$) $\delta = 24.30, 26.24, 26.85, 27.39$ (4C), 31.95, 32.81, 37.71, 40.65, 42.32, 49.80 (6C), 122.17, 122.45, 123.24, 124.64, 124.99, 125.18, 125.24, 125.26, 125.30, 125.36 (14C), 124.68, 124.83 (2C), 131.52, 133.32, 133.66, 133.67, 134.67, 140.46 (6C); MS *m*/*z* = 444 (M^+), 376, 248 (100), 222, 154, 141; HPLC for **5b**, t_R 37.5 min, for **6b**, t_R 46.6 min.

7b/**8b** [(3*R*,5*R*)/(3*S*,5*R*)]: yield 28.0%; TLC with CH_2Cl_2, R_f 0.36; white crystals after recrystallization from hexane/$CHCl_3$ (19:1), mp 143 °C; content of **7b**, 89.2%; $[\alpha]^{20}_{435} = -28.5$ (*c* 0.5, THF); CD (THF) λ (nm) [molar ellipticity] 220.1 [5.56×10^5], 225.2 [zero crossing], 228.2 [-1.19×10^6]; ^{1}H NMR ($CDCl_3$) δ = 0.70, 0.76, 1.12, 1.49 (12H, s), 2.07 (1H, dd, $J = 14.1$; 2.8 Hz), 2.23 (1H, dd, $J = 14.1$; 10.8 Hz), 2.35−2.53 (2H, m), 3.32−3.40 (1H, m), 3.84 (1H, dd, $J = 11.0$; 3.9 Hz), 7.23−7.98 (14H, m); ^{13}C NMR ($CDCl_3$) $\delta = 24.75, 26.72, 27.13, 27.22$ (4C), 31.50, 33.08, 37.95, 41.78, 43.52, 44.64 (6C), 122.13, 122.50, 123.91, 125.13, 125.18, 125.28, 125.41, 125.57, 126.05, 126.32, 127.06, 128.15, 129.04, 129.38 (14C), 124.35, 124.57 (2C), 130.89, 133.08, 133.94, 133.98, 135.17, 140.43 (6C); MS *m*/*z* = 444 (M^+), 376, 248, 222, 154 (100), 141; HPLC for **5b**, t_R 49.9 min, for **6b**, t_R 42.1 min. Anal. Calcd for $C_{32}H_{32}N_2$: C, 86.45; H, 7.26; N, 6.30. Found: C, 86.30; H, 7.27; N, 6.35.

(20) Wulff, G.; Krieger, S. *Macromol. Chem. Phys.* **1994**, *195*, 3679.

2,2,5,5-Tetramethyl-3-phenylhexane-1,6-dinitrile (9a) was obtained in 20% yield by column chromatography of the deboronation products during the preparation of **5a**−**8a** or can be prepared as follows: 1.56 g (15 mmol) of styrene and 12.3 g (75 mmol) of AIBN, dissolved in 150 mL of toluene each, were added dropwise during 4 h to 1 L of toluene heated to 80 °C. After removal of the solvent, the residue was purified by Kugelrohr distillation (at 135 °C and 2 Pa): yield 2.4 g (65%); TLC with CH_2Cl_2, R_f 0.75; white crystals were obtained after recrystallization from hexane; mp 122 °C (lit.[18] mp 121−122 °C); ^{1}H NMR ($CDCl_3$) δ = 0.97, 1.09, 1.33, 144 (12H, s), 2.20 (2H, d, J = 6.0 Hz), 2.77 (1H, t, J = 6.0 Hz), 7.24 (5H, s). When the reaction is performed at higher temperature (180 °C), an additional fraction containing **10a** and **11a** is isolated.

2,2,5,5-Tetramethyl-3-(1-naphthyl)hexane-1,6-dinitrile (9b) was obtained by column chromatography as a side product in the preparation of **5b**−**8b** in 25% yield as white crystals after recrystallization from hexane (mp 127 °C). Compound **9b** can be obtained as a racemic mixture in 25% yield from 1-vinylnaphthalene as a byproduct from the preparation of **10b** and **11b**: ^{1}H NMR ($CDCl_3$) δ = 0.82, 1.02, 1.36, 1.61 (12H, s), 2.36−2.49 (2H, m), 3.86 (1H, dd, J = 2.6; 9.2 Hz), 7.49−7.63 (3H, m), 7.76−7.91 (3H, m), 8.18 (1H, m); ^{13}C NMR ($CDCl_3$) δ = 24.27, 24.78, 27.33, 28.27 (4C), 33.21, 38.37, 43.01, 44.05 (4C), 122.55, 124.66, 125.38, 125.80, 126.90, 128.38, 129.42 (7C), 124.22, 124.38 (2C), 132.70, 133.95, 136.29 (3C); MS m/z = 290 (M^+), 222, 154, 84 (100). Anal. Calcd for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.61; H, 7.65; N, 9.72.

2,2,7,7-Tetramethyl-4,5-diphenyloctane-1,8-dinitriles (10a,11a) were formed as side products in the preparation of **5a**−**8a** as well as in the preparation of **9a**. The mixture can be prepared in a higher yield, like **9a**, but from 1.56 g (15 mmol) of styrene and 4.93 g (30 mmol) of AIBN. The yield is 1.16 g (45%) for both diastereomers. Separation was achieved by crystallization from hexane/$CHCl_3$ (19:1) (**11a** does not crystallize).

