

Practical Syntheses of Chiral α -Amino Acids and Chiral Half-Esters by Kinetic Resolution of Urethane-Protected α -Amino Acid *N*-Carboxyanhydrides and Desymmetrization of Cyclic *meso*-Anhydrides with New Modified Cinchona Alkaloid Catalysts

Yutaka Ishii, Ryosuke Fujimoto, Masafumi Mikami, Satoshi Murakami, Yasushi Miki, and Yoshiro Furukawa*

Research Laboratories, Daiso Co., Ltd., 9-Otakasu-cho, Amagasaki-shi 660-0842, Japan

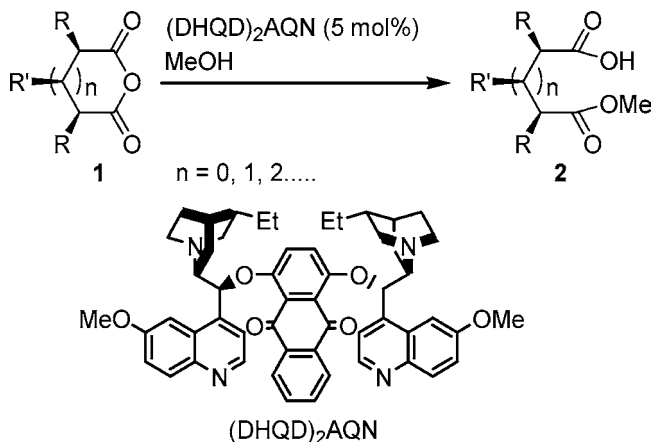
Abstract:

The large-scale applications of the kinetic resolution of urethane-protected α -amino acid *N*-carboxyanhydrides (UNCAs) and the desymmetrization of cyclic *meso*-anhydrides using modified cinchona alkaloids are described. These asymmetric reactions are effective organocatalytic methods for the synthesis of chiral α -amino acids **6** and chiral half-esters **2** on an industrial scale, because the organocatalyst recovery and product purification can be carried out by a simple extractive procedure obviating a chromatographic purification step. The modified cinchona alkaloid catalysts (DHQD)₂AQN and (DHQ)₂AQN, as reported by Deng and co-workers, are not readily available and therefore not suitable for industrial-scale synthesis. Various *O*-alkylated quinidine and quinine derivatives were prepared and screened as catalysts for the kinetic resolution of phenylalanine UNCA with alcohol. The readily prepared *O*-propargylquinidine (OPQD) and *O*-propargylquinine (OPQ) were discovered to be highly enantioselective and practical catalysts. These new catalysts were applied to the synthesis of chiral propargylglycine **24** and the key intermediate of BAY10-8888/PLD-118, **26**, on an industrial scale, by the kinetic resolution of UNCA **22** and the desymmetrization of cyclic *meso*-anhydride **25**, respectively.

Introduction

Until recently, catalysts which were employed for enantioselective synthesis of organic compounds such as pharmaceuticals, agrochemicals, or fine chemicals were either transition metal complexes or enzymes. In the past decade organocatalysis has emerged as an alternative approach for the catalytic production of enantiomerically pure organic compounds.¹ Unlike transition metal complexes where the organic ligands only function to modulate the steric and electronic properties of the catalytically active metal center, in organocatalysts the catalytic activity resides in the low-molecular-weight organic molecule itself. Organocatalysts have several important advantages. They are usually robust, inexpensive, readily available, and nontoxic. Because of their inertness toward moisture and oxygen, demanding reaction conditions such as inert atmosphere, low temperature, absolute solvents, etc. are, in many instances, not required.

Scheme 1. Desymmetrization of *meso*-anhydrides **1** with cinchona alkaloids



Because of the absence of transition metals, organocatalytic methods are especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g., active pharmaceutical ingredients. The benefit of organocatalytic reactions for large-scale production of chiral building blocks has been demonstrated, even though the number of examples is still limited.²

Since enantiopure cinchona alkaloids such as the pseudo-enantiomeric quinidine and quinine are readily available, there are a lot of reports on the use of their derivatives as organocatalysts.³ Recently, Deng and co-workers reported various asymmetric reactions catalyzed by modified cinchona alkaloids.⁴ In 2000, they reported a highly enantioselective catalytic alcoholysis of cyclic *meso*-anhydrides **1** with commercially available modified cinchona alkaloids, such as (DHQD)₂AQN (Scheme 1).^{5a} Various optically active half-esters **2** were obtained by the desymmetrization of monocyclic, bicyclic, and tricyclic succinic anhydrides, as well as glutaric anhydrides. Catalyst recovery and product purification can be carried out by a simple extractive procedure without chromatographic purification. The recovered catalyst can be reused without any loss in yield and enantioselectivity. This desymmetrization was applied to key reactions in the

* To whom correspondence should be addressed. E-mail: yfurukaw@daiso.co.jp.

(1) Recent review: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, 43, 5138. (b) Rouhi, A. M. *Chem. Eng. News* **2004**, 82 (36), 41.

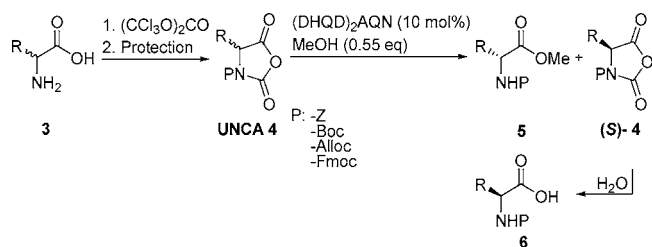
(2) Berkessel, A.; Groger, H. In *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005; Chapter 14.

(3) Recent review: Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961.

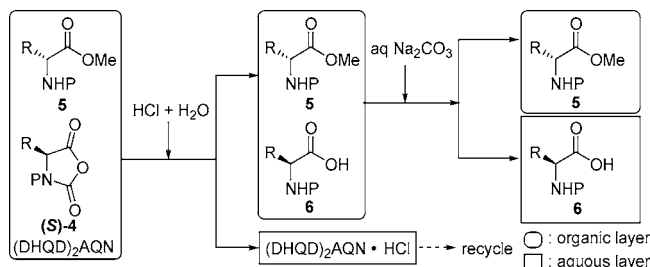
(4) Recent paper: Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, 129, 768.

