

Immobilization of Bis(Bipyridine) BINOL Ligands and Their Use in Chiral Resolution

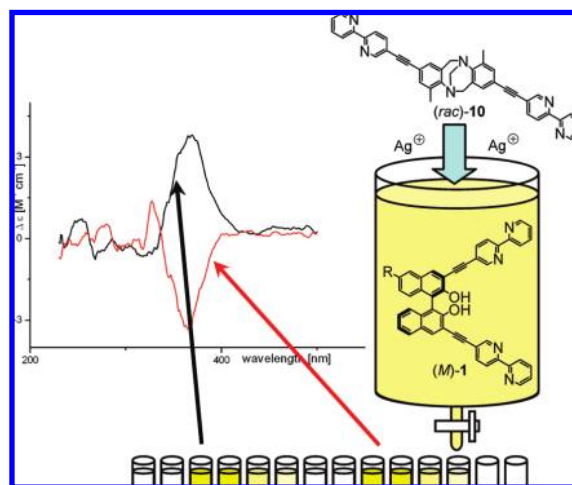
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ABSTRACT



An enantiomerically pure bis(bipyridine) BINOL ligand was synthesized which was functionalized with an iodine substituent in its periphery. Using this halogen function, the ligand was immobilized on a commercially available polystyrene gel via Suzuki cross-coupling. The functionalized gel was found to be effective in the chiral resolution of similar bis(bipyridine) ligands based on a Tröger's base core.

The last two decades have witnessed an enormous development in the field of helicates.¹ Besides the appealing beauty of these inherently chiral metallo-supramolecular compounds, one of the reasons for this interest is that the helicates can be used as model systems to study cooperative effects^{1f,2} or (dia-)stereoselective self-assembly processes³ of supramo-

lecular aggregates. Recently, however, functional aspects of helicates came into focus such as, e.g., their interaction with DNA.⁴

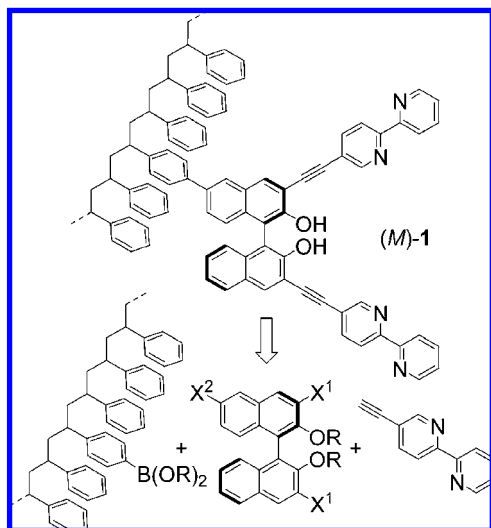
Some time ago, we were able to synthesize a bis(bipyridine) BINOL ligand and demonstrate its diastereoselective self-assembly into dinuclear helicates.⁵ Thus, we thought to make use of the chiral information of this ligand to

(1) Recent reviews: (a) Albrecht, M. *Chem. Rev.* **2001**, *101*, 3457. (b) Mamula, O.; von Zelewsky, A. *Coord. Chem. Rev.* **2003**, *242*, 87. (c) Hannon, M. J.; Childs, L. *J. Supramol. Chem.* **2004**, *16*, 7. (d) Costisor, O.; Linert, W. *Inorg. Chem.* **2005**, *17*, 289. (e) Miyake, H.; Tsukube, H. *Supramol. Chem.* **2005**, *17*, 53. (f) Piguet, C.; Borkovec, M.; Hamacek, J.; Zeckert, K. *Coord. Chem. Rev.* **2005**, *249*, 705. (g) Albrecht, M. *Top. Curr. Chem.* **2005**, *248*, 105. (h) Albrecht, M.; Fröhlich, R. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 797. (i) He, C.; Zhao, Y.; Guo, D.; Lin, Z.; Duan, C. *Eur. J. Inorg. Chem.* **2007**, 3451.

