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A novel method for the synthesis of (*R*)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylic acid by asymmetric oxidative coupling of a chiral β-naphthol derivative catalyzed by CuCl

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Abstract—Asymmetric oxidative coupling of (*S*)-1-(3-hydroxy-2-naphthylcarbonyl)pyrrolidine-2-carboxylic acid methyl ester **1** catalyzed by CuCl afforded (*S*,*S*,*R*)-2,2′-dihydroxy-3,3′-bis(2-methoxycarbonyl-1-pyrrolidinylcarbonyl)-1,1′-binapthalene **2** with diastereomeric excess up to 65.9%. (*R*)-BINOL-3,3′-diacid **3** was obtained in 30% overall yield and 97% e.e. by separating the diastereomers and hydrolyzing **2**.

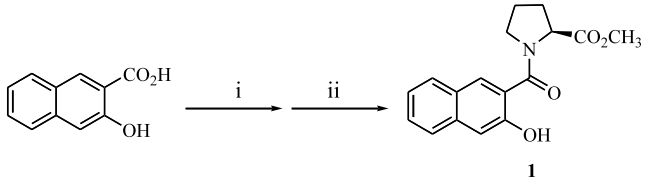
1. Introduction

Derivatives of optically active 1,1′-binapthyl-3,3′-dicarboxylic acid (BINOL-3,3′-diacid) have been widely utilized as chiral inducers in highly stereoselective reactions because of their C_2-symmetry and molecular flexibility.[1] Although syntheses of some optically pure BINOL derivatives by asymmetric oxidative coupling of naphthol derivatives have been successfully developed,[2] optically active BINOL-3,3′-diacid was prepared either from optically active BINOL or by resolution of the racemic mixture.[1e,3] Herein, we wish to report asymmetric oxidative coupling of a chiral β-naphthol derivative, and an additional method for the synthesis of diastereomerically pure BINOL-3,3′-diacid by this asymmetric oxidative coupling reaction.

2. Results and discussion

In view of the successful stereoselective coupling of β-naphthols catalyzed by CuCl complexed with a chiral diamine derived from (*S*)-proline,[4] we designed the chiral β-naphthol derivative (*S*)-**1**. We prepared (*S*)-**1** in 76% yield using commercially available 3-hydroxy-2-naphthoic acid and (*S*)-proline methyl ester (Scheme 1).

We then examined the CuCl-catalyzed asymmetric oxidative coupling reaction of (*S*)-**1** under an oxygen atmosphere (1 atm) (Scheme 2). Five different solvents were tested, and the results are summarized in Table 1 (entries 1–4, 8). The best chemical yield and diastereomeric excess (d.e.) were obtained with absolute MeOH, and it had been reported that the water in the solvent affected the stereoselectivity of the asymmetric coupling of 2-naphthol.[5] Surprisingly, only a trace of product was observed when the reaction was completed in CH_2Cl_2, which had previously been successfully employed in the catalytic oxidative coupling of 2-naphthols.[6] Reactions completed in MeOH gave generally good yields and diastereoselectivities and thus, MeOH was used in experiments designed to further optimize the reaction. As shown in Table 1, the yield and the diastereoselectivity of the reaction were dependent on



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Scheme 1. *Reagents and conditions*: (i) $SOCl_2$, reflux, 1 h; (ii) Et_3N, (*S*)-proline methyl ester, DCM, rt, 4 h.

