Asymmetric Catalysis

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Heterogenization of Shibasaki's Binol/La Catalyst for Enantioselective Epoxidation of α,β-Unsaturated Ketones with Multitopic Binol Ligands: The Impact of Bridging Spacers**

*Xingwang Wang, Lei Shi, Mingxing Li, and Kuiling Ding**

The use of homochiral metal–organic polymers[1] as heterogeneous catalysts for asymmetric reactions has provided a new strategy for chiral catalyst immobilization,[2–4] which might overcome some drawbacks of traditional approaches, such as reduced enantioselectivity or decreased activity in comparison with their homogeneous counterparts.[5–7] With this strategy, the bridged ligands spontaneously coordinate with metal ions to form homochiral metal–ligand assemblies, in which the bridged chiral ligands provide an enantiodiscrimination environment and the metal ions act as the catalytically active centers in asymmetric catalysis.[4,5] In principle, the stereochemical characteristics of the multitopic ligands should have significant impact on the microstructures of the resulting homochiral metal–organic polymers, and thus may exert a profound influence on the enantioselectivity and activity of the catalysis in a given reaction. Therefore, the design and synthesis of multitopic chiral ligands with diverse geometrical features is a central issue in the generation of homochiral metal–organic polymers for heterogeneous asymmetric catalysis (Figure 1).

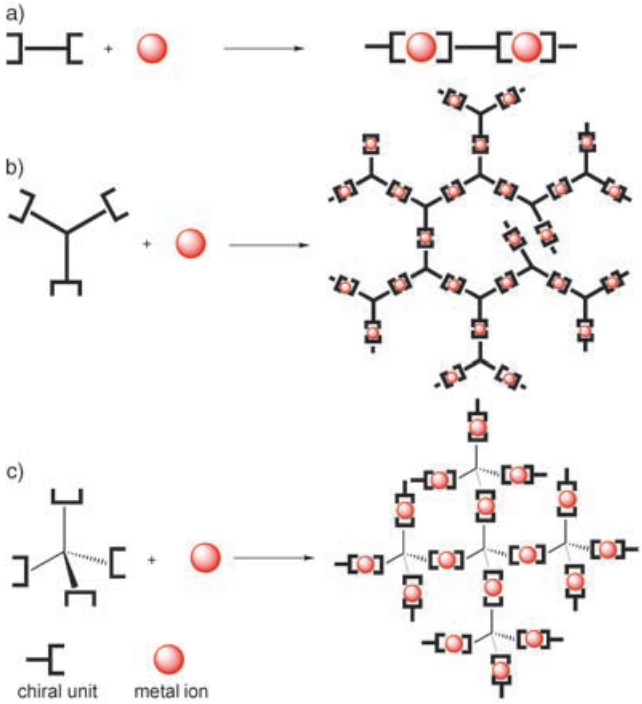

Figure 1. Schematic representation of the strategy for generation of self-supported enantioselective heterogeneous catalysts by using a) 1D, b) 2D, and c) 3D multitopic chiral ligands with metal ions.

The homogeneous catalytic asymmetric epoxidation of α,β-unsaturated ketones in the presence of Shibasaki's lanthanum catalyst,[8–10] which is based on the 2,2′-dihydroxy-1,1′-binaphthyl (binol) ligand, has provided one of the most convenient approaches to α,β-epoxy ketones among various catalytic systems developed so far.[11–15] Although excellent yields and enantioselectivity have been achieved, a catalyst loading of 5–20 mol% rendered the process less practical. However, the immobilization of this type of catalyst by an organic polymer support or stereoregular polymeric ligands often resulted in a drastic decrease of catalytic activity and enantioselectivity in the catalysis.[16] Herein, we report preliminary results on the heterogenization of Shibasaki's

[*] X. Wang, L. Shi, Prof. Dr. K. Ding
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences, 354 Fenglin Road
Shanghai 200032 (China)
Fax: (+) 21-6416-6128
E-mail: kding@mail.sioc.ac.cn
L. Shi, Prof. Dr. M. Li
Department of Chemistry
College of Sciences, Shanghai University
99 Shangda Road, Shanghai 200436 (China)