(5) (a) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, 122, 9542. (b) Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737. (c) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, 123, 11302.

Scheme 2. Kinetic resolution of UNCAs 4 with cinchona alkaloids



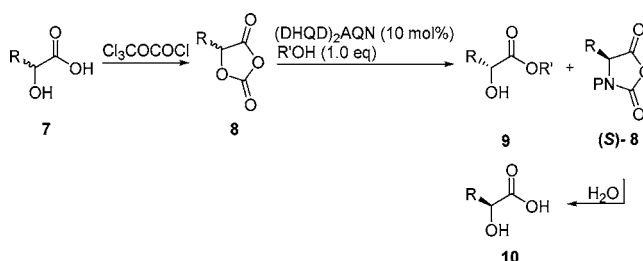
Scheme 3. Facile purification of amino ester 5, amino acid 6, and basic catalyst by simple extractive procedures



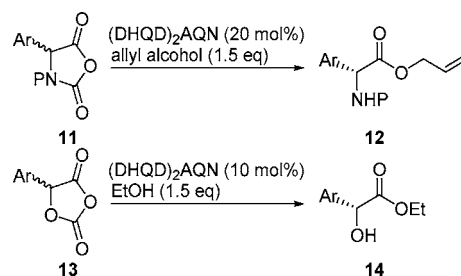
syntheses of biotin^{5b} and the γ -amino acid baclofen.^{5c} Next, in 2001, the same group developed a kinetic resolution of urethane-protected α -amino acid *N*-carboxyanhydrides **4** (UNCAs) using these modified cinchona alkaloids (Scheme 2).^{6a} Racemic **4** can be easily prepared in high yields from the corresponding readily available racemic α -amino acids **3**. It was envisioned that an efficient kinetic resolution of UNCAs with alcohol would give the carbamate-protected amino esters **5** and unreacted UNCAs (S)-**4** in high ee. The latter could be further hydrolyzed to the corresponding carbamate-protected amino acids **6**. Simple extractive procedures then could be utilized for the facile purification of acidic amino acids **6** and neutral amino esters **5** and quantitative recovery of the basic amine catalyst (Scheme 3). This facile purification represents a big advantage from an industrial application perspective. The ease of catalyst recycling can particularly offset the relatively high catalyst loadings which are typically required in asymmetric organocatalytic synthesis. An efficient catalytic kinetic resolution of UNCAs can therefore provide a highly attractive route for the synthesis of suitably protected optically active amino acids from the corresponding racemic compounds. The kinetic resolution of UNCAs was found to be remarkably general. A broad range of UNCAs bearing various alkyl and aryl substituents could be resolved cleanly with exceedingly high enantioselectivities and in excellent yields. The opposite enantiomer of the amino acids could be obtained in almost similar enantiomeric excess and yield by simply switching to the pseudo-enantiomeric alkaloid derivative.

Moreover, this methodology could also be applied to the kinetic resolution of racemic *O*-carboxyanhydrides **8** to give α -hydroxy esters **9** and unreacted *O*-carboxyanhydrides (S)-**8**. Upon hydrolysis the latter yield α -hydroxy acids **10** in high ee (Scheme 4).^{6b} In the case of α -aryl UNCAs **11** and

Scheme 4. Kinetic resolution of 5-alkyl-*O*-carboxyanhydrides 8 with cinchona alkaloids



Scheme 5. Dynamic kinetic resolution of α -aryl UNCAs 11 and 5-aryl-*O*-carboxyanhydrides 13 with cinchona alkaloids



5-aryl-*O*-carboxyanhydrides **13**, highly efficient dynamic kinetic resolution with (DHQD)₂AQN can afford the corresponding optically active amino esters **12** and hydroxyl esters **14** (Scheme 5).^{6c}

Daiso obtained a worldwide exclusive license for these asymmetric synthesis technologies from Brandeis University and has tried to develop these organocatalytic reactions for industrial production. In this paper, we report the improvement of cinchona alkaloid catalysts used in the kinetic resolution of UNCAs with an alcohol, and its large-scale application to the kinetic resolution of propargylglycine UNCA **22**. In addition, we also report on the desymmetrization of 5-methylenetetrahydrocyclopenta[*c*]furan-1,3-dione (**25**).

Results and Discussion

Improvement of Cinchona Alkaloids Catalyst. The first problem for industrial application was the availability of the modified cinchona alkaloid catalysts (DHQD)₂AQN and (DHQ)₂AQN. These were originally developed as chiral ligands for Sharpless's Os-catalyzed asymmetric dihydroxylation of simple olefins.⁷ Although these ligands are available on a laboratory scale,⁸ it is difficult to obtain them in the quantities typically required for industrial applications due to the difficulty of their synthesis.

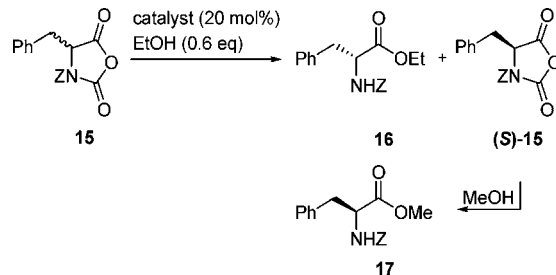
Initially we explored the use of the inexpensive quinidine itself as a catalyst in the kinetic resolution of UNCAs, even though this resulted in significantly lower enantioselectivities. However, upon careful analysis of reactions in which recovered quinidine was reused as a catalyst, we discovered that the purity of the catalyst gradually decreased. We determined that the decreasing purity was caused by a

(6) (a) Hang, J.; Tian, S.-K.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 12696. (b) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870. (c) Hang, J.; Deng, L. *Org. Lett.* **2002**, *4*, 3321.

(7) Recent review: Marko, I. E.; Svendsen, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H. Eds.; Springer: Heidelberg, 1999; Chapter 20.

(8) Although Sharpless's ligands can be purchased from Aldrich, they are too expensive: (DHQD)₂AQN: price \$71.5/500 mg (2006 catalogue).

