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Asymmetric catalysis by 1,1′-binaphthyl compounds with conformation-defined 3,3′-aryl substituents☆

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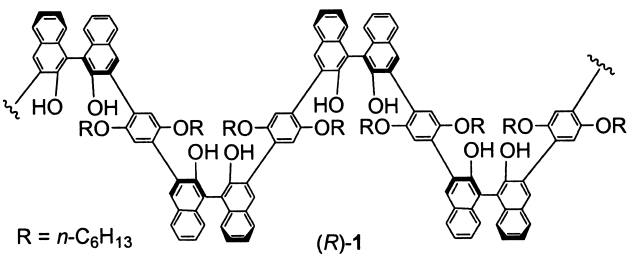
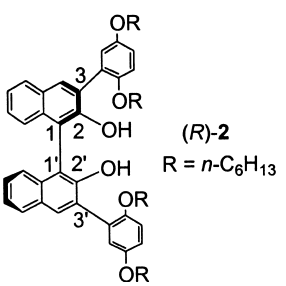
Abstract—Three 1,1′-binaphthyl-based diastereomeric chiral ligands containing conformation-defined 3,3′-aryl substituents are synthesized and characterized. These compounds are isolated from the product mixture of the Suzuki coupling of (*S*)-3,3′-diiodo-2,2′-bis-methoxymethoxy-[1,1′]binaphthalenyl with 2-methoxy-1-naphthylboronic acid. The absolute structures of these compounds are determined by a single crystal X-ray analysis of the (*S*,*S*,*S*)-diastereomer. Among the three diastereomers, i.e. (*S*,*S*,*S*), (*R*,*S*,*S*) and (*R*,*S*,*R*), the (*S*,*S*,*S*) compound shows the highest catalytic activity as well as the highest enantioselectivity for the diethylzinc addition to aldehydes. At 0°C in toluene solution, 5 mol% of the (*S*,*S*,*S*) isomer catalyzed the reaction of diethylzinc with both aromatic and aliphatic aldehydes with up to 96% ee and 90% yield. The other two isomers show quite a low catalytic activity and enantioselectivity. This demonstrates that the 3,3′-aryl conformation of the 1,1′-binaphthyl ligands plays a very important role in the catalytic process. The study of these diastereomeric compounds provides new insights into the design of chiral 1,1′-binaphthyl-based monomer as well as polymer catalysts for asymmetric catalysis.

Extensive studies on the use of axially chiral 1,1′-binaphthyl compounds in asymmetric processes have been conducted.[1–3] A particularly active area is the development of 1,1′-binaphthyl-based chiral catalysts in asymmetric catalysis. The pioneer work of Noyori on BINAP-based [BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] late transition metal complexes has led to significant progress in asymmetric hydrogenation.[4] BINOL-based (BINOL=1,1′-bi-2-naphthol) Lewis acid complexes have also found many applications in asymmetric catalysis.[5] Because it often requires the use of a large amount of catalysts in the Lewis-acid catalyzed reactions, the ability to recover the optically active ligands is practically important. Therefore, we have carried out a program to develop chiral polymer-based BINOL–Lewis acid catalysts. Using polymers in catalysis not only allows easy recovery of catalysts, but also makes continuous production possible in flow reactors.[6–9] The polybinaphthyls constructed in our laboratory are designed to be rigid and stereoregular in order to make the catalytic sites in the polymer chain to be more accessible for reaction substrates.[10] This is quite different from using flexible polymers where many shielded interior sites are not approachable. The rigid and sterically regular polybinaphthyls also permits a systematic modification of the structure and function of these polymer-based catalysts. Previously, we discovered that polymer (*R*)-**1** is highly enantioselective for the diethylzinc addition to benzaldehyde as well as *p*-substituted benzaldehydes.[10b,c] However, its enantioselectivity for other aldehydes such as *o*-substituted benzaldehydes and aliphatic aldehydes was significantly lower. In order to understand the function of the polymer and to further improve its catalytic properties, we prepared (*R*)-**2** as the monomeric model compound.[11]



