A Practical Synthesis of C_2-Symmetric Chiral Binaphthyl Ketone Catalyst

Masahiko Seki,* Shin-ichi Yamada, Tooru Kuroda, Ritsuo Imashiro, Toshiaki Shimizu

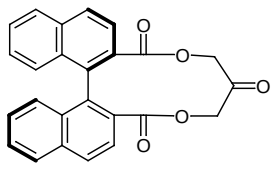
Product & Technology Development Laboratory, Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-ku, Osaka 532-8505, Japan
Fax +81(6)63002816; E-mail: m-seki@tanabe.co.jp

Received 12 June 2000; revised 27 July 2000

Abstract: A practical synthesis of 11-membered C_2-symmetric binaphthyl ketone (*R*)-**1**, a catalyst for asymmetric epoxidation, was developed. (±)-1,1'-Binaphthyl-2,2'-dicarboxylic acid [(±)-**6**] was efficiently resolved by (*R*)-(−)-1-cyclohexylethylamine to give (*R*)-**6** in >99% ee and in 38% yield. Condensation of the acid chloride derived from (*R*)-**6** with 1,3-dihydroxyacetone dimer at 60−70 °C provided the desired chiral ketone (*R*)-**1** in 61−63% yield without need for high dilution techniques.

Key words: catalysts, asymmetric epoxidation, dioxiranes, macrocycles, optical resolution

Development of a practical synthetic method for chiral catalysts is one of the most important criteria for a catalytic asymmetric synthesis to become a commercial process for large-scale preparation. In search of an epoxidation that can be applied to an industrial synthesis, we have focused on chiral dioxirane-mediated asymmetric epoxidation catalyzed by chiral C_2-symmetric binaphthyl ketone (*R*)-**1**.[1] The original synthetic method of the chiral ketone (*R*)-**1**, however, suffers from such drawbacks as 1) handling highly toxic alkaloids for the optical resolution of (±)-1,1'-binaphthyl-2,2'-dicarboxylic acid [(±)-**6**];[4,5] and 2) a poor yield (28%) to construct the 11-membered ring using 2-chloro-1-methylpyridinium iodide (Mukaiyama reagent) and a high dilution method [reaction solvent: ca 300 volume of the solvent per weight of the substrate (300 v/w)].[1]



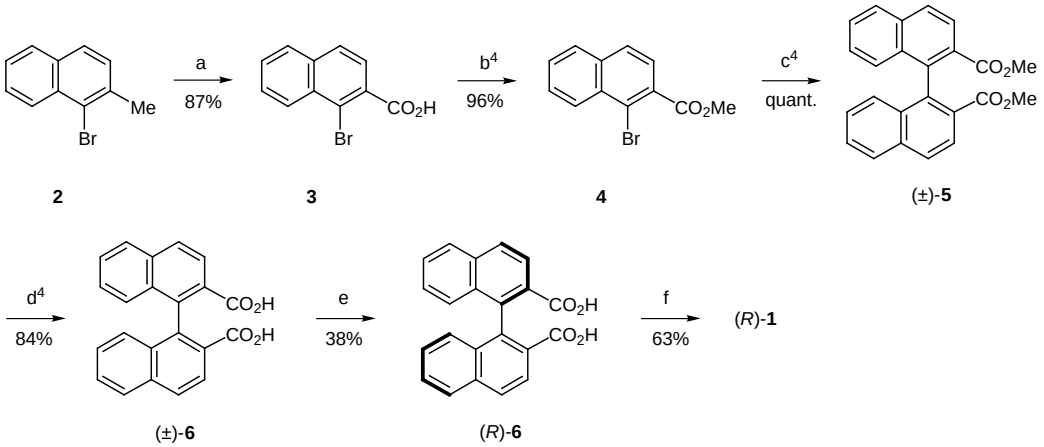
(*R*)-**1**

We have recently described some improvements in the synthesis of (*R*)-**1**, which involved an intramolecular Ullmann reaction, a Co(salen)-catalyzed macrolactonization and an enzymatic resolution.[2] However, a practical use of these methods has hitherto been restricted by the multisteps (8 steps or more) and the low concentration of the substrates in the enzymatic resolution. Reported herein is a more efficient synthesis of the chiral ketone (*R*)-**1** through a novel optical resolution of (±)-1,1'-binaphthyl-2,2'-dicarboxylic acid [(±)-**6**] and the formation of the 11-memberd ring via condensation of the acid chloride from (*R*)-**6** with 1,3-dihydroxyacetone dimer.

