

Synthesis of Chiral Polymers and Its Application in Asymmetric Reduction

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Received 20 July 2005; accepted 15 June 2006

DOI 10.1002/app.24958

Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Two new cinchona alkaloids copolymers (PMA-BQTP and PMA-QN) have been synthesized by copolymerization and their complexes (PMA-BQTP-PdCl₂ and PMA-QN-PdCl₂) have been prepared. Their structures were characterized by FTIR, GPC, and element analysis. The catalytic activity of PMA-QN-PdCl₂ in the heterogeneous catalytic asymmetric reduction of aromatic ketone by sodium borohydride was studied. The results showed that the polymer complex catalyzed the reduction of aromatic ketone to get alcohol in high optical yield, but their catalytic ef-

iciency was largely dependent on the aromatic ketone and solvent system, which relate to the accessibility of the catalytic active site. And the PdCl₂/polymeric alkaloid complex can be simply recovered at the end of the reaction by centrifugation and then reused without serious losing of activity or enantioselectivity. © 2006 Wiley Periodicals, Inc. *J Appl Polym Sci* 103: 148–152, 2007

Key words: polymeric cinchona alkaloid; chiral catalyst; asymmetric reduction

INTRODUCTION

In the past decades, research on the enantioselective synthesis using a chiral heterogeneous catalyst has been a fascinating area and has attracted much attention because of their potential applications to medical industry.^{1,2} Many polymer-metal complexes have been found to be very effective catalyst for reduction^{3–9}, but most of them were very expensive and difficult to synthesis. Thus, development of synthetically simple and efficient polymers for heterogeneous reduction is highly desirable.

Cinchona alkaloids have optical activity, and the quinine groups could copolymerize with other low molecular monomer.^{10–13} Recently, the quinine complex has been found to catalyze the asymmetric reaction of some substrate to corresponding chiral compounds, such as reaction of prochiral ketone,¹⁴ fluorination of silyl enol ether,^{15,16} Michael reaction,¹⁷ and so on.¹⁸ However, such a copolymer complex has not been used as chiral catalyst for asymmetric reaction in the previous studies. To obtain the chiral alcohol and study the reduction catalytic behavior of heterogeneous quinine group catalyst in reduction, we synthesized two new polymers (PMA-BQTP and PMA-QN)

and their complexes (PMA-BQTP-PdCl₂ and PMA-QN-PdCl₂) and studied the catalytic activity in the asymmetric heterogeneous reduction of aromatic ketone by sodium borohydride.

EXPERIMENT

Materials

Quinine and sodium borohydride were obtained from Aldrich (Milwaukee, WI). Propiophenone, *p*-nitroacetophenone, 4'-methylacetophenone, 4'-bromoacetophenone, 2-chloroacetophenone, 2-bromoacetophenone, 2-bromo-1-(4-bromophenyl)ethanone, 2-chloro-1-(4-chlorophenyl)ethanone, and 4'-ethoxyacetophenone were obtained from Aldrich (Milwaukee, WI) without purifying before use.

Acetophenone was purified by distillation under reduced pressure. 1,4-Benzenedicarbonyl chloride was the product of the Shanghai Chemical Reagent Factory (Shanghai, China). Chloroform and benzene were dried before use. Methyl acrylate and other solvents were commercial chemicals with analytical purity.

Synthesis of chiral polymer and the complex

The 1,4-bis(9-*o*-quininyl)terephthalate (BQTP) was synthesized as in the literature.¹⁹ A solution of BQTP (0.7 mmol), methyl acrylate (2.8 mmol), and AIBN (0.1%) in dry benzene (25 mL) was refluxed under nitrogen atmosphere. After 72 h of reaction, the solu-

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TABLE I
Copolymer Molecular Weight

Copolymer	Chiral monomer : second monomer (mol : mol)	\overline{M}_n	\overline{M}_w	\overline{M}_z	Molecular weight distribution (PDI)
PMA-QN	1 : 40	9,100	30,100	93,600	3.31
PMA-QN	1 : 60	7,100	22,500	45,900	3.17
PMA-BQTP	1 : 40	14,700	29,800	49,100	2.03

tion was poured into petroleum ether. The precipitate was filtered and washed with ethanol for three times. The products were dried under vacuo to give a powder of PMA-BQTP.