Table 1. Screening of *O*-alkylated cinchona alkaloid catalysts in kinetic resolution of UNCA **15**^a



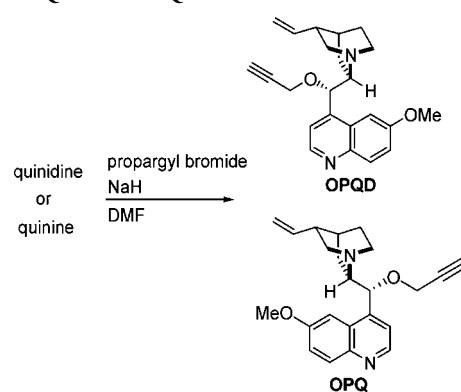
cinchona alkaloid catalyst	conv/%	ee (yield)/%		
		ester 16	(<i>S</i>)- 15 ^b	<i>s</i> ^c
(DHQD) ₂ AQN ^d	54	83 (48)	98 (40)	46
<i>O</i> -Me-QD	57	74 (51)	99 (35)	30
<i>O</i> -Bn-QD	58	70 (50)	98 (34)	22
<i>O</i> -allyl-QD	55	80 (49)	99 (37)	40
<i>O</i> -propargyl-QD (OPQD)	52	90 (45)	99 (45)	83
<i>O</i> - ^t BuO ₂ CCH ₂ -QD	51	93 (44)	98 (45)	114
(DHQ) ₂ AQN ^{d,e}	57	74 (48)	98 (38)	30
<i>O</i> -propargyl-Q (OPQ) ^e	53	86 (47)	98 (42)	55

^a The reaction was performed with **15** (1.0 equiv), catalyst (0.2 equiv), ethanol (0.6 equiv) in ether at $-60\text{ }^{\circ}\text{C}$. ^b Yield and enantiomeric excess of (*S*)-**15b** were measured as the corresponding methyl ester **17**, see Experimental Section for details. The ee of **17** is assumed to be the same as the ee of unreacted **15**. ^c Selectivity factors, $s = k_f/k_s = \ln[1 - C(1 + ee)]/\ln[1 - C(1 - ee)]$, where ee is the percent enantiomeric excess of ester and *C* is the conversion. ^d 0.1 equiv catalyst was used. ^e An opposite enantiomeric pair was obtained with (DHQ)₂AQN and OPQ as the catalysts. QD = quinidine, Q = quinine, DHQD = dihydroquinidine, DHQ = dihydroquinine.

reaction of the UNCA with the secondary alcohol group in quinidine. When kinetic resolutions of UNCAs were performed using these adducts as the catalyst, we found that the enantioselectivity of the alcoholysis was almost completely lost, confirming that the reuse of quinidine catalyst is not practical.

Thus, we decided to return to the original method which uses quinidine derivatives in which the secondary alcohol is protected. We synthesized various simple *O*-protected quinidine derivatives and screened them in the kinetic resolution of *N*-Z-phenylalanine UNCA **15** with ethanol. Consequently, we determined that *O*-alkylated quinidine derivatives displayed high enantioselectivity in this kinetic resolution (Table 1).⁹ Above all, *O*-propargylquinidine (OPQD) and *O*-tert-butoxycarbonylmethyl quinidine proved to be more enantioselective catalysts than (DHQD)₂AQN. The fact that these simple *O*-alkylated quinidines can be much more easily prepared than *O*-arylated ones such as (DHQD)₂AQN is particularly attractive.¹⁰ Cinchona alkaloids are typically reacted with alkylation agents such as benzyl and allyl halides to yield *N*-alkylated and *N*,*O*-bisalkylated derivatives. These compounds have found significant utility as phase-transfer organocatalysts in the asymmetric alkylation of glycine benzophenone imines derivatives for the synthesis of chiral α -amino acids.¹¹ When the alkylation is carried out in NaH–DMF, the nucleophilicity of the oxygen atom on the

Scheme 6. Preparation of improved cinchona alkaloids catalyst OPQD and OPQ



9-position in quinidine is increased and *O*-alkylation takes place rather than *N*-alkylation.¹² The catalytic activity of the corresponding quinine derivatives, *O*-propargylquinine (OPQ), was also superior to that of (DHQ)₂AQN. Thus, the *O*-propargyl derivatives of quinine and quinidine (OPQ and OPQD, respectively) could be readily prepared on large scale without using column chromatography for purification (Scheme 6). These catalysts are stable and can be readily recycled via pH-controlled extractions and are thus suitable for industrial application. We carried out the synthesis of OPQ on pilot-plant scale and successfully prepared 100 kg of catalyst.

Kinetic Resolution of Propargylglycine UNCA. We selected enantiopure propargylglycine as a target for non-natural amino acid production by kinetic resolution of UNCAs with our modified catalyst, because it is a useful pharmaceutical intermediate and difficult to prepare using Noyori's Rh-BINAP-catalyzed asymmetric hydrogenation of dehydroamino acids.¹³

In Deng's original procedure,^{6a} the UNCAs are prepared from racemic amino acids via a reaction with phosgene, followed by *N*-carbamate protection. Since the hydrophilic character of many amino acids makes them difficult to handle and because phosgene is highly toxic, we required another efficient route for large-scale synthesis. Our optimized procedure for the preparation of (*S*)-*N*-Boc-propargylglycine **24** is shown in Scheme 7. Racemic *N*-Z-propargylglycine **20**, which was prepared in 52% overall yield from racemic propargylglycine **19** following a literature procedure,¹⁴ was protected in situ as a benzyl carbamate. A two-step one-pot process consisting of cyclization induced by thionyl chloride¹⁵ and subsequent *N*-Boc protection provided racemic *N*-Boc-propargylglycine UNCA **22** in an overall yield of 62%.

The kinetic resolution of racemic **22** (1.0 equiv) with OPQD (0.20 equiv) and methanol (0.55 equiv) at $-60\text{ }^{\circ}\text{C}$ on a 50-L scale, followed by hydrolysis of unreacted (*S*)-

(12) An example of *O*-alkylated cinchona alkaloid: Blaser, H. U.; Jalett, H. P.; Wiehl, J. J. *Mol. Catal.* **1991**, 68, 215.

(13) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I. Ed.; Wiley-VCH: New York, 2000.

(14) Leukart, O.; Caviezel, M.; Eberle, A.; Escher, E.; Tun-kyi, A.; Schwyzler, R. *Helv. Chim. Acta* **1976**, 59, 2181.