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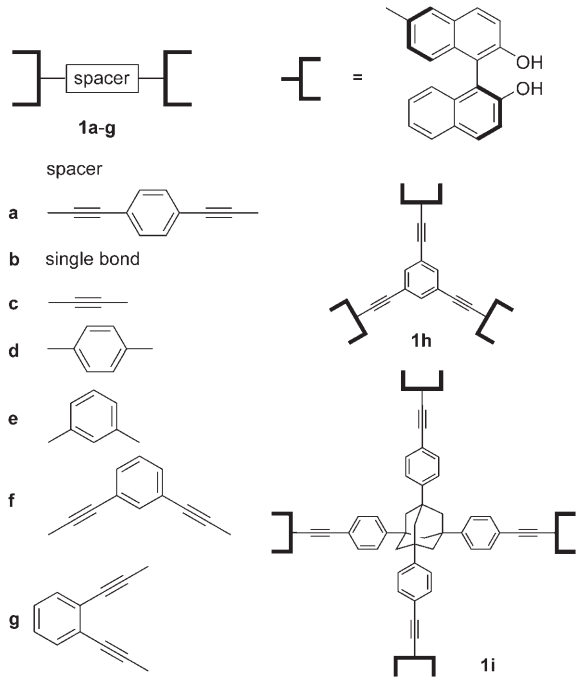
lanthanum catalyst by using multitopic binol ligands bridged by spacers with diverse shapes and sizes. These catalysts are used for the enantioselective epoxidation of α,β-unsaturated ketones, and afford optically active epoxy ketones in excellent yields and enantiomeric excesses.

Three types of multitopic ligands (**1a–i**; Scheme 1) containing different bridging linkers, including linear (**a–d**), bent



Scheme 1. Multitopic ligands employed for the generation of heterogeneous lanthanum catalysts.

(**e–g**), trigonal-planar (**h**), and tetrahedral (**i**) spacers, were designed to investigate the impact of the spatial arrangement of chiral units ((*S*)-binol) on the catalytic properties of their assemblies with the lanthanum ion. Ligands **1b**, **1d**, and **1e** were prepared by following a reported procedure.[4d] The syntheses of other ligands (**1a**, **1c**, and **1f–i**) were achieved by the Pd-catalyzed Sonogashira reactions of a methoxymethyl (MOM)-protected, 6-ethynyl-substituted binol derivative with the corresponding aryl bromides or a MOM-protected, 6-bromo-substituted binol derivative with the corresponding aryl acetylenes, followed by deprotection of the MOM groups of the Sonogashira coupling products by acidic hydrolysis (see Supporting Information).

The heterogeneous catalyst was easily prepared by dropwise addition of a solution of the corresponding multitopic ligand in THF and triphenylphosphine oxide to a solution of $La(OiPr)_3$ under an argon atmosphere. The pale yellow or white (in the case of catalysts **2b**, **2d**, **2e**, and **2i**) solids precipitated immediately. After the mixture had been stirred at room temperature for two hours, the resulting solids were collected by filtration and washed with THF to remove trace amounts of soluble low-molecular-weight species. As exemplified by catalyst **2a** in Figure 2a, these polymeric solids were completely insoluble in THF, and accordingly fulfilled the