(2) Some recent examples: (a) Zeckert, K.; Hamacek, J.; Senegas, J.-M.; Dalla-Favera, N.; Floquet, S.; Bernardinelli, G.; Piguet, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7954. (b) Hamacek, J.; Borkovec, M.; Piguet, C. *J. Chem. Soc., Dalton Trans.* **2006**, 1473. (c) Hamacek, J.; Piguet, C. *J. Phys. Chem. B* **2006**, *110*, 7783. (d) Canard, G.; Piguet, C. *Inorg. Chem.* **2007**, *46*, 3511. (e) Dalla-Favera, N.; Hamacek, J.; Borkovec, M.; Jeannerat, D.; Gmly, F.; Bünzli, J.-C. G.; Ercolani, G. *Chem.—Eur. J.* **2008**, *14*, 2994.

implement a function in our helicates. In this paper, we report on the synthesis of an immobilized enantiomerically pure bis(chelating) ligand strand that could be used in a proof of principle study for the resolution of a similar racemic bis(chelating) ligand through liquid chromatography (LC) presumably via diastereoselective helicate formation.

Scheme 1. Retrosynthetic Analysis of Immobilized Bis(bipyridine) BINOL Ligand (*M*)-1



To immobilize our ligand on a polymer gel, we had to choose a suitable position to introduce an additional functional group into the ligand structure that would allow us to covalently link our ligand to the polymer. We decided to use the 6-position of the BINOL-core for this purpose for two reasons: First, it is far away from the bipyridines and should not interfere with metal binding. Second, it can be selectively addressed by an electrophilic attack. As shown in Scheme 1, the synthesis of the immobilized ligand needed three building blocks: a polystyrene furnished with boronic acid ester groups, a protected BINOL equipped with (masked) halide functions (X^1 , X^2), and an ethynylated 2,2'-bipyridine that are coupled sequentially via cross-coupling procedures.

(3) Some recent reviews about stereoselective self-assembly of supramolecular aggregates: (a) Spector, M. S.; Selinger, J. V.; Schnur, J. M. *Top. Stereochem.* **2003**, *24*, 281. (b) Hamilton, T. D.; MacGillivray, L. R. *Crvst. Growth Design* **2004**, *4*, 419. (c) Mateos-Timoneda, M. A.; Crego-Calama, M.; Reinhoudt, D. N. *Chem. Soc. Rev.* **2004**, *33*, 363. (d) Supramolecular Chirality: Crego-Calama, M.; Reinhoudt, D. N. *Top. Curr. Chem.* **2006**, *265*. (e) Lee, S. L.; Lin, W. *Acc. Chem. Res.* **2008**, *41*, 521. For a more comprehensive list of references on the diastereoselective self-assembly of helicates, see references in: (f) Bunzen, J.; Bruhn, T.; Bringmann, G.; Lützen, A. *J. Am. Chem. Soc.* **2009**, *131*, 3621, and ref 1i.

(4) Review: (a) Hannon, M. J. *Chem. Soc. Rev.* **2007**, *36*, 280. Some recent examples: (b) Malina, J.; Hannon, M. J.; Brabec, V. *Chem.—Eur. J.* **2007**, *13*, 3871. (c) Pascu, G. I.; Hotze, A. C. G.; Sanchez-Cano, C.; Kariuki, B. M.; Hannon, M. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4374. (d) McDonnell, U.; Kerchoffs, J. M. C. A.; Castineiras, R. P. M.; Hicks, M. R.; Hotze, A. C. G.; Hannon, M. J.; Rodger, A. J. *Chem. Soc., Dalton. Trans.* **2008**, 667. (e) Malina, J.; Hannon, M. J.; Brabec, V. *Nucleic Acids Res.* **2008**, *36*, 3630. (f) Malina, J.; Hannon, M. J.; Brabec, V. *Chem.—Eur. J.* **2008**, *14*, 10408.

(5) Lützen, A.; Hapke, M.; Griep-Raming, J.; Haase, D.; Saak, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2086.

In order to prepare the boronated polystyrene, we followed a procedure described by Hodge and Zhang.⁶ Bio-Beads S-X 1 from BIO-RAD was chosen as the starting material. After cleaning of the commercial polymeric material following a procedure described by Fréchet and Farrell,⁷ the boronic acid function was introduced into the polystyrene backbone.^{6,8}

5-Ethynyl-2,2'-bipyridine could be prepared in five steps starting from 2-aminopyridine using a modified Negishi reaction as the key step.^{8,9}

