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Enantioselective synthesis of 2,3-diphenyl-1,4-butanediol via oxidative coupling of phenylacetic acid chiral 1,1′-bi-2-naphthyl ester using $TiCl_4/Et_3N$

Vutukuri Dharma Rao and Mariappan Periasamy*

School of Chemistry, University of Hyderabad, Hyderabad-500 046, India

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Abstract

Oxidative coupling of phenylacetic acid ester of homochiral 1,1′-bi-2-naphthol **2** was achieved by reaction with $TiCl_4/Et_3N$ to obtain the corresponding 2,3-diphenylsuccinic acid derivative **3**, which on reduction using the $NaBH_4/I_2$ reagent gives homochiral 2,3-diphenyl-1,4-butanediol. X-Ray structural analysis was carried out for the compounds (*R*)-(+)-**2** and (*R,R,R*)-(−)-**3**. © 2000 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

Oxidative homocoupling of enolate anions of esters is a useful reaction for the synthesis of 2,3-disubstituted succinic acids.[1–7] Diastereoselectivity in such homocoupling reactions has been reported with $Et_3N/TiCl_4$ as oxidising agent (diastereoselectivity 99%)[8] or by using carboxylic acid dianions[9] or thioamide α-anions[10] (diastereoselectivity ~92%). Chiral 2,3-disubstituted succinic acids are useful in the preparation of chiral crown ethers,[11] diamines[12] and diphosphine ligands.[13] Enantiomerically pure 2,3-diphenylsuccinic acid is generally prepared through resolution.[14,15] Recently, intermolecular asymmetric coupling of chiral oxazolidine[16] and imidazolidone[17] derivatives of aliphatic carboxylic acids and intramolecular coupling of chiral imidazolidone[17,18] with LDA–I_2 or LDA–Cu(II) have been reported. Also, oxidative homocoupling of chiral 3-(arylacetyl)-2-oxazolidones has been reported using $TiCl_4/NR_3$.[19,20]

2. Results and discussion

In continuation of our efforts on the use of $TiCl_4/Et_3N$ for organic synthesis,[21] we report here that the $TiCl_4/Et_3N$ reagent is effective for stereoselective intramolecular oxidative coupling of

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* Corresponding author. E-mail: mpsc@uohyd.ernet.in

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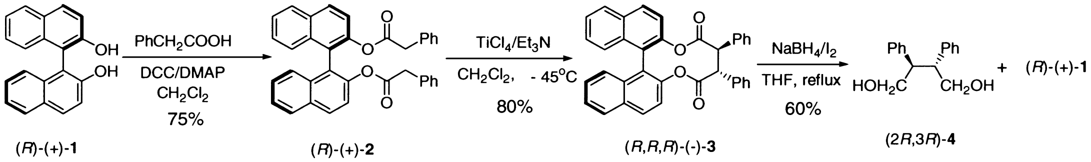
phenylacetic acid ester of 1,1′-bi-2-naphthol (Scheme 1). The reactions were carried out using 4.4 equiv. of $TiCl_4$ and 4.4 equiv. of Et_3N in CH_2Cl_2 at −45°C for 3 h. The high stereoselectivity realised in this oxidative coupling obviously results from the 1,1′-bi-2-naphthol auxiliary. The structure of the (*R*)-(+)-binaphthol diester **2** and the product **3** were confirmed by elemental analyses and X-ray structural analysis.[22] The ORTEP diagrams of the crystal structures of **2** and **3** are presented in Figs. 1 and 2.



Scheme 1.