A solution of quinine (1 mmol), methyl acrylate (5 mmol), and AIBN (0.1%) in dry chloroform (25 mL) was refluxed under nitrogen atmosphere. After 36 h of reaction, the solution was poured into petroleum ether. The precipitate was filtered, and washed with ethanol and ethyl ether for three times. The products were dried under vacuo to give a powder of white solid PMA-QN.

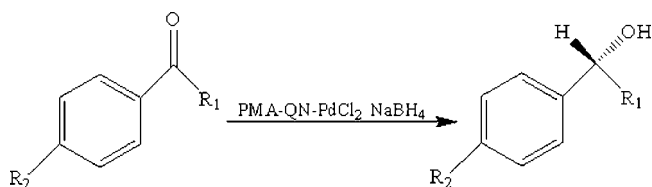
The copolymers (PMA-BQTP, 0.8 g; PMA-QN, 1.5 g) and PdCl₂ (42.5 mg) were added to chloroform (25 mL). After being refluxed for 6 h, the solution was cooled to room temperature. Then the solution of copolymer complex was separated with PdCl₂ by filtration. The precipitate of PMA-BQTP-PdCl₂ (or PMA-QN-PdCl₂) was isolated by filtration after adding petroleum ether. The precipitate was washed with ethanol and ethyl ether for three times. After drying for 24 h in vacuum, the snuff colored powder of PMA-BQTP-PdCl₂ (or PMA-QN-PdCl₂) was obtained. Copolymer molecular weight was shown in Table I.

Catalytic reduction activity

A glass flask is charged with PMA-QN-PdCl₂ (5 mg), sodium borohydride (60 mg), and ethanol (10 mL) at 0°C, and then aromatic ketone (0.2 mL) was added with stirring in for 30 min; the temperature of reactor was kept at 0°C. After 24 h of reaction, the reaction products were analyzed by GC and HPLC (see reaction Scheme 1).

Measurements

IR spectra were obtained by using a Nicolet AVATAR 360 FTIR spectrophotometer (KBr disk). Elemental



Scheme 1 Asymmetric reduction reaction.

analysis was performed on PE-2400CHN Elemental Analyzer. ICP was measured on American ARL-3520 inductivity-coupled plasma atomic emission spectrometry. The molecular weight was measured by Waters 150 gel permeation chromatography meter, using THF as eluent and polystyrene as standard sample, column temperature was 30°C. The products of reduction were determined by Shimadzu GC-16A gas chromatograph with a 5 m × 3 mm OV-17 column. The optical yield was measured by Shimadzu 1671-CHA HPLC with an OD Column (UV detector). The absolute configuration was determined by the WXG-4 polarimeter.

RESULTS AND DISCUSSION

Characterization

FTIR spectra data of copolymer were shown in Figure 1. In the spectra of characteristic absorption of copolymers, C=N, C-N, and C=O stretching vibration appeared. These suggested that the copolymerization between quinine groups and another monomer occurred as expected. In the two copolymers, the peaks of C=N appeared at 1510 cm⁻¹. The absorp-