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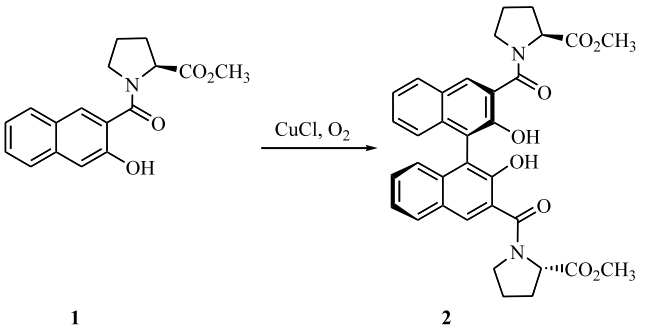


1 2

Scheme 2.

the amount of CuCl (entries 5–8). The best ratio of catalyst to starting material for diastereoselectivity was 25 mol% and the yield was also high (d.e. 65.9%, yield 80%, entry 6). The effect of reaction temperature on the stereoselectivity was also examined (entries 8–10). Higher stereoselectivity was observed at lower reaction temperature. When the reaction temperature was lowered from room temperature to −20°C, the d.e. value increased from 52.7 to 64.5%. However, it took a relatively long time for the reaction to reach completion, and the chemical yield was poor from reactions completed at low temperature.

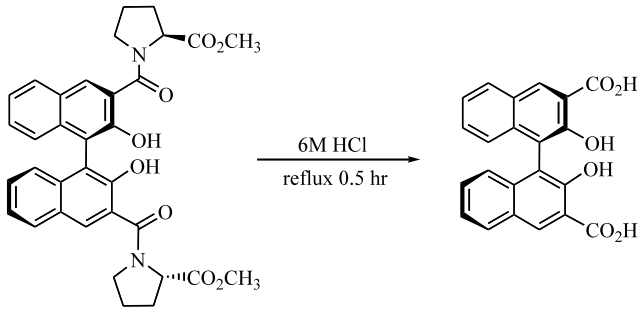
HPLC analysis was used to assign the absolute configuration of the coupling product **2**. We first prepared diastereomerically pure (*S*,*S*,*R*)-**2** from (*R*)-BINOL-3,3′-diacid in the same way as for the preparation of **1**. The absolute configuration was then assigned by comparing the retention time of the coupling product **2** with that of diastereomerically pure (*S*,*S*,*R*)-**2** in HPLC. The diastereomeric excess of the coupling product **2** was determined by the same HPLC analysis.

We also employed the unnatural (*R*)-proline as the starting material using the same procedure, and another enantiomer of **2** was obtained. The mechanism of this kind of CuCl-catalyzed asymmetric oxidative coupling reaction is unknown at present.

Several analogs of compound **2** have been designed and synthesized by Reetz's research group for application as HIV-protease inhibitors.[7] They were prepared with BINOL-3,3′-diacid and amino acid esters. In this paper we have developed another potential synthetic method by oxidative coupling reaction.

After the asymmetric coupling was finished, we separated the mixture of diastereomers by silica gel column chromatography to provide (*S*,*S*,*R*)-**2** with 97% d.e. Hydrolyzing (*S*,*S*,*R*)-**2** in 6 M aqueous HCl afforded (*R*)-BINOL-3,3′-diacid in 74% yield with 97% e.e. (Scheme 3). The enantiomeric excess of **3** was determined by HPLC analysis using a Chiralpak® AD column after compound **3** was esterified with MeOH.[4]

Kozlowski et al.[2f] reported the chiral diamine–copper complex-catalyzed enantioselective oxidation coupling of 2-methoxycarbonyl-3-naphthol, in which the effect of the C-3 substituents is important for high enantioselectivity. Specifically an ester group at the C-3 position is optimal, affording e.e. of up to 91%. It can be seen from our results that the presence of an amide group in the same position is also very promising. Additionally, the inflexibility of the pyrrolidine ring may possibly contribute to some extent to the high stereoselectivity.



2 3

Scheme 3.