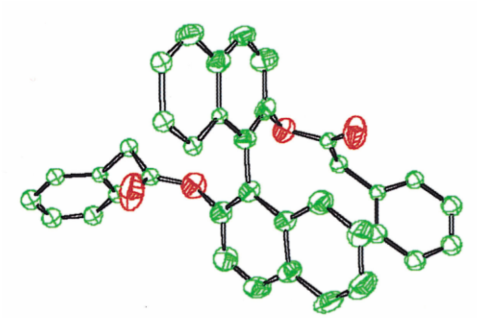


Figure 1. ORTEP diagram of **2**

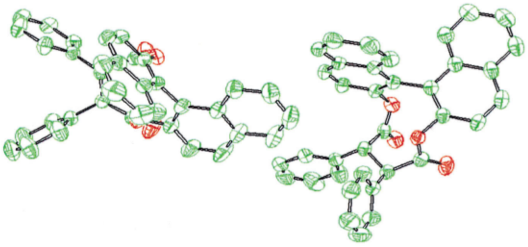
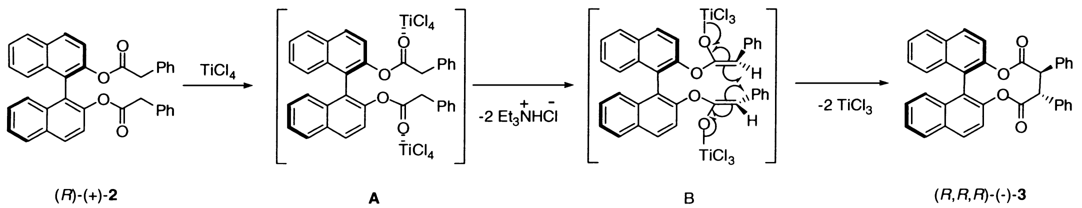


Figure 2. ORTEP diagram of **3**

The stereochemistry of the phenyl substituents of the diphenylsuccinic acid ester moiety is *trans* as revealed by the X-ray structural analysis of (*R*,*R*,*R*)-**3**. This was also further confirmed by HPLC analysis (Chiralcel OD using hexane:isopropanol (95:5) as eluent) and ^1H NMR (200 MHz) analysis using $Eu(hfc)_3$ in $CDCl_3$. The HPLC and ^1H NMR analysis for (*R*,*R*,*R*)-**3** also indicated the absence of the diastereomer derived from the (*R*,*S*)-diphenylsuccinic acid ester moiety. The results are in accordance with the report that the reaction of methyl phenylacetate with $TiCl_4/Et_3N$ under similar conditions gives only *dl*-2,3-diphenylsuccinic acid dimethyl ester without any *meso* isomer.[8] The conversion of the product (*R*,*R*,*R*)-**3** to enantiomerically pure

(*R*,*R*)-2,3-diphenyl-1,4-butanediol was readily achieved in 60% yield using the $NaBH_4/I_2$ reagent system (Scheme 1).[23,24,28] After the reduction, the 1,1′-bi-2-naphthol was recovered in good yield (85–90%) without any loss of enantiomeric excess. It was observed that the hydrolysis of (*R*,*R*,*R*)-**3** using KOH/MeOH leads to racemisation of the 2,3-diphenylsuccinic acid.

The oxidative coupling of **2** can be explained by a tentative mechanism similar to that considered for the reaction of methyl phenylacetate with $TiCl_4/Et_3N$ (Scheme 2).[8] The first step involves the formation of complex **A** that may be converted to the titanium enolate **B** through deprotonation. Intramolecular coupling of **B** with concomitant elimination of two molecules of $TiCl_3$ would produce **3**.



Scheme 2.

Since, the chiral 1,1′-bi-2-naphthol can be readily obtained in large scale through methods developed in this laboratory,[25–27] the enantioselective coupling process described here should be attractive for further synthetic applications. The following are representative procedures.

