A Strategy for the Stereoselective Synthesis of Unsymmetric Atropisomeric Ligands: Preparation of NAPhePHOS, a New Biaryl Diphosphine

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Abstract: MeO-NAPhePHOS represents the first example of a new series of atropisomeric diphosphines bearing heterotopic biaryl moieties. The key step of its synthesis is the diastereoselective, intramolecular, Cu^{I}-promoted coupling of 1-iodonaphthol and 2-iodo-3-methoxyphenol connected by a chiral tether. (*R,R*)-2,4-Pentanediol is used as the chiral auxiliary in this highly selective reaction that leads to a single enantiomer of the title diphosphine. In the Ru-promoted hydrogenations of carbonyl derivatives, NAPhePHOS affords enantioselectivity levels fully comparable to those of the C_2-symmetrical analogues, BINAP and MeO-BIPHEP respectively, thus showing that the lack of C_2 symmetry is not detrimental to the catalytic properties of atropisomeric ligands in these hydrogenation reactions.

Keywords: asymmetric catalysis · atropisomerism · diastereoselectivity · hydrogenation · P ligands

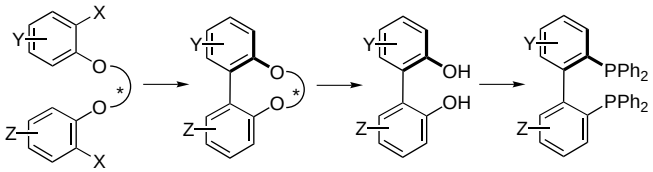
Introduction

Atropisomeric diphosphines based on binaphthyl,[1] biphenyl,[2] and other biaryl[3] backbones have played a major role in the development of asymmetric organometallic catalysis. While these ligands display uniformly high enantioselectivities in a number of catalytic reactions,[4] variations of the biaryl skeleton induce fine tuning of their properties. Representative, albeit rather partial, comparative studies are available. Thus for instance, it has been shown in early studies that H_8-BINAP-ruthenium complexes are significantly more effective than BINAP complexes as catalysts for the asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[5] Many examples of enantioselective hydrogenations are known where divergent behavior is observed for MeO-BIPHEP and BINAP.[6] Likewise, switching to asymmetric Heck reactions, the recently developed BINAPFu ligand consistently outperformed BINAP in the reaction between 2,3-dihydrofuran and phenyl triflate.[3h]

Concerning hydrogenation reactions, tentative correlation has been made recently between the observed enantioselectivities and the dihedral angle of the biaryl systems in the TunaPHOS series, first[7] and then by comparing SEGPHOS with BINAP and MeO-BIPHEP ligands.[8] The last study suggests that phosphines with smaller dihedral angles give higher selectivities in the ruthenium-catalyzed hydrogenation of 2-oxo-1-propanol. Opposite trends were observed in the iridium-promoted hydrogenation of 3-thiacyclopentanone by means of BINAP and H_8-BINAP.[8b] In other cases, divergent behavior between atropisomeric ligands have been assigned to different electronic properties.[3f,h]

Whatever the exact origin of the observed behavior might be, it is well established that variation of the biaryl skeleton allows fine-tuning of a given catalytic reaction on each single substrate. This is especially meaningful when practical, industrial use of the diphosphine ligands is targeted. In this context, with the purpose of industrial applications, we have developed a versatile approach to new, chiral, atropisomeric diphosphines, which allows easy modulation of the biaryl backbone.

Our approach, depicted in Scheme 1, takes advantage from the known stereoselective coupling reactions between two aryl moieties connected by a chiral tether, through ether



Scheme 1. General strategy for the synthesis of unsymmetrical biaryl diphosphines.

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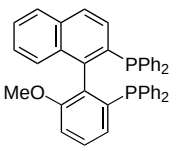


MeO-NAPhePHOS

linkages. After the coupling reaction, cleavage of the chiral auxiliary will give optically pure biphenols, which will be converted into biaryl diphosphines by well-known synthetic procedures. The paradigm of Scheme 1 is exemplified hereafter by the preparation of MeO-NAPhePHOS, a new atropisomeric ligand, devoid of C_2-symmetry, which combines the naphthyl and methoxyphenyl fragments of BINAP and MeO-BIPHEP, respectively.