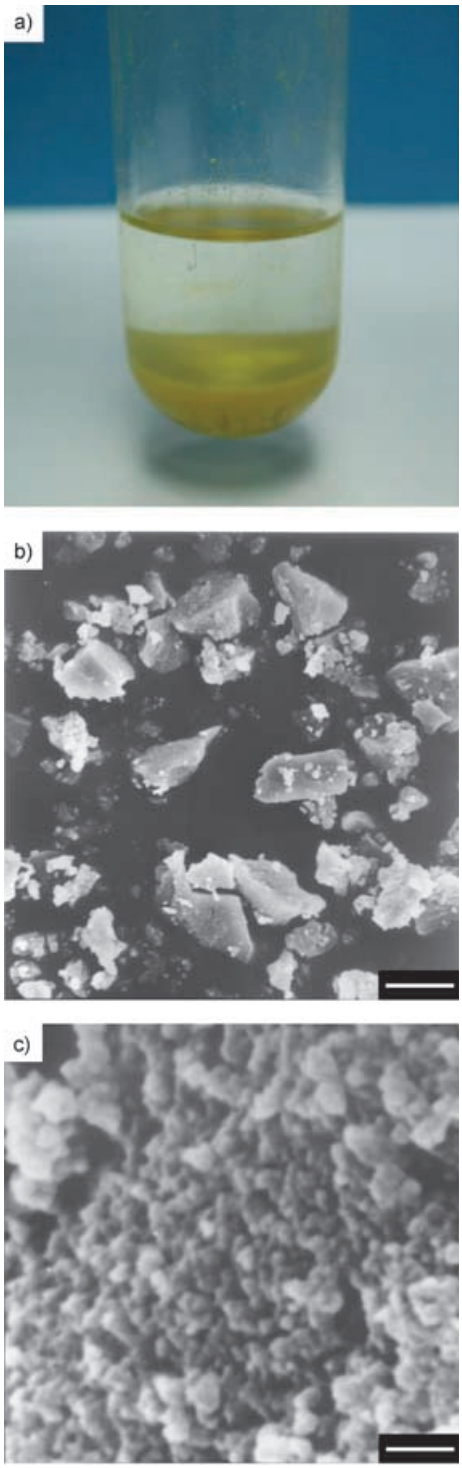


Figure 2. a) Self-supported chiral lanthanum catalyst **2a** (yellow solids at the bottom of the test tube) in THF. b) SEM image of the self-supported lanthanum catalyst **2a**; scale bar: 9.7 μm. c) Enlarged SEM image of the catalyst in (b); scale bar: 0.74 μm.

basic prerequisite for heterogeneous catalysis. SEM images showed that these solids were composed of micrometer-sized particles (Figure 2b), and the surface of the particles exhibited a microstructure with nanoscale noncrystalline species (Figure 2c). The powder X-ray diffraction patterns did not

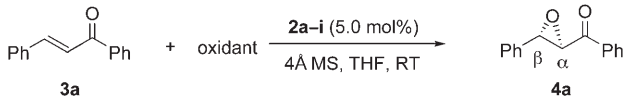
show any obvious peaks in the scanning range of 5–70° (2θ), which further confirmed the noncrystalline morphology of the catalysts (see Supporting Information).

To optimize the reaction conditions, the insoluble homochiral assembly **2a** was then tested as a self-supported heterogeneous catalyst for the enantioselective epoxidation of α,β-unsaturated ketone **3a**. The reaction was carried out at room temperature by using catalyst **2a** (5 mol%) with cumene hydroperoxide (CMHP, 88%) as the oxidant, and THF was selected as the reaction solvent after a preliminary examination of the solvent effect (see Supporting Information). As shown in Table 1, the molar ratio between the chiral binol unit and La^{III} was critical for achieving high catalytic activity and enantioselectivity. The ratio of 1:1.05 (binol unit **1a**/La(O*i*Pr)$_3$) turns out to be optimal (for details, see the Supporting Information), and affords the corresponding epoxide (*R*,*S*)-**4a** in over 99% yield and 97.6% *ee* after a reaction time of 30 min (Table 1, entry 2). In the analogous homogeneous catalyst system, the employment of Ph_3PO or Ph_3AsO as additive in the reaction system dramatically enhanced the catalytic activity but scarcely influenced the enantioselectivity.[8,9] In contrast to the homogeneous catalytic system, the addition of triphenylphosphine oxide to the heterogeneous catalytic system described herein had a significant impact on both the activity and enantioselectivity of the catalysis (Table 1, entries 2–7 versus entry 1). It seems that Ph_3PO is superior to Ph_3AsO (Table 1, entries 2–4 versus entries 5–7). The effect of molecular sieves (MS, 4 Å) was also prominent in terms of catalytic activity (Table 1, entry 2 versus entry 8). The use of *t*BuO_2H (TBHP) instead of CMHP as oxidant led to a degraded yield and enantioselectivity (Table 1, entry 9). Reduction of the catalyst loading to 1 mol% resulted in a slight drop of the enantioselectivity (Table 1, entry 2 versus entry 10) despite the high yield of product **4a**.