10a: yield 25.6%; white crystals after recrystallization from hexane/$CHCl_3$ (19:1); mp 145 °C; ^{1}H NMR ($CDCl_3$) δ = 0.97, 1.30 (12H, s), 1.95−2.10 (4H, m), 2.99−3.16 (2H, m), 6.80−7.35 (10H, m); MS m/z = 344 (M^+), 288, 240, 172, 91 (100); HPLC, t_R 26.4 min. Anal. Calcd for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.46; H, 8.21; N, 8.13.

11a: yield 19.4%; colorless resin; ^{1}H NMR ($CDCl_3$) δ = 0.83, 1.07 (12H, s), 1.60−2.25 (4H, m), 2.88−3.21 (2H, m), 6.80−7.40 (10H, m); mass spectra m/z = 344 (M^+), 288, 240, 172, 91 (100).

2,2,7,7-Tetramethyl-4,5-bis(1-naphthyl)octane-1,8-dinitriles (10b and 11b) were detected by HPLC during isolation of **5b**−**8b**. The mixture can be prepared in higher yield, like **10a** and **11a**, by converting 2.08 g (14 mmol) of 1-vinylnaphthaline and 4.44 g (27 mmol) of AIBN. Compound **10b** was isolated as described for **10a**; **11b** was not purified. The yield of **10b** is 0.97 g (31%) as white crystals after recrystallization from hexane/$CHCl_3$ (19:1); mp 198 °C; ^{1}H NMR ($CDCl_3$) δ = 0.63 (6H, s), 0.94 (6H, s), 1.73 (2H, d, J = 13.7), 2.03 (2H, dd, J = 13.7, 10.7 Hz), 4.17 (2H, dd), 7.49−8.26 (14H, m); ^{13}C NMR ($CDCl_3$) δ = 26.61, 27.91 (4C), 32.52, 43.52, 44.62 (6C), 122.63, 124.32, 125.54, 125.68, 126.64, 127.59, 129.22 (14C), 124.34 (2C), 133.23, 133.83, 139.53 (6C); MS m/z = 444 (M^+), 222 (100), 154; HPLC, t_R 30.3 min. Anal. Calcd for $C_{32}H_{32}N_2$: C, 86.45; H, 7.26; N, 6.30. Found: C, 86.49; H, 7.46; N, 6.30.

Tri-*n*-butyl-2,4-diphenylbutyltin (13a and 14a). Following a previously reported procedure,[13] 3.0 g (6 mmol) of **1a** was dissolved in 150 mL of benzene, then 3.0 g (10 mmol) of tributyltin hydride and 0.32 g of AIBN were added. After refluxing for 2 h, the solvent was removed, the crude product was suspended in 100 mL of dry diethyl ether, and 13.3 mmol of *n*-butyllithium in hexane (an excess of 15%) was added. After heating for 40 min, the mixture was hydrolyzed by being poured onto ice; the organic phase was separated and the solvent was removed. Purification was achieved by column chromatography (TLC with petroleum ether 40/60, R_f 0.35) resulting in 1.29 g (43%) of a colorless liquid with 15% ee for **14a**: $[\alpha]^{20}_{365}$ = −39.6 (*c* 1.2, THF); ^{1}H NMR ($CDCl_3$) δ = 0.51−0.68 (6H, m), 0.84 (9H, t, J = 7.1 Hz), 1.14−1.45 (14 H, m), 1.88−1.97 (2H, m), 2.44 (2H, t, J = 7.8 Hz), 2.71−2.77 (1H, m), 7.08−7.30 (10H, m); ^{13}C NMR ($CDCl_3$) δ = 9.00, 13.71, 27.40, 29.15 (12C), 18.51, 34.19, 42.88, 43.53 (4C), 125.55, 126.03, 127.19, 128.20, 128.35, 128.39 (10C), 142.58, 147.83 (2C); MS m/z = 500 (M^+), 443 (100), 387, 329; HPLC for **13a**, t_R 37.6 min, for **14a**, t_R 51.1 min. Anal. Calcd for $C_{28}H_{44}Sn$: C, 67.35; H, 8.88. Found: C, 67.51; H, 9.03.

Tri-*n*-butyl-2,4-bis(1-naphthyl)butyltin (13b and 14b) was prepared as described for **13a** and **14a**. Purification was achieved by column chromatography (TLC with $CHCl_3$/petroleum ether (60/80) 3/17, R_f 0.42), resulting in a yield of 1.37 g (38%) of a colorless liquid (36% ee for **14b**): $[\alpha]^{20}_{365}$ = −37.0 (*c* 1.2, THF); CD (THF) λ (nm) [molar ellipticity] 227.0 [2.04 × 10^4], 229.4 [zero crossing], 232.0 [−1.86 × 10^4]; ^{1}H NMR ($CDCl_3$) δ = 0.55 (6H, t, J = 8.1 Hz), 0.79 (9H, t, J = 7.1 Hz), 1.09−1.33 (12H, m), 1.43−1.46 (2H, m), 2.16−2.30 (2H, m), 2.93−3.03 (2H, m), 3.78−3.88 (1H, m), 7.15−8.02 (14H, m); ^{13}C NMR ($CDCl_3$) δ = 9.17, 13.66, 27.37, 29.09 (12C), 17.75, 31.22, 36.50, 41.54 (4C), 122.68, 122.71, 122.99, 123.06, 123.10, 123.79, 125.22, 125.28, 125.43, 125.54, 125.58, 125.87, 126.43, 128.65, 128.93, 131.75, 133.84, 134.08, 138.61, 143.98 (20C); MS m/z = 600 (M^+), 543 (100), 487, 429; HPLC for **13b**, t_R 17.5 min, for **14b**, t_R 18.6 min. Anal. Calcd for $C_{36}H_{48}Sn$: C, 72.13; H, 8.07. Found: C, 72.24; H, 8.10.

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