(*R*)-**1**



(*R*)-**2**
R = *n*-C6H13

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Keywords: asymmetric catalysis; 1,1′-binaphthyls; diethylzinc addition.
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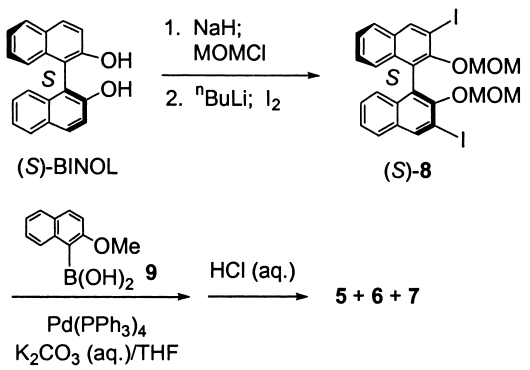
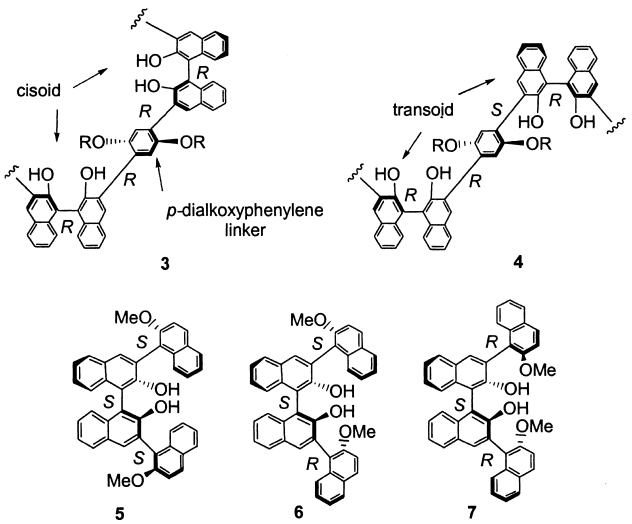


Scheme 1. Synthesis of diastereomeric binaphthyl compounds **5**–**7**.

We found that (*R*)-**2** is highly enantioselective for the reaction of diethylzinc with all types of aldehydes including *o*-, *p*-, or *m*-substituted aromatic aldehydes, linear or branched aliphatic aldehydes, alkyl or aryl substituted α,β-unsaturated aldehydes. In fact, it is the most generally enantioselective catalyst yet reported for this reaction.

The dramatic difference in enantioselectivity between the model compound and the polymer may be related to their differences in steric environment. The adjacent 1,1′-binaphthyl units in polymer (*R*)-**1** can have different relative orientations with respect to the *p*-dialkoxyphenylene. For example, in a coiled helical structure (**3**), all the binaphthyl units are *cisoid*, and in a completely extended zigzag structure (**4**), all the binaphthyl units are *transoid*. In **3**, the 3,3′-aryl conformations of the binaphthyl units are the same, either all *R* or all *S*. However, the *p*-dialkoxyphenylene linker of **4** should have two opposite conformations with respect to the two adjacent binaphthyl units. That is, if the conformation were *R* on one side, it would be *S* on the other side. Therefore, the 3,3′-aryl conformation of the binaphthyl units in the polymer is related to the relative orientation of the adjacent binaphthyl units which further determines the polymer chain conformation. In other words, there is interference between the adjacent catalytic sites in polymer (*R*)-**1**. This interference, however, does not exist in monomer (*R*)-**2**. Thus, the reduction in enantioselectivity observed for the reaction of diethylzinc with aldehydes using polymer (*R*)-**1** versus monomer (*R*)-**2** may originate



from their differences in the 3,3′-aryl conformation of the 1,1′-binaphthyl units. In order to determine the effect of the 3,3′-aryl conformation on the catalytic properties of the 1,1′-binaphthyl ligands, we have designed and synthesized compounds **5**–**7** that have well-defined 3,3′-aryl configuration. Our results on the synthesis and reactivity of these diastereomeric compounds are reported here.