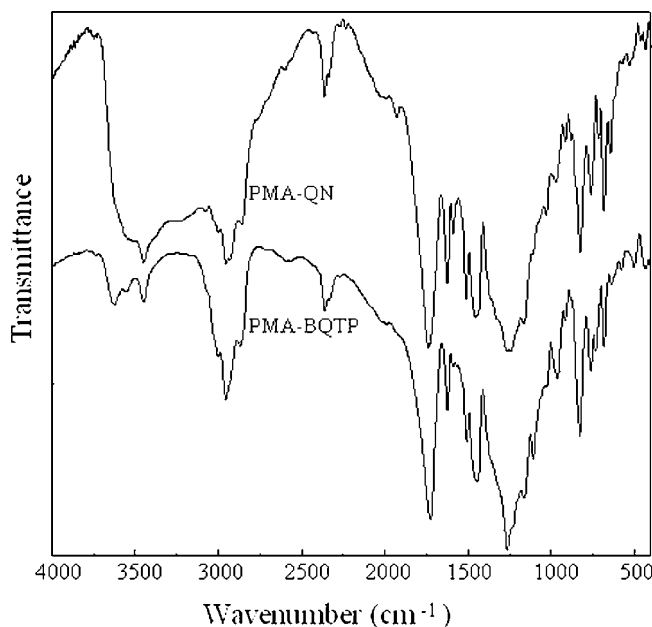
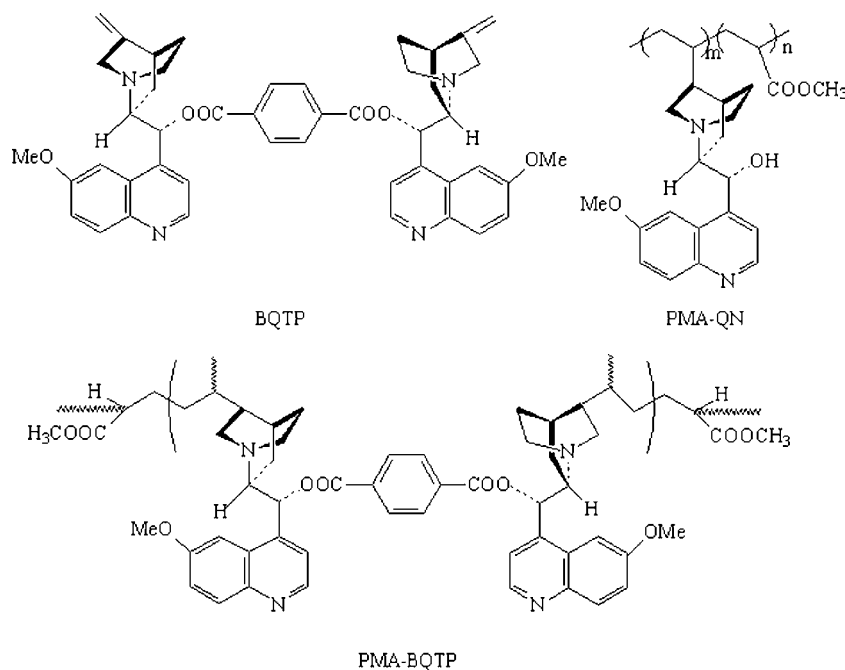


Figure 1 FTIR spectra of PMA-QN and PMA-BQTP.



Scheme 2 Structures of BQTP, PMA-QN, and PMA-BQTP.

tions of copolymer PMA-BQTP corresponding with C—N group at 1360 cm^{-1} was higher than that of PMA-QN. The stretching vibration of C—N and C=O bonds of copolymer and BQTP were different because the backbones were influenced by the other monomer (MA). The structures of the copolymers and BQTP were shown in Scheme 2.

The content of functional group (QN) in the polymer ligand was investigated by analyzing element content. Element analysis data of PMA-QN and PMA-BQTP were shown in Table II. The weight content of nitrogen in PMA-QN and PMA-BQTP showed that the molar ratio of quinine group to MA was 1 : 10.8 in PMA-QN and 1 : 11.6 in PMA-BQTP. The content of nitrogen and Pd in polymer indicated that the molar ratio of palladium to quinine group was 1 : 37 in PMA-QN-PdCl₂ and 1 : 22 in PMA-BQTP-PdCl₂.

Asymmetric reduction of aromatic ketone

In the presence of PMA-QN-PdCl₂, aromatic ketone reduction by sodium borohydride was investigated by monitoring the aromatic ketone consumption. Neither PdCl₂ nor the polymer itself was active in this

TABLE II
Elemental Analysis Data

Compound	C%	H%	N%	Pd ²⁺ % (10 ⁻⁴)
PMA-QN	61.47	6.16	2.26	—
PMA-BQTP	60.38	5.91	2.09	—
PMA-QN-PdCl ₂	—	—	—	0.234
PMA-BQTP-PdCl ₂	—	—	—	0.368

catalytic manifold. Catalytic activity of PMA-QN-PdCl₂ in the asymmetric heterogeneous reduction of aromatic ketone was shown in Table III.