Table 1. The effect of solvents, amount of CuCl and temperature on the asymmetric coupling of **1**

Entry	Solvent	CuCl (mol%)	Temperature (°C)	Time (h)	Yield (%)[a]	D.e. (%)[b]	Configuration[c]
1	CH_2Cl_2	100	rt	48	Trace	–	–
2	THF	100	rt	24	40	46.4	*S*,*S*,*R*
3	Toluene	100	rt	24	9	45.7	*S*,*S*,*R*
4	95% MeOH	50	rt	12	74	19.9	*S*,*S*,*R*
5	MeOH	50	rt	12	82	55.0	*S*,*S*,*R*
6	MeOH	25	rt	48	80	65.9	*S*,*S*,*R*
7	MeOH	10	rt	48	75	51.7	*S*,*S*,*R*
8	MeOH	100	rt	12	79	52.7	*S*,*S*,*R*
9	MeOH	100	0	24	71	57.8	*S*,*S*,*R*
10	MeOH	100	−20	120	50	64.5	*S*,*S*,*R*

[a] Isolated yield.

[b] The d.e. values were determined by HPLC.

[c] The absolute configuration was assigned using HPLC by comparing the retention time of the coupling product **2** with that of diastereomerically pure (*S*,*S*,*R*)-**2** derived from (*R*)-BINOL-3,3′-diacid.

3. Conclusion

We have demonstrated that oxidative coupling of the chiral 3-hydroxy-2-naphthoic acid derivative (*S*)-**1** catalyzed by CuCl under O_2 afforded the corresponding coupling product (*S*,*S*,*R*)-**2** with d.e. of 65.9%. Low reaction temperature, an optimal amount (25 mol%) of CuCl and the use of dry MeOH solvent were necessary to give satisfactory yields and diastereoselectivity in the asymmetric coupling reaction. Hydrolyzing (*S*,*S*,*R*)-**2**, which was purified by silica gel column chromatography afforded (*R*)-BINOL-3,3′-diacid **3** in 30% overall yield with 97% e.e.

4. Experimental

4.1. General

Reactions were monitored by thin-layer chromatography (TLC). All yields reported refer to isolated materials. Solvents were dried according to established procedures by distillation under argon atmosphere from the appropriate drying agent. Column chromatography purifications were carried out using silica gel. Melting points are uncorrected and recorded on X-4 melting point apparatus. ^{1}H NMR spectra were measured on Bruker DRX-200 NMR. IR spectra were obtained on Nicolet AVATAR 360 FT-IR. Optical rotations were measured with Perkin–Elmer 341 polarimeter. Mass spectra were recorded on VG-FAB mass spectrometor. Elemental analyses were performed on Carlo-Erba-1106 elemental analyzer. Diastereomeric excess determination was carried out using HPLC with Waters C-18 column on a Waters HPLC instrument with 996 UV detector, and enantiomeric excess was determined by HPLC with Daicel Chiralpak® AD column.

4.2. Synthesis of (*S*)-1-(3-hydroxy-2-naphthylcarbonyl)pyrrolidine-2-carboxylic acid methyl ester 1

Method 1: To a solution of (*S*)-proline (4.6 g, 40 mmol) in absolute methanol (40 mL) was added dropwise $SOCl_2$ (4.0 mL, 55 mmol) at −30°C. After warming to room temperature the reaction mixture was heated under reflux for 1 h.[8] The solvent was removed completely. The residue was dissolved in dry CH_2Cl_2 (20 mL) and then triethylamine (5.6 mL, 40 mmol) was dropped into the mixture at 0°C. The mixture was used for the next step without purification.

Method 2: A solution of 3-hydroxy-2-naphthoic acid (1.88 g, 10 mmol) in $SOCl_2$ was heated under reflux for 1 hr. The resulting acid chloride was dissolved in dry DCM (10 mL) after removal of $SOCl_2$.