(±)-1,1'-Binaphthyl-2,2'-dicarboxylic acid [(±)-**6**], the substrate for the optical resolution, was prepared from commercially available 1-bromo-2-methylnaphthalene **(2)** with some modification of the reported procedures[3,4] (Scheme). Oxidation of the methyl group of **2** to the corresponding carboxylic acid **3** was carried out by treatment with molecular oxygen with cobalt(II) acetate as a catalyst. A reported procedure[3] in which oxygen is bubbled into a mixture of **2** and cobalt(II) acetate (20 mol%) in acetic acid and butan-2-one at 90−100 °C needs a long reaction period (9 h) and a large excess of oxygen to complete the reaction. In order to reduce the reaction period and the consumption of the oxygen, the reaction was conducted in an autoclave under 3.5 kg/cm^2 of oxygen at 100−109 °C for 1 hour to provide the desired carboxylic acid **3** in 87% yield. The compound **3** was esterified[4] and was allowed to react with copper powder in refluxing DMF[4] and subsequent hydrolysis[4] provided (±)-1,1'-binaphthyl-2,2'-dicarboxylic acid [(±)-**6**] in 70% yield based on **2** without any tedious purification such as silica gel column chromatography.

Optical resolution of (±)-1,1'-binaphthyl-2,2'-dicarboxylic acid [(±)-**6**] was then investigated. So far known resolving agents for (±)-**6** are the highly toxic quinine and brucine.[4,5] We tried a number of chiral amines for the optical resolution and eventually found that the non-toxic (*R*)-(−)-1-cyclohexylethylamine [(*R*)-CHEA] (2.0 equiv) could effectively resolve (±)-**6** to give (*R*)-**6** in >99% ee and in 38% yield. In order to reduce the amount of the resolving agent, addition of achiral amine in the optical resolution was tested. As the result of the screening, dimethylamine (0.9 equiv) was found to be effective to reduce the resolving agent to give (*R*)-**6** in 38% yield by the use of 1.2 equivalents of (*R*)-CHEA. Dimethylamine has additional advantages of high water solubility and a low boiling point (bp = 7 °C), which enabled facile and high-yielding recovery (90%) of (*R*)-CHEA free from contamination by dimethylamine.

Condensation of (*R*)-**6** with 1,3-dihydroxyacetone dimer was then investigated via formation of its acid chloride. The acid chloride was prepared by treatment of (*R*)-**6** with thionyl chloride (4 equiv) in the presence of pyridine (0.96 equiv) and was allowed to react with 1,3-dihydroxyacetone dimer (1.2 equiv) at 20 °C in the presence of triethylamine (3 equiv) in dichloromethane. A high dilution method (reaction solvent: 320 v/w) was again needed to



Reagents and conditions: a) O_2 (3 kg/cm^2)/$Co(OAc)_2$•$4H_2O$ (0.2 equiv)/butan-2-one (0.3 equiv)/AcOH, 100−109 °C, 1 h; b) MeOH/$SOCl_2$ (1.2 equiv), reflux, 3 h; c) Cu (1.7 equiv)/DMF, 125 °C, 3 h; d) KOH (3.8 equiv), MeOH/H_2O, reflux, 2 h then HCl; e) (*R*)-CHEA (1.2 equiv)/Me_2NH (0.9 equiv)/MeOH, H_2O, then HCl; f) i. $SOCl_2$ (4 equiv)/pyridine (0.96 equiv)/$CHCl_3$ ii. 1, 3-dihydroxyacetone dimer (1.2 equiv)/Et_3N (3 equiv)/toluene, 60 °C, 2 h