As can be seen from Table III, change of product secondary alcohol separation yield is not obvious, but the e.e. value changed greatly, and this related to the structure of aromatic ketone; when it has electron-donating group on α -carbon, production configuration is *R*; when it has electron-withdrawing group on α -carbon, production configuration is *S*. The e.e. value of production when arene with electron-donating group are substrate is higher than that of production when arene with electron-withdrawing group are substrate, and the e.e. value is related to ability of electron-donating or electron-withdrawing. This was attributed to the change of charge density of oxygen on ketone carbonyl, the higher charge density of oxygen, and the higher e.e. value. On the other hand, the

TABLE III
Catalytic Activity of PMA-QN-PdCl₂ in the Asymmetric Heterogeneous Reduction of Aromatic Ketone

Entry	R ₁	R ₂	Yield (%)	e.e. (%)	Configuration
1	CH ₃	H	50	48	R
2	CH ₃ CH ₂	H	42	40	R
3	CH ₃	CH ₃	40	42	R
4	CH ₃	CH ₃ O	34	46	R
5	CH ₃	Br	55	32	R
6	BrCH ₂	H	38	27	S
7	CH ₃	NO ₂	40	15	R
8	BrCH ₂	Br	37	26	S
9	ClCH ₂	H	44	32	S
10	ClCH ₂	Cl	48	30	S

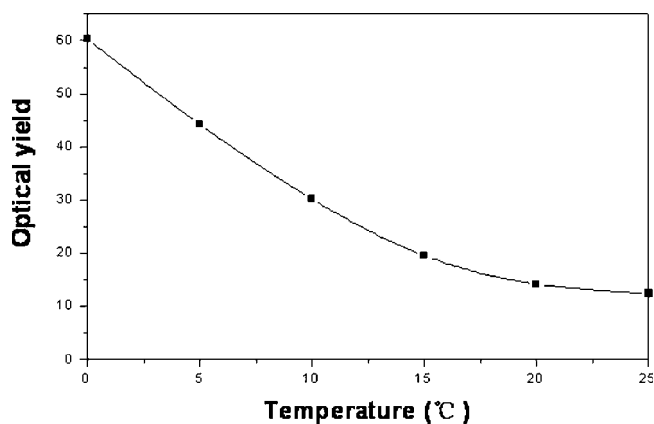


Figure 2 Relationship between the optical yield and temperature (PMA-QN-PdCl₂). Amount of catalyst, 80 mg; aromatic ketone, 0.2 mL; sodium borohydride, 60 mg; ethanol, 10 mL; reaction time, 72 h.

substituted group of R_1 and R_2 could affect the e.e. value of production to some extent, since the steric hindrance of R_1 and R_2 hampered the coordination between carbonyl oxygen and metal ion. This caused the e.e. value to decrease finally.

Effect of catalytic reaction temperature

The catalytic activity of PMA-QN-PdCl₂ was investigated as a function of temperature. The optical yield with 80 mg of PMA-QN-PdCl₂ as a function of temperature for 24 h of reaction is shown in Figure 2. It was shown that the lower the reaction temperature, the higher the optical yield, because the mobility of polymer's chiral segments was enhanced by the rise of the temperature, the increased mobility did not favor the asymmetric addition. At 0°C, the optical yield was 3.1 times than that at 25°C. At 5°C, the optical yield was 2.2 times than that at 15°C. When the

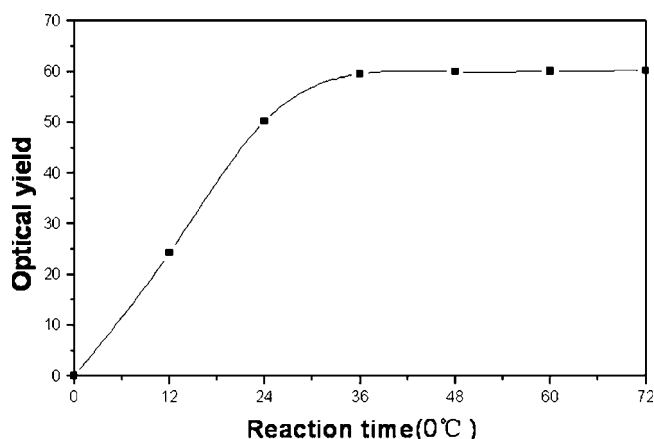


Figure 3 Relationship between the optical yield and reaction time (PMA-QN-PdCl₂). Temperature, 0°C; amount of catalyst, 80 mg; acetophenone, 0.2 mL; sodium borohydride, 60 mg; ethanol, 10 mL.