The solution of acid chloride was added into the mixture which contained (*S*)-proline methyl ester at 0°C, after warming to room temperature the reaction mixture was stirred for 4 h. The mixture was filtered by suction through a Büchner funnel, and the filtrate was concentrated in vacuo. The residue was acidified to pH 2 with 5% HCl and extracted with ethyl acetate three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was separated by chromatography on a silica gel (CH_2Cl_2: MeOH = 60: 1) to give (*S*)-**1** as white crystals (2.27 g, 76%). Mp: 138–142°C; $[\alpha]_D^{18} = -58.7$ (*c* 0.476, EtOAc); ^{1}H NMR ($CDCl_3$, δ ppm): 1.85–2.23 (m, 3H), 2.30–2.55 (m, 1H), 3.81 (s, 3H), 3.87–4.04 (m, 2H), 4.76 (t, 1H), 7.20–7.40 (m, 2H), 7.40–7.56 (m, 1H), 7.58–7.85 (m, 2H), 8.04 (s, 1H), 9.99 (br, 1H); IR (KBr): 3399, 3217, 1679, 1513, 1442, 1322, 1281, 1216, 1142, 1073 cm^{-1}; MS *m*/*z*: 299 (M^+), 239, 171, 142; Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68; Found: C, 68.08; H, 5.44; N, 4.74%.

4.3. General procedure for asymmetric coupling of 1

To a solution of (*S*)-**1** (0.30 g, 1 mmol) in absolute MeOH (5 mL) was added CuCl (0.025 g, 0.25 mmol). The mixture was stirred under an oxygen atmosphere (1 atm) at room temperature for 48 h. After the reaction was complete, the diastereomeric excess of the coupling product was determined by HPLC analysis on a C-18 column (MeOH: H_2O = 9: 7, 1 mL/min, (*S*,*S*,*R*) 7.2 min and (*S*,*S*,*S*) 11.2 min). Then the solvent was evaporated and the residue was purified using silica gel column chromatography (CH_2Cl_2: MeOH = 50:1). The yield of the diastereomeric mixture was 80% (0.24 g, 65.9% d.e.), while the yield of the compound (*S*,*S*,*R*)-**2** was 53% (0.16 g, 97% d.e.). Mp: 135–138; $[\alpha]_D^{20} = -10$ (*c* 1.12, CH_3OH); ^{1}H NMR ($CDCl_3$, δ ppm): 1.85–2.20 (m, 6H), 2.32–2.55 (m, 2H), 3.80 (s, 6H), 3.90–4.15 (m, 4H), 4.77 (t, 2H), 7.0–7.15 (m, 2H), 7.20–7.40 (m, 4H), 7.75–7.90 (m, 2H), 8.21 (s, 2H), 10.1 (br, 2H); FAB-MS *m*/*z*: 597.3 (M^++1); IR: 3387, 2490, 2361, 1642, 1397, 1206, 1150 cm^{-1}.

4.4. Synthesis of (*R*)-BINOL-3,3′-diacid 3

(*S*,*S*,*R*)-**2** (0.6 g, 1 mmol) was added into 6 M aqueous HCl (10 mL), and the mixture was heated under reflux for 0.5 h. The pH of the mixture was modified to pH 2 by adding solid Na_2CO_3 and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was triturated with chloroform and the resulting crystallines **3** (0.28 g, 74%) were collected by filtration. Mp >290°C; $[\alpha]_D^{20} = +180$ (*c* 1.08, pyridine), Lit. $[\alpha]_D^{25} = +189$ (*c* 1.06, pyridine);[1e] ^{1}H NMR ($(CD_3)_2CO$, δ ppm): 3.34 (s, 2H), 7.09–7.15 (m, 2H), 7.33–7.41 (m, 4H), 8.01–8.09 (m, 2H), 8.79 (S, 1H); FAB-MS *m*/*z*: 375.2 (M^++1); IR: 3058, 2578, 1664, 1504, 1454, 1277, 1209, 747 cm^{-1}. The enantiomeric excess of **3** were determined by HPLC analysis after compound **3** was esterified with MeOH. HPLC: Chiralpak® AD column, hexane–isopropyl alcohol 9:1, 1 mL/min, 11.0 (*S*) and 20.0 (*R*) min.

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