Protection of optically pure (*S*)-1,1′-bi-2-naphthol[(*S*)-BINOL] with methoxymethyl (MOM) group followed by orthometalation and iodonation gave (*S*)-**8** (Scheme 1).[12] The Suzuki coupling[13] of (*S*)-**8** with 2-methoxy-1-naphthylboronic acid (**9**)[14] followed by hydrolysis produced a mixture of the three diastereomeric tetranaphthalene compounds **5**–**7**. Unlike compound (*R*)-**2** whose 3,3′-aryl substituents undergoes rapid rotation around the aryl–aryl bonds at room temperature, the rotation barriers in compounds **5**–**7** are much higher which allow them to be separated at room temperature by column chromatography on silica gel. On the silica gel column, it showed that the least polar isomer was **5** and the most polar isomer was **7** when eluted with ethyl acetate and hexane.

The ^{1}H NMR spectra of compounds **5** and **7** showed a singlet methoxyl signal at δ 3.95 (s, 6H) and 3.83 (s, 6H), respectively, consistent with the expected C_2 symmetry. The ^{1}H NMR spectrum of **6** showed two methoxyl signals at δ 3.81 (s, 3H) and 3.94 (s, 3H), indicating a C_1 symmetric compound. A single crystal X-ray analysis of the C_2 symmetric diastereomer **5** established its absolute structure. As shown in Fig. 1, the configuration of the tetranaphthalene units of **5** is (*S*,*S*,*S*). The dihedral angle of the top binaphthyl unit is 73°, the middle binaphthyl unit is 69°, and the bottom binaphthyl is 74°. The three enantiomers of **5**–**7** were also obtained by starting with (*R*)-BINOL. They gave the same spectroscopic characteristics as their corresponding enantiomers except their opposite optical rotations.

The isolated diastereomers were stored at −5°C which showed no isomerization after a long period of time. A solution of **7** in chloroform-*d* was found to slowly isomerize back to the mixture of the three diastereomers at room temperature when monitored by ^{1}H NMR spectrometry. An equilibrium was reached after 30 days which contained compounds **5**–**7** in a 1.1:2.2:1.0 ratio. This demonstrates that there is essentially no thermodynamic preference for any one of the three diastereomers in solution.

Compounds **5**–**7** were used to catalyze the reaction of diethylzinc with *p*-anisaldehyde in toluene-d_8 at room temperature and the reactions were monitored by using ^{1}H NMR spectroscopy (Scheme 2).[15] As shown in Table 1, the three diastereomeric compounds exhibited very different catalytic properties from each other. Compound **5** had the highest catalytic activity as well as enantioselectivity. It catalyzed the diethylzinc addition to *p*-anisaldehyde to give (*S*)-(*p*-anisyl)propanol with 87% ee and a reaction half-life of 95 min. Both compounds **6** and **7** showed much lower reaction rates as well as much lower enantioselectivity. The two C_2 symmetric ligands (**5** and **7**) showed better enantioselectivity than the C_1 symmetric one (**6**). All the three diastereomers produced (*S*)-1-(4-methoxy-phenyl)-propan-1-ol as the major enantiomer.