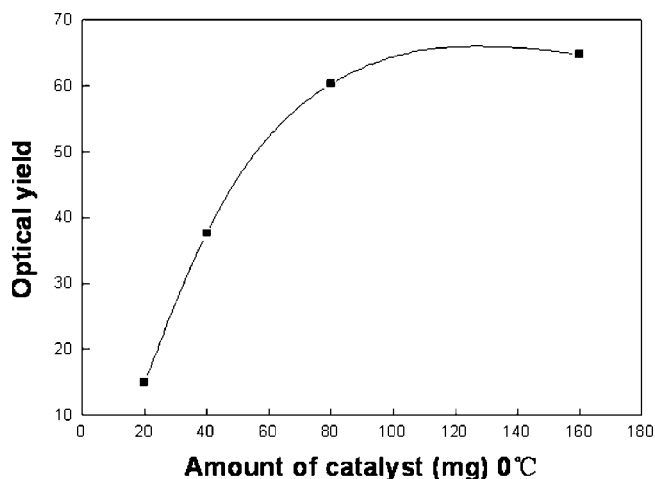


Figure 4 Relationship between the optical yield and amount of catalyst (PMA-QN-PdCl₂). Temperature, 0°C; acetophenone, 0.2 mL; sodium borohydride, 60 mg; ethanol, 10 mL; reaction time, 72 h.

temperature decreased, the optical yield increased quickly, and the conversion decreased slowly.

Effect of catalytic reaction time

The effect of reaction time on the optical yield was shown in Figure 3. As it was expected, the optical yield increased rapidly with the increase of reaction time up to 24 h, and kept stable after about 36 h. After 24 h, prolonging the reaction time hardly increased the optical yield.

Effect of catalyst amount

Figure 4 showed the relationship between optical yield and the amount of catalyst in the reduction of aromatic ketone. It indicated that the asymmetric cata-

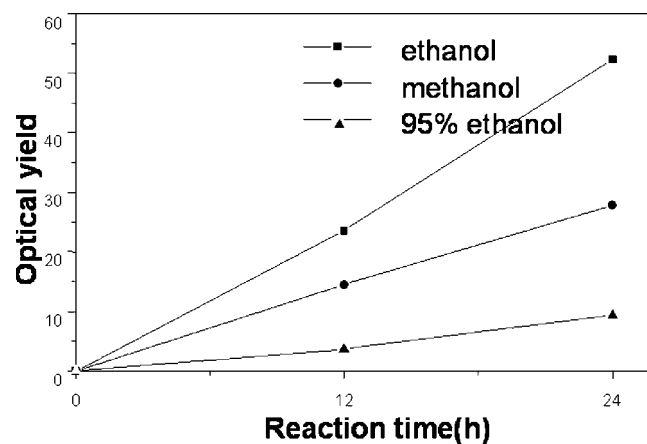


Figure 5 Relationship between the optical yield and solvent (PMA-QN-PdCl₂). Temperature, 0°C; amount of catalyst, 80 mg; acetophenone, 0.2 mL; sodium borohydride, 60 mg; ethanol, 10 mL; ethanol, 10 mL; methanol, 10 mL; 95% ethanol, 10 mL.

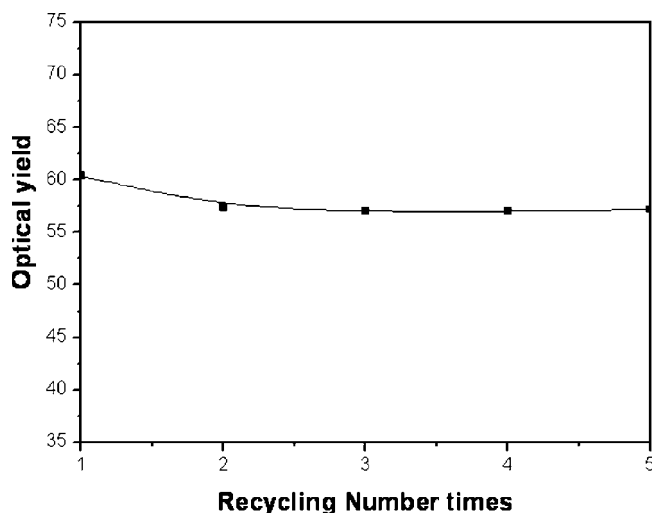


Figure 6 Relationship between the optical yield and recycling number times (PMA-QN-PdCl₂). Temperature, 0°C; amount of catalyst, 80 mg; aromatic ketone, 0.2 mL; sodium borohydride, 60 mg; ethanol, 10 mL; reaction time, 72 h.

lytic activity of PMA-QN-PdCl₂ increased with increasing amount of the catalyst, but not with the same rate. When the amount of catalyst was more than 80 mg, the optical yield kept stable.