3. Experimental

3.1. Preparation of (R)-(+)-1,1′-bi-2-naphthol ester of phenylacetic acid (R)-2

Dicyclohexylcarbodiimide (12 mmol, 2.47 g) and phenylacetic acid (12 mmol, 1.63 g) were taken in dry CH_2Cl_2 (75 mL) and stirred at 0°C for 30 min. (*R*)-(+)-1,1′-Bi-2-naphthol (5 mmol, 1.43 g) and DMAP (0.14 g) were added at 0°C and the contents were stirred at 25°C for 24 h. The solvent was evaporated under reduced pressure and ethyl acetate (75 mL) was added. The precipitate was removed by filtration. The organic layer was washed with 5% HCl solution (25 mL), H_2O (15 mL), brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was recrystallised from hexane. Yield: 1.95 g (75%); mp 98–100°C; $[\alpha]_D^{25} = +11.5$ (c 0.872, $CHCl_3$); IR (KBr): ν (cm^{-1}) 3063, 3032, 1757; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.4 (4H, s), 6.8–8.1 (22H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 40.92, 121.8, 123.4, 125.8, 126.1, 126.8, 128.0, 128.3, 129.1, 129.5, 131.6, 133.1, 133.4,146.8, 169.8. Anal. calcd for $C_{36}H_{26}O_4$: C, 82.74; H, 5.01; found: C, 83.34; H, 4.79. The *S*-(−)-**2** was also prepared following the above procedure. $[\alpha]_D^{25} = -11.5$ (c 0.918, $CHCl_3$). Anal. calcd for $C_{36}H_{26}O_4$: C, 82.74; H, 5.01; found: C, 83.25; H, 4.65. Identical physical constant and spectral data were obtained as outlined above for the *R*-enantiomer.

3.2. Oxidative coupling of (R)-(+)-2 for (S)-2 starting from (S)-1 with $TiCl_4/Et_3N$

To a solution of (*R*)-(+)-**2** (2 mmol, 1.04 g,) in dry CH_2Cl_2 (30 mL) was added dropwise $TiCl_4$ (8.8 mmol, 0.96 mL) in CH_2Cl_2 (10 mL) at −45°C and the solution was stirred for 30 min. Et_3N

(8.8 mmol, 1.22 mL) in CH_2Cl_2 (10 mL) was added and the solution was stirred at −45°C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with H_2O (10 mL), brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to obtain a white solid. The solid was chromatographed on silica gel using hexane:ethyl acetate/98:2 as eluent giving (*R,R,R*)-**3**. Yield: 0.83 g (80%); mp 228–230°C; $[\alpha]_D^{25} = -102.45$ (c 0.244, $CHCl_3$); IR (KBr): ν (cm^{-1}) 3065, 3035, 1768; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.5 (2H, s), 7.0–8.1 (22H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 56.7, 121.0, 121.9, 125.9, 126.8, 127.1, 128.1, 128.3, 128.6, 130.3, 131.7, 133.4, 133.6, 148.0, 169.5. Anal. calcd for $C_{36}H_{24}O_4$: C, 83.07; H, 4.61; found: C, 83.22; H, 4.68. In the case of (*S*)-(−)-**2**, identical physical constant and spectral data were obtained for (*S,S,S*)-**3**. $[\alpha]_D^{25} = +102.5$ (c 0.234, $CHCl_3$). Anal. calcd for $C_{36}H_{24}O_4$: C, 83.07; H, 4.61; found: C, 82.49; H, 4.31.