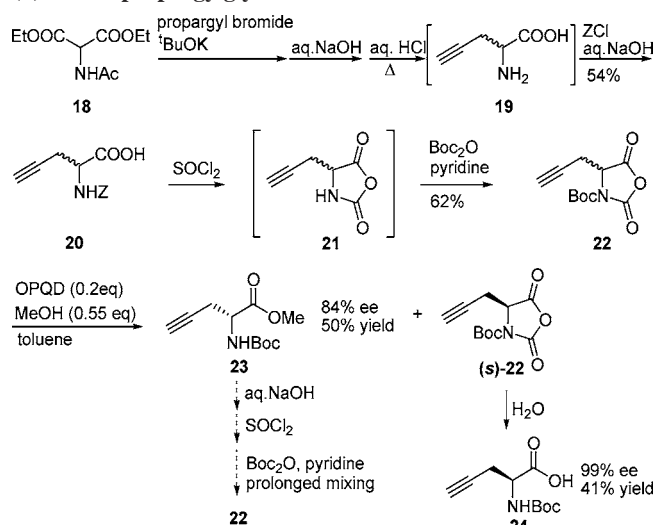
(15) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; John Wiley and Sons: New York, 1961; Vol. 2, p 861.

(9) Ishii, Y.; Miki, Y.; Furukawa, Y.; Murakami, S. WO2003/064420.

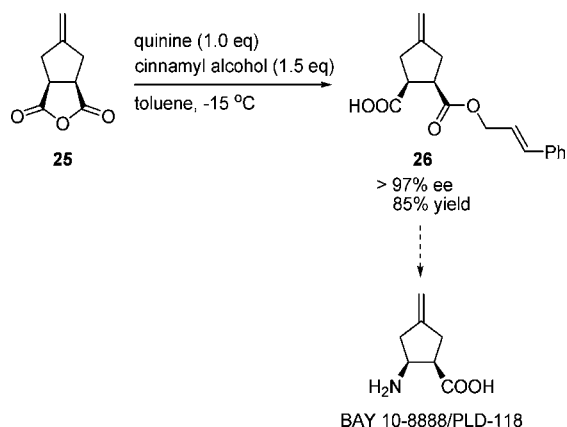
(10) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, 35, 448.

(11) (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, 37, 506. (b) Lygo, B.; Andrews, B. J. *Acc. Chem. Res.* **2004**, 37, 518.

Scheme 7. Optimized procedure for the preparation of (S)-N-Boc-propargylglycine 24



Scheme 8. Desymmetrization of meso-anhydride 25 with cinchona alkaloid



22, afforded (S)-N-Boc-propargylglycine **24** in 41% yield and with 99% ee via a simple extraction procedure. The catalyst was easily recovered quantitatively by treatment of the aqueous solution with NaOH followed by extraction with toluene. The recovered catalyst was pure according to ^1H NMR and could be used for repeat kinetic resolutions to give the desired product with consistently high ee and yield. The byproduct (R)-N-Boc-propargylglycine ester **23** has a lower ee. However, it can be easily recycled to the racemic starting material **22** by regenerating the UNCA and stirring this under basic conditions at room temperature for a few hours.

Desymmetrization of 5-Methylenetetrahydrocyclopenta[c]furan-1,3-dione. The β -amino acid BAY 10-8888/PLD-118 is known as a novel antifungal agent for the treatment of yeast infections,¹⁶ and an efficient large-scale asymmetric synthesis of this compound was reported by Mittendorf and co-workers.¹⁷ In Mittendorf's report, the key step employed a highly enantioselective, quinine-mediated alcoholysis of cyclic meso-anhydride intermediate **25** (Scheme 8). These workers found that alcoholysis of anhydride **25** with cin-

Table 2. Optimization in desymmetrization of meso-anhydride 25 with cinnamyl alcohol catalyzed by OPQ^a

catalyst (equiv)	temp/°C	time/h	ee of 26 /%	yield of 26 /%
quinine (1.0)	-15	8	85	94
OPQ (1.0)	-15	6	92	97
OPQ (1.0)	-10	4	91	98
OPQ (0.8)	-10	6	90	96
OPQ (0.7)	-10	8	89	96
OPQ (0.6)	-10	13	87	95
OPQ (0.5)	-10	24	85	93

^a The reaction was performed with anhydride **25** (10 mmol), catalyst, and cinnamyl alcohol (15 mmol) in toluene (35 mL).

namyl alcohol in the presence of a stoichiometric amount of quinine in toluene at -15 °C afforded crude (+)-half-ester **26** with 85% ee. A filtration of the less racemic **26** increased the purity and gave pure (+)-half-ester **26** with >97% ee in 84% yield. The group also investigated the desymmetrization of anhydride **25** in the presence of a catalytic amount of (DHQD)₂AQN instead of quinine. The anhydride **25** was treated with 5 mol % of (DHQD)₂AQN and 10 equiv of cinnamyl alcohol in diethyl ether at room temperature for 72 h to give (-)-half-ester in 54% yield and with 89% ee. Because the reaction was still not complete after 72 h, they concluded that this method was less attractive for large-scale production.¹⁸ Thus, we decided to examine the desymmetrization of anhydride **25** with our modified cinchona alkaloid, OPQ.

Anhydride **25**, 5-methylenetetrahydrocyclopenta[c]furan-1,3-dione, was prepared from commercially available butanetetra-carboxylic acid as described in Mittendorf's report. After some optimization of the reaction conditions, we found that desymmetrization of **25** using 0.5 equiv of OPQ gave (+)-half-ester **26** with a yield and enantioselectivity which was equal to that with 1.0 equiv of quinine, albeit in a slower reaction (Table 2). Considering the ease of recovering the catalyst, we decided to use 0.7 equiv of OPQ for scale up to reduce the reaction time. This reaction was successfully carried out in a controlled manner on pilot-plant scale to afford crude (+)-half-ester **26** with 90% ee. As described in Mittendorf's report, we stirred the crude product in a small amount of toluene and filtered the crystalline racemic half-ester *rac*-**26**. The filtrate contained cinnamyl ester **26** in 85% overall yield and with >98% ee. Straightforward recycling of the filtered racemic half-ester *rac*-**26** as well as catalyst OPQ makes this process highly efficient and economical. The (+)-half-ester **26** could be converted to the β -amino acid BAY 10-8888/PLD-118 in another three steps.