We then turned our attention to investigating the impact of the bridging spacers in the multitopic ligands on the enantioselectivity of the catalysis under the optimized reaction conditions. The heterogeneous catalysts **2b–i**, generated from the reactions of multitopic ligands **1b–i** and La(O*i*Pr)$_3$, were subsequently applied to the epoxidation of **3a** with CMHP as the oxidant in the presence of Ph_3PO (15 mol%) and MS (4 Å). As shown in Table 1 (entries 11–18), all of the examined catalysts demonstrated excellent catalytic activity, and afforded **4a** in 99% yields in 30 min. The influence of the structure of the spacer on the enantioselectivity of the catalysis was dramatic. For ligands with linear spacers (**1a–d**), shortening the length of the linker between two chiral units generally had a disadvantageous effect on the enantioselectivity (Table 1, entries 11–13 versus entry 2). However, the reduction of the extension angles of the spacers was clearly unfavorable for the enantioselectivity (Table 1, entries 15–16 versus 2; also entry 13 versus entry 14). The catalysts (**2h** and **2i**) composed of planar tritopic (**1h**) or tetrahedral tetratopic (**1i**) ligands with relatively longer spacers also demonstrated high activity and enantioselectivity (91.5–95% *ee*; Table 1, entries 17 and 18). All these facts clearly indicate that both the length and the spatial orientation of the spacers in the multitopic ligands have a significant impact on the enantioselectivity of the heterogeneous epoxidation. It can be concluded that the structural variation of the spacer moieties in the ligands may alter the supramolecular structures of the assemblies and, as a result, affect their catalytic behavior, particularly the enantioselectivity of the catalysis. Given the modular nature of the multitopic ligands, it can be envisioned that both the reactivity and enantioselectivity may be fine-tuned by judicious choice of the spacer part of the ligands.

Encouraged by these preliminary results, the heterogeneous catalysis of the enantioselective epoxidation of a variety of α,β-unsaturated ketones (**3a–h**) was then investigated by using catalyst **2a** with CMHP as oxidant. As shown in Table 2, the reactions proceeded efficiently to give the corresponding epoxides (**4a–g**) in 99% yield with excellent enantioselectivities (94.3–97.6% *ee*, Table 2, entries 1–7), although the electron-withdrawing group at the *para* position of chalcones (Table 2, entries 5 and 6) may reduce the reaction activities. The reactivity and enantioselectivity for

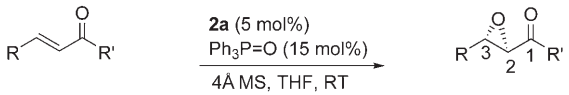
Table 1: Enantioselective epoxidation of α,β-unsaturated ketone (**3a**) catalyzed by self-supported catalyst **2a–i**.[a]



Entry	Cat. ([mol%])	Additive ([mol%])	Oxidant	*t* [h]	Yield [%][b]	*ee* [%][c] (config.)[d]
1	**2a** (5)	–	CMHP	20	99	71.7 (*R*,*S*)
2	**2a** (5)	Ph_3PO (15)	CMHP	0.5	99	97.6 (*R*,*S*)
3	**2a** (5)	Ph_3PO (10)	CMHP	0.5	99	96.6 (*R*,*S*)
4	**2a** (5)	Ph_3PO (5)	CMHP	0.5	91	94.5 (*R*,*S*)
5	**2a** (5)	Ph_3AsO (15)	CMHP	1.0	94	60.9 (*R*,*S*)
6	**2a** (5)	Ph_3AsO (10)	CMHP	1.0	99	90.3 (*R*,*S*)
7	**2a** (5)	Ph_3AsO (5)	CMHP	0.5	99	96.0 (*R*,*S*)
8	**2a** (5)[e]	Ph_3PO (15)	CMHP	20	81	95.1 (*R*,*S*)
9	**2a** (5)	Ph_3PO (15)	TBHP	3	90	66.9 (*R*,*S*)
10	**2a** (1)	Ph_3PO (15)	CMHP	1	99	93.8 (*R*,*S*)
11	**2b** (5)	Ph_3PO (15)	CMHP	0.5	99	83.7 (*R*,*S*)
12	**2c** (5)	Ph_3PO (15)	CMHP	0.5	99	82.9 (*R*,*S*)
13	**2d** (5)	Ph_3PO (15)	CMHP	0.5	99	95.5 (*R*,*S*)
14	**2e** (5)	Ph_3PO (15)	CMHP	0.5	99	93.3 (*R*,*S*)
15	**2f** (5)	Ph_3PO (15)	CMHP	0.5	99	95.1 (*R*,*S*)
16	**2g** (5)	Ph_3PO (15)	CMHP	0.5	99	84.2 (*R*,*S*)
17	**2h** (5)	Ph_3PO (15)	CMHP	0.5	99	91.5 (*R*,*S*)
18	**2i** (5)	Ph_3PO (15)	CMHP	0.5	99	95.0 (*R*,*S*)