Results and Discussion

Coupling reactions between two aryl moieties connected by a chiral tether are known to allow chemoselective and highly diastereoselective couplings between constitutionally different aryl fragments. Thus, Lipshutz and co-workers introduced the use of enantiomerically pure 1,2-diphenyl-1,2-ethanediol,[9] 2,3-butanediol, and 1,4-di-*O*-benzylthreitol as chiral auxiliaries for copper-mediated intramolecular biaryl couplings.[10] Various chiral 1,2-amino alcohols have also been used.[11] Recently, Sugimura and co-workers demonstrated the high efficiency of the 2,4-pentanediol-based tether in the same and analogous reactions.[12] For instance, biaryl coupling reactions followed by removal of the chiral tether led to optically pure BINOL and trinaphthol derivatives.[12a,b] Herein, the Lipshutz–Sugimura's approach has been applied to the synthesis of the unsymmetrical biaryl alcohol **4** (Scheme 2).

The unsymmetrical biaryl scaffold of **4** was synthesized from α-iodo-β-naphthol[13] and 2-iodo-3-methoxyphenol.[14] The diether derivative **2** was prepared by two successive Mitsunobu reactions involving (*S,S*)-2,4-pentanediol,[15] first with α-iodo-β-naphthol, and then with 2-iodo-3-methoxyphenol. Compound **2** was obtained as a single diastereoisomer, whose absolute configuration is assumed to be (*R,R*) (Scheme 2).[16]

The aryl–aryl bond was then formed by applying Lipshutz's method, namely the cuprate-mediated oxidative coupling of the corresponding dianion.[17] The dianionic derivative of **2** was obtained by iodine–lithium exchange and was then treated then with copper cyanide to afford the mixed cyanocuprate. Oxidation with molecular oxygen led to the cyclic biaryl derivative **3**. A single diastereoisomer of the coupling product was obtained in moderate yield (50%), after purification by column chromatography.

The configuration of the biaryl moiety of **3** has been established to be *S* by an X-ray diffraction study (relative stereochemistry with respect to the known *R,R* configuration of the chiral diether fragment). Figure 1 shows the X-ray structure of **3**.[20] The observed stereochemistry is in good agreement with the stereochemical issue of the analogous Sugimura's biaryl coupling[12a] showing that, starting from the (*S,S*)-configurated pentanediol, an (*S*)-configurated binaphthyl diether derivative is obtained.

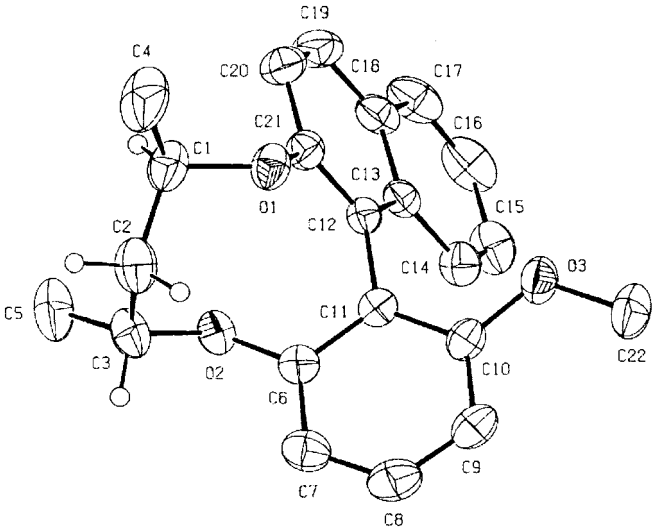
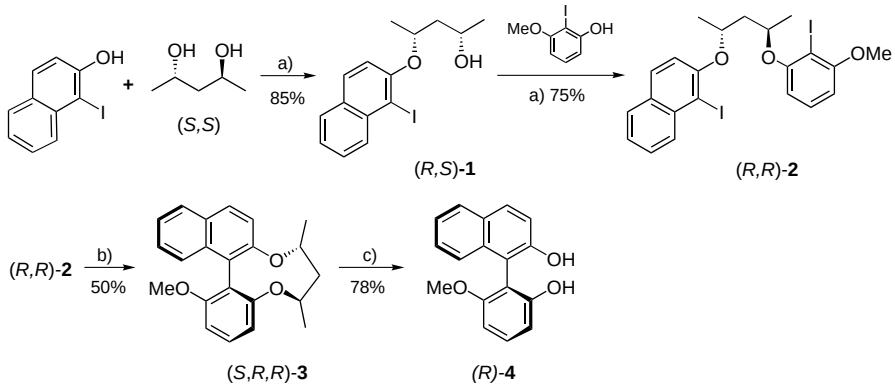


Figure 1. Structure of **3** (ORTEP drawing).