Scheme

obtain 53% yield of (*R*)-**1** (Table, Entries 1, 2). This may be due to the poor reactivity of 1,3-dihydroxyacetone dimer. Indeed, a dramatic improvement in the yield with considerably reduced amount of the reaction solvent was achieved by elevating the reaction temperature: addition of 1,3-dihydroxyacetone dimer and Et_3N to the solution of the acid chloride in 1,2-dichloroethane (total volume of the reaction solvent: 50 v/w) at 70 °C over 1.5 hours provided (*R*)-**1** in 61% yield (Table, Entry 4). Under the same reaction conditions except the reaction temperature (60 °C), environmentally acceptable toluene (60 v/w) could also be used to give good yield (63%) of the coupling product (*R*)-**1** (Table, Entry 6). Further investigations to reduce the amount of toluene were not undertaken because of the low solubility of the reactants (acid chloride and 1,3-dihydroxyacetone dimer). When the reaction was conducted at 50 °C, a remarkable decrease in the yield was observed (63 to 16%) (Table, Entries 6 and 7). Under the best reaction conditions (Table, Entry 6), almost all the dicarboxylic acid (*R*)-**6** was consumed. While the structure of the byproducts in the cyclization reaction has not been determined yet, alkaline hydrolysis of the mother liquor of (*R*)-**1** regenerated (*R*)-**6** in 34% yield based on the initially added (*R*)-**6**.

Table Optimization of the Synthesis of (*R*)-**1**

Entry	Solvent (v/w)[a]	Conditions		Yield (%)[c]
		Temp (°C)	Addition Time (h)[b]	
1	CH_2Cl_2 (320)	20	9	53
2	CH_2Cl_2 (50)	20	9	12
3	$ClCH_2CH_2Cl$ (100)	70	1.5	60
4	$ClCH_2CH_2Cl$ (50)	70	1.5	61
5	$ClCH_2CH_2Cl$ (22)	70	1.5	49
6	toluene (60)	60	1.5	63
7	toluene (60)	50	1.5	16

[a] Volume of the solvent per weight of (*R*)-**6**.
[b] Addition time of a mixture of 1,3-dihydroxyacetone dimer and Et_3N to the solution of the acid chloride of (*R*)-**6**.
[c] Isolated yield.

In conclusion, the 11-membered binaphthyl ketone (*R*)-**1** was synthesized from readily accessible 1-bromo-2-methylnaphthalene in 6 steps and in 17% overall yield through the novel and efficient optical resolution with the non-toxic resolving agent and the formation of the 11-membered ring without using the high dilution method. Simple operations, ready availability of the reagents and short steps of the present synthesis permit a practical access to the chiral ketone catalyst of recent interest.

Melting points were measured using a Yamato melting point apparatus and are uncorrected. IR were taken by the use of a Perkin Elmer 1600 infrared spectrometer. ^{1}H NMR were recorded on a Bruker AC-200 (200 MHz) spectrometer and are reported in δ values. Mass spectra were taken by using a Hitachi M-2000A mass spectrometer at an ionizing potential of 70 eV. Microanalyses were performed by a Perkin-Elmer 2400 Series II CHNS/O analyser. Optical rotations were measured on a Perkin-Elmer 243 polarimeter and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. TLC was performed on E. Merck 0.25 mm precoated glass backed plates (60 F_{254}). Development was accomplished using either 5% phosphomolybdic acid in EtOH-heat or visualized by UV-light where feasible. Flash chromatography was accomplished using Kieselgel 60 (230−400 mesh, E. Merck). The copper powder (particle size: 100−200 mesh) was purchased from Kanto Chemicals Co., Lnc. and used without further purification.

1-Bromo-2-naphthoic Acid (3)

A mixture of 1-bromo-2-methylnaphthalene (106.5 g, 0.482 mol), $Co(OAc)_2•4H_2O$ (24 g, 0.096 mol) and butan-2-one (13 mL, 0.145 mol) in AcOH (400 mL) was stirred at 100−109 °C under O_2 atmosphere (3 kg/cm^2) in an autoclave for 1 h. After cooling the mixture to 30 °C, the mixture was poured into ice-water (2 L). The crystals formed were collected, washed with H_2O (5 × 300 mL) and dried at 60 °C for 17 h to give **3** (105.3 g, 87%) as slightly brown crystals; mp 187−189 °C (Lit.[4] mp 186−188 °C).

IR (KBr): ν = 1692 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.68−7.81 (m, 3 H), 8.04−8.09 (m, 2 H), 8.31−8.35 (m, 1 H), 13.6 (br s, 1 H).

MS: m/z = 251 (M^+).