The most effort, however, had to be spent on the synthesis of the BINOL building block. As a first step, enantiomerically pure (*M*)-BINOL was desymmetrized by introducing a bromine substituent at the 6-position of the BINOL following an approach of Cai et al.:¹⁰ one of the hydroxyl functions of the BINOL was transformed into a pivaloyl ester. The bulky ester group largely prevents acylation of the second hydroxyl group due to steric hindrance. Thus, we obtained the desired monoester in 91% yield and only 9% of the readily crystallizing diester. Due to the deactivating ester group, electrophilic bromination in dichloromethane at $-78\text{ }^{\circ}\text{C}$ occurred only at the other naphthalene unit. After that, the ester was saponified with sodium hydroxide solution and the reactive hydroxyl functions were protected as methoxymethyl ethers by a Williamson ether synthesis with methoxymethyl chloride ((*M*)-2).^{8,11}

Since the BINOL building block still needed to be furnished with the two bipyridine units which we decided to introduce before we immobilized the whole ligand on the polymer, the bromine had to be masked in order to make the following transformations regioselective. For this purpose, we adopted a protocol by Kobayashi et al.¹² and exchanged the bromine for a trimethylsilyl group affording BINOL (*M*)-3. (*M*)-3 was then lithiated in the 3,3'-position making use of the ortho-directing effect of the acetal protecting groups and subsequently quenched with iodine solution to give the diiodinated building block ((*M*)-4) needed for the Sonogashira coupling with 5-ethynyl-2,2'-bipyridine (5) (Scheme 2).

(*M*)-4 and 5 were then coupled in a 2-fold Sonogashira reaction to give (*M*)-6 in an excellent yield of 90% (Scheme 3).

The next task was an *ipso*-substitution of the trimethylsilyl group at the 6-position of the BINOL using iodine monochloride¹² in order to reactivate this position for the final Suzuki reaction. Interestingly, this turned out to be the most challenging step in our synthesis. Optimization of the reaction conditions finally allowed quantitative conversion of (*M*)-6 to the desired iodide (*M*)-7 without any byproducts (Scheme 3).

(6) Yuan, X.-Y.; Li, H.-Y.; Hodge, P.; Kilner, M.; Tastard, C. Y.; Zhang, Z.-P. *Tetrahedron: Asymmetry* **2006**, *17*, 2401.

(7) Farrell, M. J.; Fréchet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877.

(8) See the Supporting Information for details.

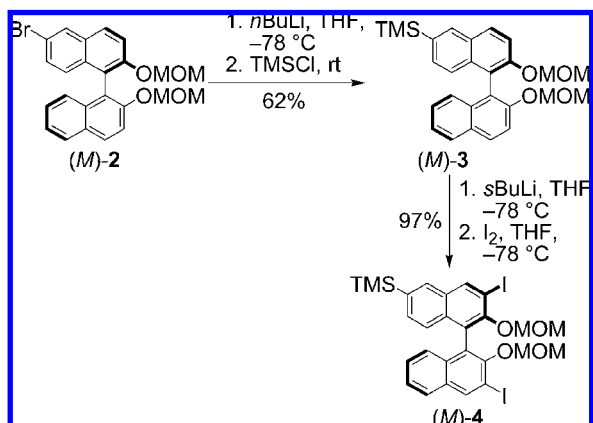
(9) Lützen, A.; Hapke, M. *Eur. J. Org. Chem.* **2002**, 2292. (b) Kiehne, U.; Bunzen, J.; Staats, H.; Lützen, A. *Synthesis* **2007**, 1061. (c) Hapke, M.; Brandt, L.; Lützen, A. *Chem. Soc. Rev.* **2008**, *37*, 2782.

(10) Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4055.

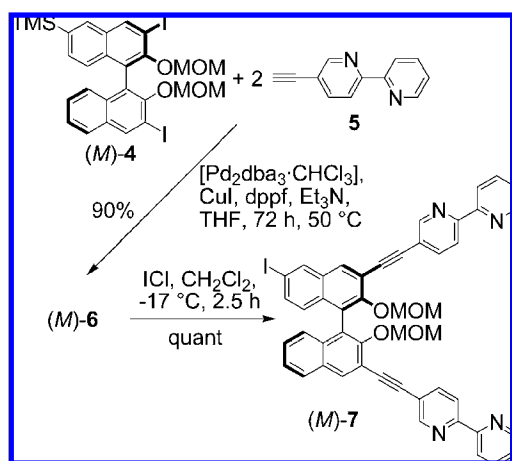
(11) Bai, X.-L.; Liu, X.-D.; Wang, M.; Kang, C.-Q.; Gao, L.-X. *Synthesis* **2005**, 458.

(12) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292.