Conclusion

An efficient and practical process for the preparation of chiral α -amino acids and chiral half-esters has been developed, which provides significant advantages over the original

(16) Ziegelbauer, K.; Babczinski, P.; Schoenfeld, W. *Antimicrob. Agents Chemother.* **1998**, *42*, 2197.

(17) Mittendorf, J.; Benet-Buchholz, J.; Fey, P.; Mohrs, K.-H. *Synthesis* **2003**, 136.

(18) Another example of desymmetrization of a cyclic meso-anhydride catalyzed with (DHQD)₂AQN showed high enantioselectivity but too slow reaction speed at low temperature: Keen, S. P.; Cowden, C. J.; Bishop, B. C.; Brands, K. M. J.; Davis, A. J.; Dolling, U. H.; Lieberman, D. R.; Stewart, G. W. *J. Org. Chem.* **2005**, *70*, 1771.

process described by Deng and co-workers. The improved organocatalysts OPQD and OPQ can be easily prepared and are highly enantioselective in the kinetic resolution of UNCAs and in the desymmetrization of *meso*-anhydrides. Processes for the preparation of (*S*)-*N*-Boc-propargylglycine **24** and the key intermediate **26** for β -amino acid BAY 10-8888/PLD-118 using these new catalysts were successfully performed on multikilogram scale.

Experimental Section

General. Starting materials were obtained from commercial suppliers and were used without further purification unless otherwise mentioned. Dry solvents were used as purchased. HPLC analyses were performed on a Shimadzu 14A liquid chromatograph equipped with a UV detector. NMR spectra were obtained at 270 MHz for ^1H NMR and 67.5 MHz for ^{13}C NMR. All coupling constants are reported in Hertz (Hz). Melting points were determined in open capillary tubes and uncorrected. *N*-Z-Phenylalanine UNCA **15**^{6a} and 5-methylenetetrahydrocyclopenta[*c*]furan-1,3-dione (**25**)¹⁷ were synthesized according to the literature procedure. (DHQD)₂AQN and (DHQ)₂AQN were purchased from Aldrich and used without further purification.

General Procedure for Synthesis of *O*-Alkylated Quinidine. Under N_2 atmosphere, NaH (400 mg, 10 mmol, 60% in mineral oil) was added at 0 °C to a solution of quinidine (1.62 g, 5 mmol) in DMF (30 mL). After cessation of H_2 evolution, alkyl halide (6 mmol) was added dropwise over a period of 30 min, while maintaining the temperature below 0 °C, followed by stirring for 3 h at room temperature. Water (50 mL) was added to quench the reaction, followed by extraction with toluene (50 mL). The toluene layer was washed with brine (20 mL), concentrated, and purified on silica gel chromatography (25:25:1 = hexanes/acetone/diethylamine) to afford *O*-alkylated quinidine as a colorless oil (52–92%).

***O*-Methylquinidine:** yield = 52%; ^1H NMR (CDCl_3): δ 1.10–1.25 (m, 1H), 1.50–1.70 (m, 2H), 1.70–1.80 (m, 1H), 2.15–2.45 (m, 2H), 2.70–3.05 (m, 4H), 3.39 (s, 3H), 3.50–3.62 (m, 1H), 4.00 (s, 3H), 5.05–5.20 (m, 2H), 5.52 (br, 1H), 6.02–6.15 (m, 1H), 7.29–7.45 (m, 3H), 8.04 (d, J = 9.2 Hz, 1H), 8.75 (d, J = 4.6 Hz, 1H). ^{13}C NMR (CDCl_3): δ 20.3, 25.5, 28.0, 39.2, 49.0, 49.7, 56.2, 57.2, 59.5, 80.9, 100.9, 115.4, 118.2, 122.0, 127.1, 131.6, 139.1, 143.0, 144.4, 147.2, 158.0. HRMS ($\text{M} + \text{H}$)⁺ Calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_2$: 339.2072. Found: 339.2113.

***O*-Benzylquinidine:** yield = 66%; ^1H NMR (CDCl_3): δ 1.20–1.60 (m, 3H), 1.70–1.80 (m, 1H), 2.02–2.15 (m, 1H), 2.20–2.30 (m, 1H), 2.65–2.91 (m, 3H), 3.00–3.15 (m, 1H), 3.20–3.35 (m, 1H), 3.89 (s, 3H), 4.38 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.90–5.05 (m, 2H), 5.25 (br, 1H), 5.87–6.02 (m, 1H), 7.27–7.47 (m, 8H), 8.05 (d, J = 9.2 Hz, 1H), 8.76 (d, J = 4.3 Hz, 1H). ^{13}C NMR (CDCl_3): δ 22.4, 26.6, 28.2, 40.1, 49.5, 50.1, 55.6, 60.1, 71.2, 80.8, 101.1, 114.2, 119.0, 121.6, 127.4, 127.6, 127.8, 128.2, 131.7, 137.7, 140.6, 144.5, 144.6, 147.5, 157.5. HRMS ($\text{M} + \text{H}$)⁺ Calcd for $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_2$: 415.2386. Found: 415.2405.

***O*-Allylquinidine:** yield = 72%; ^1H NMR (CDCl_3): δ 1.16–1.30 (m, 1H), 1.40–1.60 (m, 2H), 1.70–1.80 (m, 1H),

2.01–2.20 (m, 1H), 2.20–2.30 (m, 1H), 2.71–3.13 (m, 4H), 3.25–3.40 (m, 1H), 3.80–4.05 (m, 2H), 3.92 (s, 3H), 5.00–5.40 (m, 5H), 5.85–6.15 (m, 2H), 7.29–7.45 (m, 3H), 8.03 (d, J = 9.2 Hz, 1H), 8.74 (d, J = 4.6 Hz, 1H). ^{13}C NMR (CDCl_3): δ 21.7, 26.6, 28.3, 40.2, 49.7, 50.3, 55.6, 59.8, 70.1, 80.9, 101.0, 114.3, 116.8, 118.7, 121.5, 127.2, 131.7, 134.3, 140.7, 144.5, 144.5, 147.5, 157.5. HRMS ($\text{M} + \text{H}$)⁺ Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_2$: 365.2229. Found: 365.2316.