(±)-1,1'-Binaphthyl-2,2'-dicarboxylic Acid [(±)-6]

To a mixture of **3** (105.3 g, 0.419 mol) in MeOH (350 mL) was added $SOCl_2$ (36.7 mL, 0.503 mol) over 10 min under cooling with ice-water. The mixture was refluxed for 3 h and evaporated. The residue was dissoved in toluene (300 mL) and washed successively with H_2O (300 mL), sat. aq $NaHCO_3$ 300 mL) and brine (300 mL), treated with active charcoal (25 g), dried ($MgSO_4$) and evaporated to give **4** (106.3 g, 96%) as brown crystals. A mixture of the crude **4** (106.3 g) and copper powder (43.3 g, 0.682 mol) in DMF (150 mL) was stirred at 117−120 °C for 3 h. The mixture was filtered through a pad of Celite and the undissolved materials were washed with DMF (2 × 30 mL). The filtrate and the washings were combined and evaporated. The solid formed was washed with H_2O (3 × 250 mL) and dried at 90 °C for 17 h to give **5** (74 g, quant.) as brown crystals. To the crude **5** (74 g) were added MeOH (570 mL), H_2O (110 mL) and KOH (85%, 50.7 g, 0.768 mol) and the mixture was refluxed for 2 h. After evaporating the solvent, the residue dissolved in H_2O (300 mL) was washed with toluene (3 × 300 mL) and acidified (pH 1.0) by concd HCl (75 mL). The mixture was extracted with EtOAc (2 × 300 mL), washed with brine (300 mL), treated with active charcoal (10 g), dried ($MgSO_4$) and evaporated. The crystals formed were collected by adding hexanes and dried at 90 °C for 17 h to give (±)-**6** (57.6 g, 84%) as slightly yellow crystals; mp 277−278 °C (Lit.[4] 272−274 °C).

IR (KBr): ν = 1691 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.04−7.26 (m, 4 H), 7.44−7.53 (m, 4 H), 7.89−8.00 (m, 4 H), 8.11−8.15 (m, 2 H).

MS: m/z = 342 (M^+).

(*R*)-1,1'-Binaphthyl-2,2'-dicarboxylic Acid [(*R*)-6]

To a suspension of (±)-**6** (10.3 g, 30 mmol) in MeOH (22 mL) were added Me_2NH (50 wt% solution in H_2O, 2.44 g, 27 mmol) and (*R*)-CHEA (4.58 g, 36 mmol) and the mixture was dissolved at 65 °C. To this mixture was added boiling water (50 mL) and the mixture was gradually cooled down to 25 °C under mechanical stirring for 2.5 h. After further stirring at 25 °C for 1 h, the crystals formed were collected, washed with 40% MeOH/H_2O (20 mL) and dried at 60 °C for 5 h to give (*R*)-**6**•[(*R*)-CHEA]$_2$ (6.85 g) as colorless crystals. The salt (*R*)-**6**•[(*R*)-CHEA]$_2$ (6.85 g, 11.5 mmol) was dissolved in 1 N aq NaOH solution (25.3 mL, 25.3 mmol) and washed with CH_2Cl_2 (2 × 5 mL). The aqueous layer was acidified by concd HCl and extracted with EtOAc (20 mL). The organic layer was washed with H_2O, treated with active charcoal (0.1 g), dried ($MgSO_4$) and evaporated. The crystals formed were dried at 90 °C for 17 h to provide (*R*)-**6** (3.91 g, 38%) in colorless crystals: the product (*R*)-**6** showed the same ^{1}H NMR and mass spectra as (±)-**6**; mp 200 °C (dec.) [Lit.[5] mp 197−199 °C (dec.)]; $[\alpha]_{546}^{25}$ +127.0 (*c* = 1.0, 0.1 N NaOH)(Lit.[5] $[\alpha]_{546}^{25}$ +127.0 (*c* = 1.0, 0.1 N NaOH). Optical purity: >99% ee [HPLC: Chiralcel OD (Daicel), hexane/EtOH/trifluoroacetic acid = 90:10:0.1, 1 mL/min, 35 °C, 254 nm].

IR (KBr): ν = 1696 cm^{-1}.

Anal. calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 77.15; H, 3.99.

The mother liquor of the optical resolution was evaporated and treated with 1 N aq NaOH solution (47 mL). The mixture was extracted with CH_2Cl_2 (2 × 5 mL) and combined with the CH_2Cl_2 extracts obtained in the decomposition of the (*R*)-CHEA•(*R*)-**6** salt. The organic solution was treated with active charcoal (0.3 g), dried ($MgSO_4$) and evaporated to give (*R*)-CHEA (4.1 g, 90%) as colorless liquid which could be used without further purification.