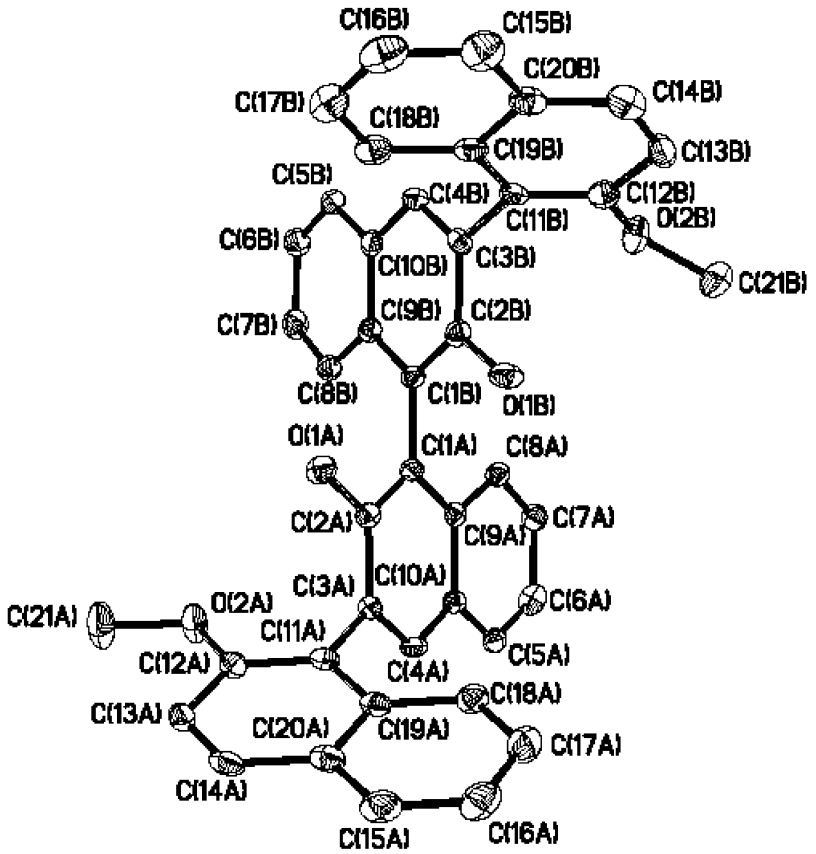
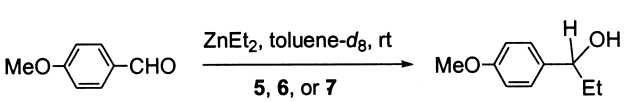


Figure 1. The X-ray structure of diastereomer **5**.

The X-ray structure of **5** indicates that a zinc center can only interact with no more than two of the adjacent oxygen atoms in this compound. The molecular modeling (MacSpartan-Plus-AM1) suggests that all the four oxygen atoms in **7** could coordinate to a single zinc center and up to three of the oxygen atoms in **6** could coordinate to a zinc center. Such differences in coordination ability may be responsible for the observed differences in catalytic activity. Because of the least number of oxygen coordination, the proposed zinc catalyst **10** generated from the reaction of **5** with diethylzinc may have the highest Lewis acidity, leading to the highest catalytic activity among the three diastereomeric catalysts.

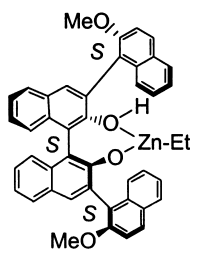


Scheme 2. Catalytic asymmetric reaction of *p*-anisaldehyde with diethylzinc in the presence of compounds **5**, **6** or **7**.

Table 1. Reaction of diethylzinc with *p*-anisaldehyde catalyzed by compounds **5**–**7**

Entry	Et_2Zn (M)	*p*-Anisaldehyde (M)	Compound	$t_{1/2}$ (min)	ee (%)	Configuration
1	0.267	0.133	**5**	95	87	*S*
2	0.270	0.130	**6**	340	14	*S*
3	0.263	0.133	**7**	1440	61	*S*

5 mol% of compound **5**, **6** or **7** was used in each reaction.



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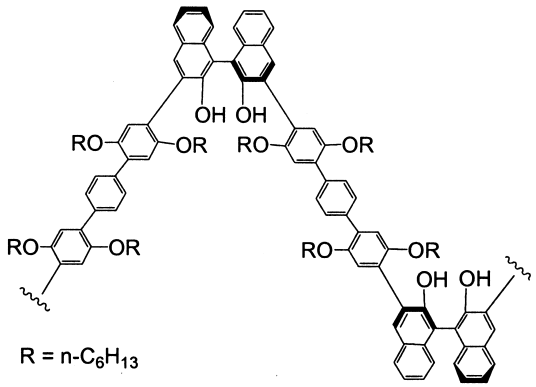
We also studied the use of **5** to catalyze the reaction of diethylzinc with other aldehydes. At 0°C in toluene, 5 mol% of **5** showed 89–96% ee for the diethylzinc addition to both aromatic and aliphatic aldehydes (Table 2). The high enantioselectivity of **5** is similar to (*R*)-**2** but with the opposite alcohol product configuration because of their

Table 2. Enantioselectivity of the catalytic asymmetric reaction of aldehydes with diethylzinc in the presence of compound **5**