[a] All of the reactions were carried out at 25 °C with 1.5 equivalents of oxidant in **3a** (0.4 mmol) in the presence of MS (80 mg, 4 Å). The catalyst loading was based on the binol/La unit of the assemblies. [b] Yield of isolated product. [c] Determined by HPLC on a Chiralcel OB-H column. [d] Determined by comparison of their optical rotations with those reported in the literature.[8d,10] [e] In the absence of MS (4 Å).

Table 2: Enantioselective epoxidation of α,β-unsaturated ketones (**3a–g**) catalyzed by self-supported catalyst **2a**.[a]



Entry	R	R′	Enone	*t* [h]	Epoxide	Yield [%][b]	*ee* [%][c] (config.)[d]
1	Ph	Ph	**3a**	0.5	**4a**	>99	97.6 (*R*,*S*)
2	4-F-C_6H_4	Ph	**3b**	0.5	**4b**	>99	96.2 (*R*,*S*)
3	4-Cl-C_6H_4	Ph	**3c**	0.5	**4c**	>99	96.0 (*R*,*S*)
4	4-Br-C_6H_4	Ph	**3d**	0.5	**4d**	>99	95.6 (*R*,*S*)
5	4-NO_2-C_6H_4	Ph	**3e**	1.0	**4e**	>95	95.7 (*R*,*S*)
6	4-NC-C_6H_4	Ph	**3f**	1.0	**4f**	>99	94.3 (*R*,*S*)
7	Ph	4-MeO-C_6H_4Ph	**3g**	0.5	**4g**	>99	95.0 (*R*,*S*)
8	*i*Pr	Ph	**3h**	3.0	**4h**	91	84.9 (*R*,*S*)

[a] All of the reactions were carried out under the reaction conditions of entry 2, Table 1. The catalyst loading was based on the binol/La unit of the assemblies. [b] Yield of isolated product. [c] Determined by HPLC on a Chiralcel OB-H or AD column. [d] Determined by comparison of their optical rotations with those reported in the literature.[8d, 9b, 10]

the epoxidation of alkyl-substituted α,β-unsaturated ketone **3h** diminished to some extent, and afforded the corresponding epoxide **4h** in 91% yield with 84.9% *ee*. The performance of the heterogeneous catalytic systems was comparable to that attained with their homogeneous counterparts.[8]

In an effort to identify the heterogeneous or homogeneous nature of the above catalyst system, a supernatant of **2a** in THF was employed for the catalysis of the epoxidation of **3a** under the same experimental conditions. In this case, no product was observed at all after 24 h. This experiment unambiguously demonstrated the heterogeneous nature of the catalytic systems studied. The inductively coupled plasma (ICP) spectroscopic analysis of the supernatant indicated that the concentration of La^{III} was 0.093 ppm, which again supports the heterogeneous nature of the catalyst system.

The remarkable advantage of the self-supported heterogeneous catalysts over their homogeneous counterparts was exemplified by the facile recovery and recycling of catalyst **2a** in the epoxidation of **3a**. After completion of the epoxidation, simple filtration of the reaction mixture under an argon atmosphere allowed the separation of the solid-state catalyst from the product-containing solution. The isolated solids were recharged with THF, substrate (containing 10 mol% Ph_3PO), and the oxidant for the next run. As shown in Table 3, catalyst **2a** could be used for at least six cycles in the epoxidation of **3a** without significant loss of enantioselectivity (93.2–96.5% *ee*), at a cost of slightly reduced activity in the last two runs (95 and 83% yields, respectively). Moreover, the leaching of lanthanum in each cycle during recycling of the catalyst was less than 0.4 ppm, as determined by ICP spectroscopy. In comparison with heterogeneous catalysts with organic polymer supports,[16] the catalyst system described herein represents the best case reported so far in terms of both activity and enantioselectivity.