3.3. Reduction of the product 3 using $NaBH_4/I_2$

The $NaBH_4$ (24 mmol, 0.9 g) was taken in dry THF (50 mL) under an N_2 atmosphere. To the slurry, iodine (10 mmol, 2.53 g) dissolved in dry THF (30 mL) was added slowly during 2.5 h at 0°C. The (*R*,*R*,*R*)-(−)-**3** (5 mmol, 2.6 g) in THF (30 mL) was added through a cannula at 0°C. The reaction mixture was refluxed for 6 h and then cooled to 0°C and quenched with 3N HCl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (2×20 mL). The combined organic extract was washed with H_2O (10 mL), brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel using hexane:ethyl acetate/70:30 as eluent to obtain the diol (*R,R*)-**4** (0.9 g, 75%). It was recrystallised from hexane to yield 0.72 g (60%); mp 101°C (lit.[28] 101–102°C); $[\alpha]_D^{25} = -48.0$ (c 0.266, $CHCl_3$) (lit.[28] $[\alpha]_D^{21} = -48.2$ (c 0.249, $CHCl_3$)). IR (KBr): ν (cm^{-1}) 3290, 3060, 1602; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 2.2 (2H, bs) 3.25 (2H, m), 4.0 (4H, m), 6.9–7.0 (4H, m), 7.0–7.2 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 51.0, 65.5, 126.5, 128.1, 128.6, 140.6. The (*S*,*S*,*S*)-(+)-**3** was also reduced using $NaBH_4/I_2$ reagent as described for (*R*,*R*,*R*)-(−)-**3** to give the diol (*S*,*S*)-**4** (0.75 g, 60%); mp 101°C; $[\alpha]_D^{25} = +48.0$ (c 0.382, $CHCl_3$).

Acknowledgements

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22. The X-ray diffraction measurements were carried out at 293 K on an automated Enraf–Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα ($\lambda = 0.71073$ Å) radiation. Intensity data were collected by the ω-scan mode. The data were reduced using the XTAL programme. No absorption correction was applied. Crystal structure data for compound **2**: θ range for data collection is 1.92 to 27.98°. Empirical formula $C_{36}H_{26}O_4$, colourless needles ($0.8 \times 0.5 \times 1.2$ mm), crystal system is orthorhombic, space group $P2_12_12_1$, unit cell dimensions: $a = 8.452(13)$ Å, $b = 11.382(4)$ Å, $c = 28.699(9)$ Å; volume 2761(4) Å^3, $Z = 4$, $D_{\text{calcd}} = 1.257$ Mg/m^3, absorption coefficient is 0.081 mm^{-1}, $F(000) = 1096$, index ranges $0 \le h \le 11$, $0 \le k \le 15$, $0 \le l \le 37$, total reflections collected were 3758, of which 2196 were independent reflections with $R(\text{int}) = 0.000$ and $R(\text{sigma}) = 0.0287$. The structure was solved by direct methods and refined by full-matrix least-squares procedure using the SHELX 86 and SHELX 97 programme packages, respectively. The refinement was carried out using 2196 observed $[F > 4\sigma(F)]$ reflections and converged to a final $R1 = 0.0729$, $wR2 = 0.2046$ and goodness of fit is 1.130 with largest difference peak and hole at 0.231 and -0.196 e Å^{-3}, respectively. Crystal structure data for compound **3**: θ range for data collection is 1.72 to 27.47°. Empirical formula $C_{36}H_{24}O_4$, colourless needles ($0.6 \times 0.6 \times 0.6$ mm), crystal system is monoclinic, space group $P2_1$, unit cell dimensions: $a = 9.737(4)$ Å, $b = 16.625(5)$ Å, $c = 17.152(5)$ Å, $\beta = 101.13(3)$ Å; volume 2724.4(17) Å^3, $Z = 2$, $D_{\text{calcd}} = 1.269$ Mg/m^3, absorption coefficient is 0.082 mm^{-1}, $\mathrm{F}(000) = 1088$, index ranges $0 \le \mathrm{h} \le 12$, $0 \le \mathrm{k} \le 21$, $0 \le \mathrm{l} \le 21$, total reflections collected were 6457, of which 3477 were independent reflections with $R(\text{int}) = 0.0130$ and $R(\text{sigma}) = 0.0442$. The structure was solved by direct methods and refined by full-matrix least-squares procedure using the SHELX 86 and SHELX 97 programme packages, respectively. The refinement was carried out using 3477 observed $[F > 4\sigma(F)]$ reflections and converged to a final $R1 = 0.0433$, $wR2 = 0.0898$ and goodness of fit is 0.981 with largest difference peak and hole 0.231 and -0.196 e Å^{-3}, respectively. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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