(*R*)-5*H*-Dinaphtho[2,1-*g*:1',2'-*i*][1,5]dioxacycloundecin-3,6,9(7*H*)-trione [(*R*)-1]

To a suspension of (*R*)-**6** (5.0 g, 14.6 mmol) and pyridine (300 mg, 14 mmol) in $CHCl_3$ (stabilized with amylenes, 100 mL) was added $SOCl_2$ (4.26 mL, 58.4 mmol) at 25 °C and the mixture was stirred at 25 °C for 2 h. The mixture was evaporated to give the corresponding acid chloride. To a suspension of 1,3-dihydroxyacetone dimer (306 mg, 1.8 mmol) in toluene (150 mL) were simultaneously added the acid chloride in toluene (100 mL) and Et_3N (6.1 mL, 43.8 mmol) in toluene (50 mL) at 60 °C for 1.5 h. During the reaction, 1,3-dihydroxyacetone dimer (4 × 306 mg, 7.2 mmol) was added portionwise at an interval of 15 min. After the addition was completed, the mixture was further stirred at 60 °C for 30 min. The mixture was washed with brine (50 mL) and the aqueous layer was extracted with toluene (50 mL). The combined extracts were washed with H_2O (2 × 50 mL), dried ($MgSO_4$) and evaporated. To the residue was added acetone (15 mL) and the mixture was stirred at 25 °C for 20 min. The crystals formed were collected and washed with acetone to provide (*R*)-**1** (3.64 g, 63%); mp 300 °C (dec.); $[\alpha]_D^{25}$ +10.9 (*c* = 1.0, $CHCl_3$); optical purity: >99% ee [HPLC: Chiralcel OD (Daicel), hexane /propan-2-ol = 10:1, 1 mL/min, 40 °C, 224 nm).

IR (KBr): ν = 1755, 1730, 1593 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.04 (d, *J* = 8.5 Hz, 2 H), 7.97 (d, *J* = 8.2 Hz, 2 H), 7.66 (d, *J* = 8.5 Hz, 2 H), 7.56 (dd, *J* = 1.5, 6.6 Hz, 2 H), 7.30−7.37 (m, 2 H), 7.25 (d, *J* = 14.1 Hz, 2 H), 5.56 (d, *J* = 15.4 Hz, 2 H), 4.20 (d, *J* = 15.4 Hz, 2 H).

MS: m/z = 396 (M^+).

Anal. calcd for $C_{25}H_{16}O_5$: C, 75.71; H, 4.07. Found: C, 75.42; H, 3.99;

Recovery of (*R*)-6

The filtrate and washings were combined and evaporated and the residue was dissolved in 1,4-dioxane (17 mL). To the solution were added H_2O (3 mL) and KOH (2 g, 30 mmol) and the mixture was refluxed for 2 h. The mixture was evaporated and H_2O (20 mL) was added. The mixture was washed with EtOAc (2 × 10 mL), acidified with concd HCl (2.4 mL) and extracted with EtOAc (2 × 10 mL). The extracts were combined, washed with H_2O, treated with active charcoal (0.5 g), dried ($MgSO_4$) and evaporated. The crystals formed were collected and dried at 90 °C for 17 h to provide (*R*)-**6** [1.7 g, 34% based on the initially added (*R*)-**6**]. The product was identical to an authentic sample of (*R*)-**6** with respect to mp, IR, ^{1}H NMR, mass spectrum and specific rotation.

References

(1) (a) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491.
(b) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311.
(c) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943.

(2) (a) Seki, M.; Furutani, T.; Hatsuda, M.; Imashiro, R. *Tetrahedron Lett.* **2000**, *41*, 2149.
(b) Kuroda, T.; Imashiro, R.; Seki, M. *J. Org. Chem.* **2000**, *65*, 4213.
(3) Hellwinkel, D.; Bohnet, S. *Chem. Ber*. **1987**, *120*, 1151.
(4) Hall, D. M.; Turner, E. E.; *J. Chem. Soc.* **1955**, 1242.
(5) Kanoh, S.; Hongoh, Y.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1032.

Article Identifier:
1437-210X,E;2000,0,12,1677,1680,ftx,en;F03400SS.pdf