In conclusion, Shibasaki's binol/La catalyst has been successfully heterogenized by a self-supporting strategy through the reactions of multitopic ligands with La(O*i*Pr)$_3$. The self-supported heterogeneous catalysts showed excellent activities and enantioselectivities in the catalysis of the epoxidation of α,β-unsaturated ketones. The bridging spacers in the multitopic ligands were found to have significant impact on the enantioselection of the corresponding self-supported catalysts, which demonstrated the importance of the supramolecular structures of the assemblies on their catalytic behavior. This understanding is particularly important in directing the design of chiral metal–organic assemblies for enantioselective catalysis. Research on the application of this conceptually new strategy in the development of other types of heterogeneous asymmetric catalysts is in progress.

Table 3: Recycling and reuse of the heterogeneous catalyst **2a** in the enantioselective epoxidation of **3a**.[a]

Run	Ph_3PO [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c] (config.)[d]
1	15	0.5	>99	96.5 (*R*,*S*)
2	10	0.5	>99	96.3 (*R*,*S*)
3	10	0.5	>99	95.8 (*R*,*S*)
4	10	0.5	>99	94.9 (*R*,*S*)
5	10	0.5	95	94.5 (*R*,*S*)
6	10	1	83	93.2 (*R*,*S*)

[a] All of the reactions were carried out under the reaction conditions of entry 2, Table 1 in substrate **3a** (0.8 mmol) in the presence of MS (160 mg, 4 Å). The catalyst loading (5 mol%) was based on the binol/La unit. [b] Yield of isolated product. [c] Determined by HPLC on a Chiralcel OB-H column. [d] Determined by comparison of its optical rotation with that reported in the literature.[8d, 10]

Experimental Section

In a Schlenk tube, a solution of ligand **1a** (13.88 mg, 0.02 mmol) and Ph_3PO (33.4 mg, 0.12 mmol) in THF (2 mL) was added dropwise to a solution of La(O*i*Pr)$_3$ (0.05 M, 0.84 mL, 0.042 mmol) in THF, and the pale yellow solids precipitated immediately. The resultant suspension was stirred at room temperature for 2 h. Solid **2a** was isolated by filtration and washed with dry THF (3 mL). MS (4 Å, 160 mg, dried at 180 °C for 8 h under reduced pressure before use), THF (2 mL), and CMHP (80% in cumene, 0.22 mL, 1.2 mmol) were added to the solid-state catalyst **2a**. The mixture was stirred at room temperature for 15 min before addition of enone **3a** (168 mg, 0.8 mmol) in THF (1 mL). The resultant heterogeneous mixture was stirred at RT for an additional period of time until the disappearance of **3a** (monitored by TLC). After the isolation of the solids by filtration under argon, the insoluble catalyst was recharged with THF (4 mL), Ph_3PO (22.4 mg, 0.08 mmol), CMHP (80% in cumene, 0.22 mL, 1.2 mmol), and substrate **3a** (168 mg, 0.8 mmol) for the next run. The filtrate was concentrated and the residue was submitted to column chromatography on silica gel with hexane/ethyl acetate (30:1) as mobile phase to give the epoxide (2*R*,3*S*)-**4a** as a white solid (179 mg, >99% yield). $[\alpha]_D^{20} = -266.5$ ($c = 2$ in $CHCl_3$) [ref. [10]: $[\alpha]_D^{20} = -253.7$ ($c = 1$ in $CHCl_3$), 2*R*,3*S* enantiomer, 95% *ee*]; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.97$–8.00 (m, 2H), 7.57–7.62 (m, 1H), 7.44–7.49 (m, 2H), 7.34–

7.40 (m, 5H), 4.29 (d, $J = 1.8$ Hz, 1H), 4.05 ppm (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.9$, 135.3, 135.2, 133.8, 128.9, 128.7, 128.6, 128.1, 125.6, 60.8, 59.2 ppm. The *ee* value was determined to be 97.6% by HPLC on a Chiralcel OB-H column: UV detector, $\lambda = 254$ nm; 20 °C, hexane/*i*PrOH = 60:40, flow rate 0.5 mL min^{-1}; $t_{R1} = 28.2$ min (minor isomer), $t_{R2} = 35.6$ min (major isomer).

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