Scheme 2. Synthesis of BINOL Building Block (*M*)-4



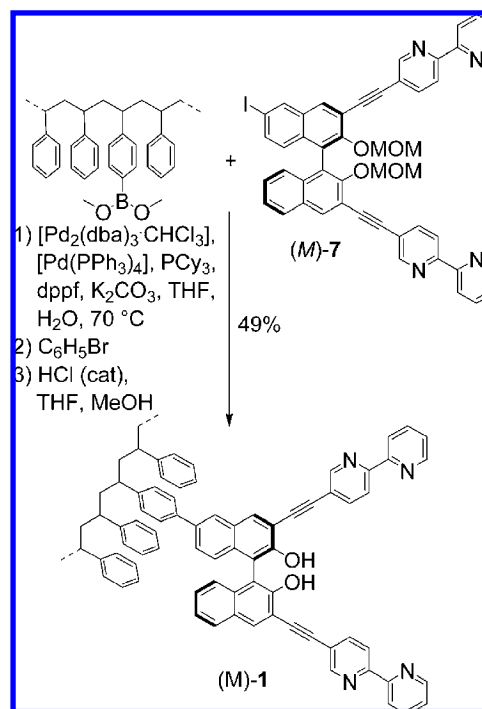
Scheme 3. Synthesis of Bis(bipyridine) BINOL (*M*)-6 and (*M*)-7



(*M*)-7 was then coupled with the boronated polystyrene (Scheme 4). For this a ratio of boronic acid ester groups to (*M*)-7 of 4:1 was used in order to get a moderate loading of the chiral component on the gel. Although we also used THF, because the swelling of the polystyrene beads is at a maximum in this solvent, and aqueous potassium carbonate solution as the base, we had to make several modifications compared to the protocol of Hodge and Zhang to immobilize 6-bromo-1,1'-binaphthyl onto polystyrene⁶ to give credit to the bipyridines that can inactivate the palladium based catalyst: we raised the amount of [Pd(PPh₃)₄] to 40 mol %. Additionally, we used 10 mol % of tris(dibenzylidenacetone)-dipalladium(0) chloroform adduct [Pd₂dba₃·CHCl₃] combined with 30 mol % of tricyclohexylphosphane (PCy₃) and 20 mol % of 1,1'-bis(diphenylphosphino)ferrocene (dppf) because the combination of [Pd₂dba₃·CHCl₃] and PCy₃ has proven to be remarkably active for Suzuki couplings and the combination of the same Pd(0) source and dppf could be demonstrated to be especially active in Sonogashira reactions where bipyridines are involved, e.g., the synthesis of **6**. Furthermore, the reaction time was increased to 8 days

before bromobenzene was added to react with unconverted boronic acid ester functions.

Scheme 4. Synthesis of Immobilized Bis(bipyridine) BINOL (*M*)-1



The gel was filtrated off and suspended in a 1:1 mixture of THF and methanol containing a catalytic amount of hydrochloric acid. After filtration, purification, and drying, the light brown product was studied by infrared spectroscopy. No boron–oxygen bands could be detected. To measure the loading of the gel a C,H,N-elementary analysis was conducted. Since the only source of nitrogen comes from the chiral building block **7**, the loading of the gel can be estimated by this method to be 5.37×10^{-4} mol/g of dried gel. This translates to a yield of 49%.

Having achieved the immobilization of our bis(bipyridine) BINOL ligand, we employed it for the chiral resolution of a racemic mixture of a bis(bipyridine)-substituted derivative of Tröger's base (**8**)¹³ (Figure 1) that could not be resolved by HPLC on commercially available chiral stationary Whelk-01 or DAICEL CHIRALPAK IA phases.

One enantiomer of this ligand **8** should interact stronger with the (*M*)-1 and silver(I) ions because it should form the more stable diastereomeric complex than the other enantiomer. Figure 1 depicts one possible complex that could be formed when the (*5R*,11*R*)-enantiomer of the Tröger's base ligand forms a dinuclear heteroleptic complex with the solid supported (*M*)-configured BINOL ligand. In order to test this hypothesis 1.5 g of (*M*)-1 was used to pack a column with

(13) (a) Kiehne, U.; Weilandt, T.; Lützen, A. *Org. Lett.* **2007**, 9, 1283.
(b) Kiehne, U.; Weilandt, T.; Lützen, A. *Eur. J. Org. Chem.* **2008**, 2056.