Cleavage of the chiral tether of **3** by BBr_3 requires optimized conditions (stoichiometric amount of BBr_3, reaction temperature of $-50\,^{\circ}C$) to avoid the concurrent cleavage of the O–Me bond. Diol **4** was obtained in 78% yield. As shown by literature data, the optical purity of the biaryl moiety is not affected by these cleavage reactions,[12a] thus a diastereomerically pure intermediate **3** must give an optically pure diol **4**.



Scheme 2. Synthesis of diol **4**. a) PPh_3, $EtO_2CN{=}NCO_2Et$, THF, 5 °C; b) *n*BuLi, −78 °C, THF, CuCN, O_2; c) BBr_3, CH_2Cl_2, −50 °C.

Diol **4** was easily converted into the corresponding diphosphine **5** through Ni^0-catalyzed coupling of the bistriflate with diphenylphosphane[18] (Scheme 3).

The nonequivalent phosphorus atoms of **5** give distinct ^{31}P NMR signals at $\delta = -12.9$ and -14.8 ppm ($CDCl_3$), with a rather large $^5J_{P,P}$ coupling constant of 15.9 Hz.

Ligand **5** has been evaluated in the hydrogenations of a few functionalized carbonyl derivatives; however, the hydrogena-

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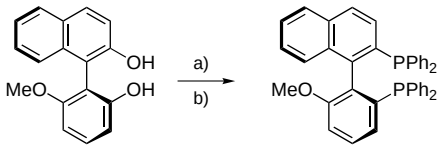
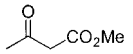
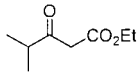
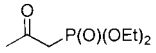
tion conditions, that is reaction temperature, time, pressure, and amount of catalyst, are not optimized (Table 1).



(*R*)-**4** (*S*)-**5**

Scheme 3. Synthesis of the atropisomeric diphosphine **5**. a) Tf_2O, pyridine, CH_2Cl_2, room temperature, 12 h: 70% yield; b) $HPPh_2$, [$NiCl_2$(dppe)], DABCO, DMF, 100 °C, three days: 60% yield. dppe = 1,2-bis(diphenylphosphanyl)ethane; DABCO = 1,4-diazabicyclo[2.2.2]octane.

Table 1. Hydrogenation of functionalized carbonyl derivatives using ruthenium–diphosphine (*S*)-**5** complexes.[a]

	Substrate	PH_2 [bar]	*T* [°C]	*t* [h]	*ee* (config.)
1		50	50	3	97 (*S*)
2		4	50	24	99 (*R*)
3		2	50	72	> 95 (*S*)
4		50	50	72	98 (*S,S*) *de* 97%

[a] Catalyst: 1% [(cod)Ru(2-Me-allyl)$_2$] + **5** + 2 HBr.[6b] cod = cyclooctadiene.

The enantiomeric excesses of the hydrogenations of β-oxoesters, β-oxophosphonates, and 1,3-diketones are comparable to those obtained by using classical, C_2-symmetric atropisomeric diphosphines. This supports previous data showing that, in these and analogous hydrogenation reactions, homotopism of the aryl moieties is not a prerequisite to attain high enantioselectivities.[19]

In conclusion, the synthetic approach to unsymmetrical biaryl diphosphines shown in Scheme 1 has been validated and the catalytic efficiency of such ligands has been demonstrated. An entire, new family of chiral heterotopic diphosphines with easily tunable biaryl scaffolds should be available by this highly modular strategy.