Entry	Aldehyde	ee (%)	Configuration
1	*p*-Anisaldehyde	93	*S*
2	Benzaldehyde	93	*S*
3	*o*-Chlorobenzaldehyde	89	*S*
4	*m*-Chlorobenzaldehyde	96	*S*
5	*p*-Chlorobenzaldehyde	92	*S*
7	1-Naphthaldehyde	91	*S*
8	2-Naphthaldehyde	93	*S*
9	Nonylaldehyde	94	*S*

opposite 1,1′-binaphthyl configuration. This indicates that the catalytically active species generated from **5** may be structurally similar to that generated from (*S*)-**2**, the enantiomer of (*R*)-**2**.

The results described above demonstrate that the 3,3′-aryl conformation of the 1,1′-binaphthyl-based catalysts is very important for both the stereoselectivity and catalytic activity. The most favorable catalyst should have a (*S*,*S*)-3,3′-aryl conformation for the (*S*)-1,1′-binaphthyl ligand. Correspondingly, the (*R*,*R*)-3,3′-aryl conformation should be most favorable for the (*R*)-1,1′-binaphthyl ligand. The interference of the adjacent binaphthyl units in polymer (*R*)-**1** might have reduced the population of the most favorable catalyst conformation and significantly decreased the catalytic activity and enantioselectivity over the monomer ligand (*R*)-**2**. This is also supported by our work on another polymer (*R*)-**11** that contains a rigid and long tris-*p*-phenylene linker.[10d] In this polymer, the conformations of the phenylene linkers are independent of the relative orientation of the binaphthyl units and there is minimum interference between the catalytic sites. This polymer has shown almost the same high and general enantioselectivity as monomer (*R*)-**2**.



(*R*)-**11**

Although tremendous amount of study has been conducted on 1,1′-binaphthyl-based Lewis-acid catalysts, how the conformation of their 3,3′-aryl substituents affects their use in catalysis has not been investigated.[16] Our work on the catalytic properties of the diastereomeric 1,1′-binaphthyl compounds **5**–**7** sheds new light on the design of the 1,1′-binaphthyl-based monomer and polymer ligands for asymmetric catalysis.

1. Experimental

1.1. Synthesis and characterization of diastereomers 5–7

Under nitrogen, (*S*)-**8** (1.2 g, 1.80 mmol) was combined with **9** (1.3 g, 6.4 mmol), $Pd(PPh_3)_4$ (0.240 g, 0.21 mmol), THF (30 mL), and aqueous potassium carbonate (2 M, 20 mL, 40 mmol). The resulting mixture was heated at reflux for 48 h. The organic layer was then separated from the aqueous layer at room temperature. The aqueous layer was then extracted twice with ether and the combined organic layers were dried with Na_2SO_4 and concentrated by rotoevaporation. The crude residue (1.3 g) was purified by column chromatography (silica gel, 3–20% gradient of ethyl acetate in hexanes). The diastereomer mixture was hydrolyzed by treating with 6 M HCl in ethanol and dichloromethane at 60–65°C under nitrogen. After column chromatography on silica gel eluted with ethyl acetate/hexanes, the final products (*S*,*S*,*S*)-**5**, (*S*,*S*,*R*)-**6**, and (*R*,*S*,*R*)-**7** were obtained in an overall yield of 77%.

1.1.1. The C_2 symmetric (*S*,*S*,*S*)-5. Yield 50 mg, (4.6%). $[\alpha]_{25}^{D}=-137.0$ (0.25, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 6H), 5.19 (br, 2H), 7.29–7.54 (m, 12H), 7.55–7.72 (m, 2H), 7.79–8.01, (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.94, 113.55, 113.65, 119.69, 123.79, 123.83, 124.79, 124.93, 125.41, 126.85, 126.89, 128.01, 128.32, 128.38, 129.31, 130.20, 132.44, 133.48, 133.75, 151.03, 154.74. MS (CI) *m*/*z* 599 (M^++1), 581 (M^+-H_2O, 100%).