***O*-Propargylquinidine (OPQD):** yield = 92%; ^1H NMR (CDCl_3): δ 1.20–1.40 (m, 1H), 1.43–1.60 (m, 2H), 1.72–1.83 (m, 1H), 2.00–2.13 (m, 1H), 2.18–2.34 (m, 1H), 2.46 (t, J = 2.4 Hz, 1H), 2.70–2.97 (m, 3H), 3.04–3.16 (m, 1H), 3.21–3.35 (m, 1H), 3.87–3.95 (m, 1H), 3.93 (s, 3H), 4.24 (dd, J = 16.0, 2.3 Hz, 1H), 5.05–5.16 (m, 2H), 5.36 (d, J = 4.0 Hz, 1H), 6.02–6.17 (m, 1H), 7.33–7.45 (m, 3H), 8.03 (d, J = 9.8 Hz, 1H), 8.77 (d, J = 4.5 Hz, 1H). ^{13}C NMR (CDCl_3): δ 22.6, 26.7, 28.2, 40.2, 49.4, 50.1, 55.6, 56.4, 59.9, 74.9, 79.4, 79.8, 101.1, 114.4, 119.0, 121.6, 127.4, 131.7, 140.7, 143.8, 144.5, 147.4, 157.6. HRMS ($\text{M} + \text{H}$)⁺ Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_2$: 363.2073. Found: 363.2144.

***O*-tert-Butoxycarbonylmethylquinidine:** yield = 55%; ^1H NMR (CDCl_3): δ 1.20–1.40 (m, 1H), 1.44 (s, 9H), 1.50–1.58 (m, 1H), 1.67–1.90 (m, 2H), 2.16–2.30 (m, 2H), 2.70–3.00 (m, 3H), 3.05–3.16 (m, 1H), 3.28–3.40 (m, 1H), 3.77 (d, J = 15.9 Hz, 1H), 3.93 (s, 3H), 3.95 (d, J = 15.9 Hz, 1H), 5.07–5.14 (m, 2H), 5.33 (br, 1H), 6.09–6.22 (m, 1H), 7.28–7.44 (m, 3H), 8.03 (d, J = 9.2 Hz, 1H), 8.75 (d, J = 4.1 Hz, 1H). ^{13}C NMR (CDCl_3): δ 22.2, 26.5, 28.1, 28.4, 40.3, 49.5, 50.1, 55.6, 55.6, 60.0, 66.9, 81.5, 101.0, 114.4, 119.0, 121.7, 127.3, 131.7, 140.7, 143.6, 144.5, 147.4, 157.7, 168.5. HRMS ($\text{M} + \text{H}$)⁺ Calcd for $\text{C}_{26}\text{H}_{35}\text{N}_2\text{O}_4$: 439.2629. Found: 439.2616.

Large-Scale Procedure for *O*-Propargylquinine (OPQ). Under N_2 atmosphere in a glass-lined reactor, a solution of quinine (130 kg, 400 mol) in DMF (460 kg) was added below 20 °C to a NaH (35.2 kg, 880 mol, 60% in mineral oil) suspension in DMF (220 kg) over a period of 2 h. (CAUTION: there have been explosive accidents in NaH–DMF mixtures, and evaluation of the reaction hazard and the safety treatment have been reported.¹⁹ Buckley and co-workers reported that the NaH–DMF mixtures were observed to self-heat beginning as low as 26 °C by ARC (accelerating rate calorimeter) analysis.^{19a,20} DeWall reported observing that an exothermic reaction involving NaH–DMF started to occur at about 40 °C only in the stainless steel reactor.^{19b} Kinoshita and co-workers concluded that the reaction hazard in NaH–DMF mixtures was suppressed dramatically when the weight ratio of NaH to DMF was below 0.16 and the reaction temperature maintained at less than 60 °C by ARC analysis and Dewar vessels methods.^{19d} Moreover these workers recommended to use NaH–DMI (1,3-dimethyl-2-imidazolidinone) mixtures to avoid hazardous NaH–DMF ones. Our reaction conditions in NaH–DMF

- (19) (a) Buckley, J.; Webb, R. L.; Laird, T.; Ward, R. J. *Chem. Eng. News* **1982**, 60 (28), 5. (b) DeWall, G. *Chem. Eng. News* **1982**, 60 (37), 5 and 43. (c) Laird, T. *Chem. Ind.* **1986**, 17, 134. (d) Kinoshita, N.; Takeuchi, H.; Kawai, N. *Proc. Annu. Meet. Jpn. Soc. Saf. Eng.* **2000**, Abstr. 15.
(20) Thermal stability: A review of methods and interpretation of data. Rowe, S. M. *Org. Process Res. Dev.* **2002**, 6, 877.

mixtures are under all their safety ranges. In addition, we confirmed that our improved catalyst synthesis using NaH–DMI mixtures instead of NaH–DMF mixtures also led to an identical yield.) After cessation of H₂ evolution, propargyl bromide (57.2 kg, 480 mol) was added dropwise over a period of 12 h, while maintaining the temperature below 0 °C, followed by stirring for 2 h at 10 °C. To quench the reaction 18% HCl (54 kg) was added at 10 °C, followed by concentrating to about 300 L in vacuo while maintaining the internal temperature below 70 °C. Toluene (350 kg) and 5% NaOH (170 kg) were added, and the product was extracted into the organic layer, which was washed with brine (2 × 160 kg). Activated carbon (65 kg) was added to the separated organic layer, stirred for 2 h, filtered, and rinsed with toluene (4 × 140 kg). The filtrate was evaporated until about 240 L in vacuo. Ethyl acetate (34 kg) and hexanes (400 kg) were added at room temperature, followed by crystallization by cooling to 5 °C. The product was stirred overnight at 5 °C, filtered, rinsed with hexanes (2 × 140 kg), and dried under vacuum at 40 °C overnight to obtain OPQ as an off-white solid (106.2 kg, 73%). Mp 88–90 °C; ¹H NMR (CDCl₃): δ 1.42–1.82 (m, 5H), 2.20–2.33 (m, 1H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.56–2.72 (m, 2H), 3.04–3.24 (m, 2H), 3.35–3.50 (m, 1H), 3.87–3.95 (m, 1H), 3.94 (s, 3H), 4.22 (dd, *J* = 15.9, 2.4 Hz, 1H), 4.89–4.99 (m, 2H), 5.33 (d, *J* = 4.3 Hz, 1H), 5.69–5.82 (m, 1H), 7.36–7.43 (m, 3H), 8.04 (d, *J* = 9.7 Hz, 1H), 8.76 (d, *J* = 4.6 Hz, 1H); ¹³C NMR (CDCl₃): δ 23.1, 27.9, 27.9, 40.1, 43.1, 55.7, 56.2, 57.2, 60.1, 75.0, 77.2, 79.3, 101.2, 114.1, 119.1, 122.0, 127.4, 131.8, 141.9, 143.7, 144.6, 147.5, 157.6. Anal. Calcd for C₂₃H₂₆N₂O₂: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.29; H, 7.31; N, 7.66.