Experimental Section

(2*S*,4*R*)-4-(α-Iodo-β-naphthyloxy)-2-pentanol (1): A solution containing α-iodo-β-naphthol (18.2 g, 67 mmol) and diethyl azodicarboxylate (DEAD; 12.5 mL, 80 mmol) in THF (100 mL) was cooled to 5 °C. A solution of (*S,S*)-2,4-pentanediol (7.0 g, 67 mmol) and PPh_3 (21.1 g, 80 mmol) in THF (100 mL) was then added slowly. The mixture was stirred overnight at room temperature. After evaporation of the solvent, the residue was taken up in cyclohexane, filtered, and purified by chromatography on a silica gel column with cyclohexane/ethyl acetate (80:20 mixture) as the eluent (R_f = 0.3). Compound **1** was isolated as a pale yellow oil in 85% yield (20.2 g). $[\alpha]_D = -50$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (d, ^3J = 6.1 Hz; Me), 1.35 (d, $^3J = 6.0$ Hz; Me), 1.80 (ddd, $^2J = 14.3$ Hz, $^3J = 7.7$, 3.0 Hz, 1H; CH_2), 2.10 (dt, $^2J = 14.3$ Hz, $^3J = 8.5$ Hz, 1H; CH_2), 4.1–4.2 (m, 1H; CHOH), 4.7–4.8 (m, 1H; CH–O), 7.16 (d, $J = 9.0$ Hz, 1H), 7.38 (ddd, $^3J = 8.0$, 7.0 Hz, $^4J = 1.1$ Hz, 1H), 7.53 (ddd, $^3J = 8.3$, 6.9 Hz, $^4J = 1.3$ Hz, 1H), 7.70 (d, $^3J = 8.1$ Hz, 1H), 7.75 (d, $^3J = 8.9$ Hz, 1H), 8.14 ppm (d, ^3J = 8.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.2$ (Me), 23.8 (Me), 45.6 (CH_2), 66.5 (OCH), 75.9 (OCH), 90.5 (C–I), 115.6, 124.5, 128.0, 128.1, 130.1, 131.3 (CH), 135.7 (C), 154.4 ppm (C–O); elemental analysis calcd (%) for $C_{15}H_{17}IO_2$ (356.20): C 50.58, H 4.81; found: C 50.39, H 5.01.

(2*R*,4*R*)-4-(α-Iodo-β-naphthyloxy)-2-(2″-iodo-3″-methoxyphenyloxy)pentane (2): The procedure used for the synthesis of **1** was applied to the preparation of **2** from **1** (7.2 g, 20 mmol) and 2-iodo-3-methoxyphenol (5.0 g, 20 mmol). The final product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (95:5 mixture) as the eluent. Compound **2** was isolated as a pale yellow solid in 75% yield (8.8 g). M.p. 104 °C. $[\alpha]_D = -149$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (d, $^3J = 5.9$ Hz; Me), 1.44 (d, $^3J = 6.0$ Hz; Me), 2.2 (m, 2H; CH_2), 3.82 (s; OMe), 4.86 (m, 1H; CH–O), 4.99 (m, 1H; CH–O), 6.26 (d, $J = 8.2$ Hz, 1H), 6.31 (d, $J = 8.4$ Hz, 1H), 6.91 (t, $^3J = 8.3$ Hz, 1H), 6.96 (d, $^3J = 9.0$ Hz, 1H), 7.34 (t, $J = 7.4$ Hz, 1H), 7.46–7.65 (m, 3H), 8.09 ppm (d, $^3J = 8.8$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.4$ (Me), 20.8 (Me), 45.0 (CH_2), 56.4 (OMe), 72.7 (OCH), 73.9 (OCH), 79.5 (C–I), 90.1 (C–I), 103.6, 106.8, 116.0, 124.2, 127.7, 128.0, 129.5, 129.9 (C), 130.0, 131.3, 135.5 (C), 155.5 (C–O), 158.0 (C–O), 159.3 ppm (C–O); HRMS: *m/z* calcd 587.9658; found 587.9651.