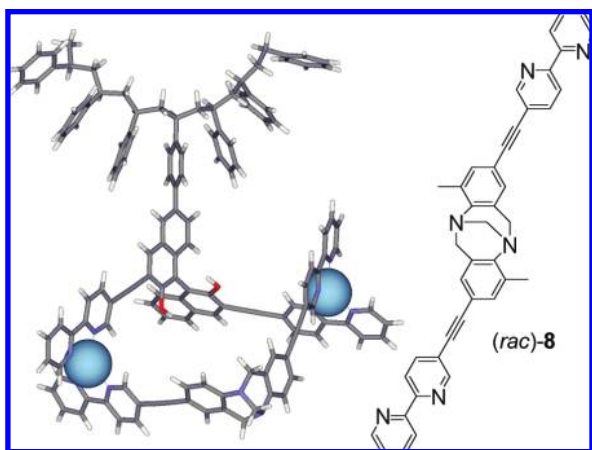


Figure 1. MMFF-minimized structure of the dinuclear silver(I) complex of (5*R*,11*R*)-**8** and (*M*)-**1** (the polystyrene backbone is indicated as a heptameric strand).

a diameter of 1 cm and a height of 11 cm. Therefore, the gel was suspended in a mixture of dichloromethane and acetonitrile in a ratio of 3:1. After packing, swelling of the beads, and washing was complete (no leakage of chiral building blocks or low molecular polystyrene could be detected), the mobile phase was switched to a 0.1 mol/L solution of silver(I)tetrafluoroborate in dichloromethane/acetonitrile 3:1. When the exchange of the mobile phase was complete, 5 mg of the racemic ligand **8** dissolved in 200 μ L of dichloromethane/acetonitrile 3:1 was put on top of the column, and cuts with a volume of 100 μ L were collected. After elution of 900 μ L, the eluate became strongly yellow colored, characteristic for a solution of a bipyridine silver(I) complex. A 1.1 mL portion of this fraction (A) was collected before the eluted solution began to pale again. After elution of another 1.7 mL a second more intensively yellow colored fraction (B) (1.9 mL) could be obtained. Both fractions A and B were then studied by ECD spectroscopy¹⁴ (see Figure 2) and mass spectrometry.

As can be seen, the two fractions exert opposite Cotton effects indicating a chiral enrichment of each enantiomer in the two fractions. ESI-mass spectra of both fractions showed a signal at m/z 411.0 as the base peak $[\text{Ag}_2\text{8}]^{2+}$ and a signal

(14) *Circular Dichroism: Principles and Applications*; Berova, N., Nakanishi, K., Woody R. W., Eds.; Wiley-VCH: New York, 2000; p 877.

at m/z 715.1 $[\text{Ag8}]^+$. It is very important to notice that when we tried to use our immobilized ligand to resolve (*rac*)-**8** without adding the silver(I) salt we only obtained one single fraction of CD-silent (*rac*)-**8**, thus indicating that the resolution obtained with our immobilized ligand (*M*)-**1** in the presence of silver(I) ions indeed occurs via diastereoselective self-assembly of heteroleptic complexes.

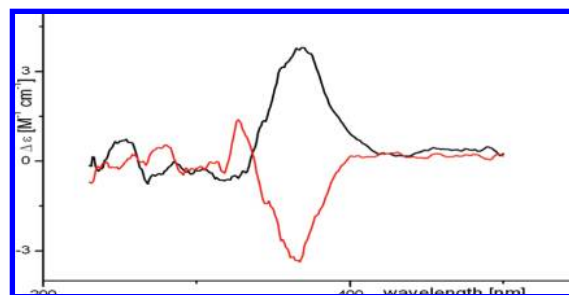


Figure 2. ECD spectra of fraction A (black) and fraction B (red) obtained from the chiral resolution of (*rac*)-**8** on our chiral phase (*M*)-**1**.

In conclusion, we were able to synthesize a new enantiomerically pure bis(bipyridine)BINOL ligand and immobilized it on polystyrene beads in 18 overall steps. This can be used as a chiral phase in the chiral resolution of a racemic mixture of a similar bis(bipyridine) ligand based on a Tröger's base derivative most probably by diastereoselective helicate formation. After this proof of principle we are currently trying to improve the performance of our approach in order to establish it as a generic high-performance liquid chromatography methodology for the resolution of other racemic materials, e.g., by exploring other polymeric materials with superior properties. Furthermore, we are also starting studies to explore the potential of (*M*)-**1** as a ligand for stereoselective reactions.

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Supporting Information Available: Synthetic schemes and experimental and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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