General Procedure for Kinetic Resolution of *N*-Z-Phenylalanine UNCA **15 with Ethanol Catalyzed by *O*-Alkylated Cinchona Alkaloid.** The kinetic resolution of **15** was performed according to Deng's original procedure.^{6a} Anhydrous diethyl ether (35 mL) was added to a mixture of **15** (163 mg, 0.5 mmol), *O*-alkylated cinchona alkaloid (0.1 mmol), and 4 Å molecular sieves (100 mg); the resulting mixture was stirred at room temperature for 15 min and then cooled to –60 °C. An ethanol solution in ether (5% v/v, 0.3 mmol of ethanol) was introduced dropwise via a syringe. The resulting reaction mixture was stirred at –60 °C for 20 h. UNCAs are unstable under the conditions of GC and HPLC analysis. Therefore, the conversion of the reaction and the enantiomeric excess were determined by converting the unreacted UNCA into methyl ester **17** and subsequently analyzing the resulting mixture of ethyl ester **16** and methyl ester **17** by GC and chiral HPLC as follows: A small aliquot (50 μL) of the reaction mixture was added to dry methanol (200 μL). The resulting mixture was stirred at room temperature for 30 min and then allowed to pass through a plug of silica gel with ether as the eluent. The resulting solution of ethyl ester **16** and methyl ester **17** was concentrated and then subjected to GC analysis (HP-5 column, 200 °C; 4 min, 10 °C/min to 250 °C, 250 °C 8–12 min) and to chiral HPLC analysis (Daicel Chiralpac OJ, hexane/IPA = 8:2, 0.7 mL/min, λ = 220 nm, (*R*)-**17** = 39 min; (*S*)-**17** =

26 min; (*R*)-**16** = 22 min; (*S*)-**16** = 19 min).

***N*-Z-Propargylglycine **20**.** Diethyl acetamidomalonate (**18**, 6.52 kg, 30 mol) was added at 10 °C to a solution of potassium *tert*-butoxide (4.21 kg, 37.5 mol) in ethanol (36.5 L). After cooling to 5 °C, propargyl bromide (4.46 kg, 37.5 mol) was added dropwise over a period of 9 h, while maintaining the temperature below 10 °C, followed by stirring for 4 h at 10 °C. After filtration and concentration, H₂O (15 L) was added to the residue. After heating at 50 °C, 48% NaOH (6.25 kg, 75 mol) was added for hydrolysis. The mixture was heated at 65 °C and stirred for 3 h. The solvent (approximately 7.5 L) was removed by distillation at normal pressure. The aqueous solution was acidified to pH 5.0 with 35% HCl (approximately 3.5 L). After an extra addition of 35% HCl (7.5 L), the reaction mixture was heated to reflux and stirred for 5 h until CO₂ evolution ceased. After cooling to 20 °C, the aqueous solution was neutralized under ice, cooling to pH 6.3 with 48% NaOH (approximately 4.5 L), and an additional 48% NaOH (2.50 kg, 30 mol) was added. After cooling to 5 °C, 48% NaOH (3.13 kg, 37.5 mol) and benzyloxycarbonyl chloride (6.39 kg, 37.5 mol) were simultaneously added dropwise while maintaining the pH between 7.5 and 10.0 and the temperature below 10 °C over a period of 8 h. After stirring for 3 h at 10 °C, the reaction mixture was washed by toluene (20 L). The aqueous layer was acidified to pH 2.0 with 35% HCl (approximately 4.0 L) and extracted with ethyl acetate (6.5 L). The organic layer was concentrated. Toluene (20 L) was added and heated at 60 °C to be homogeneous. The solution was cooled to 4 °C and stirred for 5 h at 4 °C. The precipitated solid was collected by filtration, washed with ice-cooled toluene, and dried in vacuo to afford **20** (4.01 kg, 54%) as a white solid. Mp 132–133 °C; ¹H NMR (CDCl₃): δ 2.10 (t, *J* = 2.7 Hz, 1H), 2.80–2.90 (m, 2H), 4.55–4.62 (m, 1H), 5.12 (s, 2H), 5.66 (d, *J* = 8.4 Hz, 1H), 7.31–7.36 (m, 5H), 8.51 (br, 1H).

***N*-Boc-Propargylglycine UNCA **22**.** To a solution of **20** (3.71 kg, 15 mol) in THF (15 L), was added dropwise thionyl chloride (3.57 kg, 30 mol) over a period of 1 h at ambient temperature. After the evolution of SO₂ and HCl ceased (ca. 7 h), the solvent and excess thionyl chloride were removed by distillation in vacuo. To the residue, hexanes (8 L) was added. After stirring for an hour, the precipitated solid (crude NCA, **21**) was collected by filtration under N₂ atmosphere, washed with hexanes (3 × 4 L), and dried in vacuo. To the solid were added ethyl acetate (15 L) and di-*tert*-butyl dicarbonate (3.60 kg, 16.5 mol) under N₂ atmosphere. After cooling to –10 °C, pyridine (1.78 kg, 22.5 mol) was added and stirred for 14 h at –10 °C. The reaction mixture was acidified at –10 °C by 4 M HCl in 1,4-dioxane solution until the pH of the mixture was approximately 3. Under N₂ atmosphere the precipitate (pyridinium salt) was removed by filtration through Celite. After concentration of the filtrate, ethyl acetate (3 L) was added, and then hexanes (15 L) were added dropwise over a period of 2 h. After stirring for 8 h at –15 °C, the precipitated solid was collected by filtration, washed with hexanes (2 × 3 L), and dried in vacuo to afford **22** (2.24 kg, 62%) as a white solid. Mp 52–54 °C; ¹H NMR (CDCl₃): δ 1.68 (s, 9H), 2.28 (t, *J* = 2.7 Hz, 1H), 3.03 (dt,

$J = 17.3, 2.7$ Hz, 1H), 3.34 (dt, $J = 17.3, 2.7$ Hz, 1H), 4.83 (t, $J = 2.7$ Hz, 1H).