Effect of solvent

Figure 5 showed the relationship between optical yield and the solvent. It can be seen that the catalytic activity was different in different solvents. In ethanol, the optical yield was 1.9 times than that in methanol. In methanol, the optical yield was 4.0 times than that in 95% ethanol. The optical yields in methanol and 95% ethanol were lower than that in ethanol, because the reaction rate was very rapid and the coordination between PMA-QN-PdCl₂ and sodium borohydride was not very well.

Effect of catalyst recycling number times

To study the stability of the chiral copolymer catalyst, the recycling efficiency was tested and shown in Figure 6. The optical activity did not seriously change after five times. The 2.0 wt % loss of metals from catalyst was found by metal analysis after repeated use and the FTIR spectrum of polymer was identical to the original. This indicated that the structure of the catalyst was unchanged.

CONCLUSIONS

Two new chiral copolymers (PMA-BQTP and PMA-QN) and their complexes (PMA-BQTP-PdCl₂ and PMA-QN-PdCl₂) were synthesized and characterized. It was demonstrated that the PMA-QN-PdCl₂ was an effective asymmetric catalyst for aromatic ketone reduction. The product of the reaction was (*R*)-phenylethanol. The results showed that the alcohol optical yield of the reduction increased with the increase of the catalyst content and the decrease of reaction temperature. It was also seen that alcohol yield increased with the increase of reaction time and the increase of catalyst content. This kind of catalyst is a potentially important catalyst in prochiral ketone reduction. The advantage of chiral polymer-palladium complex catalyst is that it is very easy to prepare, and could be reused without obviously change in optical activity. Further studies on the chiral catalytic activity of the complex catalyst with various compositions, as well as the nature of the interaction between Pd and the polymers, are being carried out.

References

- Blaser, H. U. *Tetrahedron: Asymmetry* 1991, 2, 843.
- Brunner, H. *Top Stereochem* 1998, 18, 129.
- Liu, X. *Chin J Appl Chem* 1997, 14.
- Blaser, H. U. *Chem Rev* 1992, 92, 9355.
- Corey, E. J.; Bakshi, R. K.; Shibaka, S. *J Chem Soc Perkin Trans 1* 1983, 8, 1673.
- Caze, C.; Moualij, N. E.; Hodge, P. *J Chem Soc Perkin Trans 1* 1995, 4, 345.
- Adjidjonou, K. A.; Caze, C. *Eur Polym J* 1995, 31, 749.
- Adjidjonou, K. A.; Caze, C. *Eur Polym J* 1995, 30, 395.
- Yin, M. Y.; Yuan, G. L.; Jiang, Y. Y. *J Mol Catal A* 1999, 147, 93.
- Nandanna, E.; Sudalal, A.; Ravindranathan, T. *Tetrahedron Lett* 1997, 38, 2577.
- Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S. G. *Tetrahedron: Asymmetry* 1996, 7, 645.
- Lohray, B. B.; Andanan, E.; Bhushan, V. *Tetrahedron Lett* 1994, 35, 6559.
- Pini, D.; Petri, A.; Nardi, A.; Rosini, C.; Salvadori, P. *Tetrahedron Lett* 1991, 32, 5175.
- Liu, X.; Li, J. G.; Zhang, Z. *J Mol Catal (China)* 1997, 11, 305.
- Shibata, N.; Suzuki, E.; Takeach, Y. *J Am Chem Soc* 2000, 122, 10728.
- Takahashi, T.; Fukushima, A.; Tanaka, Y. *Chirality* 2000, 12, 456.
- Alvarez, R.; Hourdin, M. A.; Cazve, C. *Tetrahedron Lett* 1999, 7091.
- Blaser, H. U.; Jalett, H. P.; Lottenbach, W. *J Am Chem Soc* 2000, 122, 12675.
- Lohray, B. B.; Bhusan, V. *Tetrahedron Lett* 1992, 33, 5113. 20.