1.1.2. The C_1 symmetric (*S*,*S*,*R*)-6. Yield 360 mg (33.1%). $[\alpha]_{25}^{D}=-117.6$ (0.21, CH_2Cl_2). This compound contains ~5% of other isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.94 (s, 3H), 5.25 (s, 1H), 5.39 (br s, 1H), 7.3–7.5 (m, 12H), 7.6–7.7 (m, 2H), 7.8–8.0 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.73, 56.96, 113.18, 113.26, 113.62, 113.81, 119.47, 120.28, 123.72, 123.80, 123.86, 124.58, 124.87, 124.92, 125.06, 125.32, 125.46, 126.66, 126.87, 127.99, 128.04, 128.09, 128.31, 128.37, 129.21, 129.29, 129.36, 129.94, 130.20, 132.53, 132.71, 133.47, 133.70, 133.74, 133.78, 151.07, 151.21, 154.71, 154.75. MS (CI) *m*/*z* 599 (M+1) 581 (M^+-H_2O, 100%).

1.1.3. The C_2 symmetric (*R*,*S*,*R*)-7. Yield 421 mg (39.1%). $[\alpha]_{25}^{D}=-101.3$ (0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 6H), 5.47 (s, 2H), 7.3–7.5 (m, 12H), 7.69 (d, J=1.6 Hz, 2H), 7.8–8.1 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.83, 112.74, 113.85, 123.79, 123.86, 124.80, 125.03, 125.44, 126.76, 127.01, 128.09, 128.37, 128.41, 129.23, 129.36, 130.00, 132.96, 133.70, 133.77, 151.33, 154.71. MS (CI) *m*/*z* 599 (M+1) 581 (M^+-H_2O, 100%).

Since it was much easier to purify the third diastereomer (*R*,*S*,*R*)-**7** from the crude reaction mixture, we also isolated (*R*,*S*,*R*)-**7** first and then heated it in solution to regenerate a 1:2:1 equilibrium mixture of (*S*,*S*,*S*)-**5**), (*R*,*S*,*S*)-**6** and (*R*,*S*,*R*)-**7**. This made the purification of the other two diastereomers much easier than the direct isolation from the crude. Compound (*R*,*S*,*R*)-**7** (3.212 g) was heated in benzene (75 mL) at 70–75°C for 12 h. The resulting equilibrium mixture was subjected to column chromatography on silica gel eluted with ethyl acetate (5–30%)/hexane which gave pure products (*S*,*S*,*S*)-**5** (0.797 g), (*R*,*S*,*S*)-**6** (1.242 g) and (*R*,*S*,*R*)-**7** (0.484 g) sequentially.

1.2. A typical procedure for the asymmetric diethylzinc addition

In drybox, to a 100 mL round-bottomed flask containing distilled toluene (10 mL) was added diethylzinc (210 μL, 2.1 mmol) and (*S*,*S*,*S*)-**5** (26.9 mg, 0.045 mmol). After stirring for 30 min, the solution was cooled to 0°C and *p*-anisaldehyde (128 μL, 1.0 mmol) was added dropwise to the reaction solution. The resulting mixture was stirred at 0°C for 24 h, and then quenched with 2 M HCl at the same temperature. Diethyl ether (2×10 mL) was used to extract

and the resulting organic layer was washed with brine until neutral pH. After removal of the solvent, the oil residue was purified with column chromatography on silica gel (eluted with 10% ethyl acetate in hexanes) to give 4-methoxy-1-phenyl-1-propanol as a colorless oil (89.5 mg, 54%). ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 0.90 (t, J=7.1 Hz, 3H), 1.77 (m, 2H), 3.80 (s, 3H), 4.54 (m, 1H), 6.88 (d, J=6.8 Hz, 2H), 7.27 (d, J=6.8 Hz, 2H). Specific optical rotation: $[\alpha]_{25}^{D}$= −34.3 (c=4.48, C_6H_6) GC analysis: initial 50°C, 2°C per min to 150°C on a Supelco β-Dex 120 column 30 m× 0.25 mm (ID), 0.25 μm film thickness. Comparison to racemic compound gave 93% ee. (The R enantiomer T_R=112.1 min, The S enantiomer T_S=112.5 min).

2. Supplementary materials

Supplementary materials available for the X-ray crystallographic data of compound **5** on request.

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