Kinetic Resolution of *N*-Boc-Propargylglycine UNCA **22 with Methanol Catalyzed by OPQD.** Under a N_2 atmosphere, OPQD (0.40 kg, 1.10 mol) in toluene (8 L) was added to a solution of **22** (1.32 kg, 5.50 mol) in toluene (30 L) at -60 °C. After stirring for 10 min, methanol (0.97 kg, 3.03 mol) was added dropwise over a period of 12 h. A solution of 2 M HCl (5.5 L, 11 mol) was added to the reaction mixture, and the resulting mixture was allowed to warm to room temperature. The organic phase was collected, washed with 2 M HCl (2×1.5 L, the acidic aqueous phases were collected for catalyst recovery) and brine (1.5 L), and concentrated in vacuo. The residue was dissolved in H_2O /THF (v/v: 1/4, 2.5 L), and the resulting solution was stirred at ambient temperature for 12 h. The solution was concentrated, and the residue was dissolved in ethyl acetate (2.5 L). The resulting solution was extracted with 1 M aqueous Na_2CO_3 (2×1.5 L). The basic aqueous phases were combined, acidified carefully to pH 3 by the addition of 2 M HCl, and then extracted with ethyl acetate (2×4 L). The combined organic phases were washed with brine (2×1.5 L) and concentrated to afford (*S*)-*N*-Boc-propargylglycine (**24**, 0.48 kg, 41%, purity 97%, 99% ee) as an off-white solid. Mp $97-99$ °C; 1H NMR ($CDCl_3$): δ 1.46 (s, 9H), 2.08 (t, $J = 2.7$ Hz, 1H), 2.79 (m, 2H), 4.53 (m, 1H), 5.42 (br, 1H), 11.98 (s, 1H). Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD, hexane/IPA/TFA = 90:10:0.002, 1.5 mL/min, $\lambda = 210$ nm, (*R*)-**24** = 5 min; (*S*)-**24** = 9 min).

The organic layer was washed with brine (1 L) and concentrated to give (*R*)-*N*-Boc-propargylglycine methyl ester (**23**, 0.62 kg, 50%, 84% ee) as a colorless oil. 1H NMR ($CDCl_3$): δ 1.46 (s, 9H), 2.06 (t, $J = 2.7$ Hz, 1H), 2.74 (m, 2H), 3.80 (s, 3H), 4.58 (m, 1H), 5.37 (d, $J = 8.0$ Hz, 1H). Enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/IPA = 99:1, 1.0 mL/min, $\lambda = 210$ nm, (*S*)-**23** = 47 min; (*R*)-**23** = 52 min).

For the catalyst OPQD recovery, the acidic aqueous phases were washed with ethyl acetate (2×1.5 L) and basified with 48% NaOH to adjust the pH value to approximately 4 and then with Na_2CO_3 to pH 11. The resulting mixture was extracted with toluene (3×4 L). The combined extracts were washed with brine (2×1.5 L) and concentrated to give the recovered catalyst, OPQD, in NMR-pure form and in quantitative yield. The recovered catalyst can be directly used for another reaction cycle with no deterioration in activity and selectivity.

Desymmetrization of 5-Methylenetetrahydrocyclopenta[c]furan-1,3-dione (25**) with Cinnamyl Alcohol Catalyzed by OPQ.** To a solution of **25** (4.90 kg, 32.2 mol) and OPQ (8.21 kg, 22.7 mol) in toluene (64 L) was added dropwise over a period of 3 h a solution of cinnamyl alcohol (6.48 kg, 48.3 mol) in toluene (16.1 L) at -10 °C, and the reaction mixture was stirred for 5 h at -10 °C. The mixture was allowed to warm to 0 °C and washed with 1.2 M HCl (3×40 L) and H_2O (50 L). The organic layer was extracted with 7% Na_2CO_3 (43 L + 30 L + 30 L). After washing the combined aqueous solutions with ethyl acetate (3×70 L), toluene (48 L) was added, and the mixture was acidified under vigorous stirring to pH 1.5 with 10% HCl (46 L). The aqueous layer was separated and extracted with toluene (74 L). The combined toluene solutions were washed with H_2O (50 L) and evaporated in vacuo at 50 °C. The oily residual (crude **26**; 90% ee) was stirred with toluene (10 L) at room temperature for 2 h. The precipitated solid was collected by filtration, washed with toluene (2 L) and dried in vacuo to afford almost racemic **26** (0.89 kg, 9.7%, 10% ee). The filtrate was evaporated in vacuo to afford (+)-(1*S*,2*R*)-4-methylene-2-[(2*E*)-3-phenyl-2-propenyloxycarbonyl]cyclopentanecarboxylic acid (**26**) as a slightly yellow oil (7.80 kg, 85%, 98.7% ee). The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OD-H, hexane/IPA/AcOH = 92:5:3, 1.0 mL/min, $\lambda = 254$ nm, (+)-**26** = 12 min; (–)-**26** = 19 min). The product was stored as a 35% solution in toluene. 1H NMR ($CDCl_3$): δ 2.58–2.88 (m, 4H), 3.05–3.25 (m, 2H), 4.71 (d, $J = 6.4$ Hz, 2H), 4.91–4.97 (m, 2H), 6.23 (dt, $J = 15.9, 6.4$ Hz, 1H), 6.62 (dd, $J = 15.9, 1.0$ Hz, 1H), 7.20–7.42 (m, 5H), 11.1 (br, 1H).

For the catalyst OPQ recovery, the acidic aqueous layer was washed with ethyl acetate (2×20 L) and basified with 48% NaOH to adjust the pH value to approximately 4 and then with Na_2CO_3 to pH 11. The resulting mixture was extracted with toluene (2×30 L). The combined extracts were washed with brine and concentrated to give recovered catalyst, OPQ, in NMR-pure form and in quantitative yield. The recovered OPQ can be directly used for another reaction cycle with no deterioration in activity and selectivity.

Acknowledgment

We thank Professor Li Deng and Emeritus Professor Shinji Murai for their expert help.

Received for review January 29, 2007.

OP700023H