Oxidative coupling of 2: The diiodoether **2** (4.7 g, 8 mmol) was dissolved in THF (100 mL) and the solution cooled to −78 °C. *n*BuLi (10.4 mL, 2.3 M solution in hexane) was added dropwise and the reaction mixture was stirred at −78 °C for 1 h. Then a suspension of CuCN (1.1 g, 12 mmol) in THF (80 mL) was added. After 2 h at −78 °C, dry oxygen was bubbled through the reaction mixture for 2 h. The mixture was allowed to warm to room temperature and hydrolyzed with ammonium chloride. After extraction with diethyl ether and drying over $MgSO_4$, the final product was purified by chromatography on silica gel with cyclohexane/ethyl acetate (90:10 mixture) as eluent. The biaryl derivative (*S,R,R*)-**3** was obtained as a colorless solid in 50% yield (1.3 g) as a single diastereoisomer. M.p. 160 °C. $[\alpha]_D = +250$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.29$ (d, $^3J = 6.5$ Hz; Me), 1.42 (d, $^3J = 6.5$ Hz; Me), 1.77 (ddd, $^2J_{A,B}$ = 15.2 Hz, $^3J = 4.5$, 3.0 Hz, 1H; CH_2), 1.97 (ddd, $^2J_{A,B} = 15.2$ Hz, $^3J = 5.3$, 3.4 Hz, 1H; CH_2), 3.67 (s; OMe), 4.6 (m, 2H; CH–O), 6.78 (d, $J = 8.3$ Hz, 1H), 6.87 (d, $J = 8.2$ Hz, 1H), 7.3–7.4 (m, 4H), 7.5 (m, 1H), 7.8 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 22.1$ (Me), 22.7 (Me), 41.6 (CH_2), 55.5 (OMe), 75.0 (OCH), 105.5, 111.0, 117.6 (C), 118.7, 122.1 (C), 123.8, 125.7, 126.4, 127.8, 128.9, 129.1, 130.1 (C), 133.1, 154.2 (C–O), 158.1 (C–O), 158.8 ppm (C–O); EI MS: *m/z* (%): 334 ([*M*]$^+$, 40), 82 (100); elemental analysis calcd (%) for $C_{22}H_{22}O_3$ (334.41): C 79.02, H 6.63; found: C 79.06, H 6.65.

(*R*)-5′,6′-Benzo-6-methoxy-2,2′-biphenol (4): A solution of boron tribromide in CH_2Cl_2 (6.0 mL, 1 M) was added to a cooled solution (−78 °C) of **3** (1.0 g, 3 mmol) in CH_2Cl_2 (15 mL). Stirring was maintained while the reaction mixture was warmed up to −50 °C over about 3 h. An aqueous solution of HCl (10%) was then added at the same temperature. Extraction with ethyl acetate, drying over $MgSO_4$, and purification by column chromatography (cyclohexane ethyl acetate 70:30) gave **4** (0.62 g; 78% yield). M.p. 145 °C, $[\alpha]_D = -51$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.71$ (s; OMe), 4.77 (s; OH), 5.26 (s; OH), 6.69 (d, J = 8.4 Hz, 1H), 6.79 (d, $J = 8.4$ Hz, 1H), 7.3–7.5 (m, 5H), 7.8 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 55.8$ (OMe), 103.3, 107.3 (C), 108.7, 109.8 (C), 117.6, 123.6, 123.8, 127.0, 128.2, 129.1 (C), 130.8, 131.0, 132.7 (C), 152.2 (C–O), 155.2 (C–O), 158.5 ppm (C–O); EI MS: *m/z* (%): 266 ([*M*]$^+$, 73), 43 (100); elemental analysis calcd (%) for $C_{17}H_{14}O_3$ (266.29): C 76.68, H 5.30; found: C 76.48, H 5.50.

(*S*)-5′,6′-benzo-6-methoxy-2,2′-bis(diphenylphosphanyl)biphenyl (5): Preparation of the bis-triflate of **4** was carried out under standard conditions, with triflic anhydride in CH_2Cl_2, in the presence of pyridine at 0–25 °C. The bis-triflate was purified by filtration through a silica gel plug, with CH_2Cl_2 as the eluent; starting from **4** (0.50 g; 1.9 mmol) the bis-triflate (0.70 g, 1.3 mmol) was obtained in 70% yield.

A solution of [$NiCl_2$(dppe)] (138 mg, 0.26 mmol) in anhydrous DMF (2 mL) was degassed. $HPPh_2$ (140 μL, 0.78 mmol) was added and the mixture was heated at 100 °C for 45 min. A degassed solution containing the bis-triflate of **4** (0.7 g, 1.3 mmol) and DABCO (0.59 g, 5.2 mmol) in DMF (5 mL) was added to the nickel solution. The mixture was heated at 100 °C and further portions of $HPPh_2$ (140 μL for each portion; total

amount of $HPPh_2 = 3.1$ mmol) were added after 1, 3, and 8 h. Heating was maintained for further 60 h. After evaporation of the solvent, the final product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95:5). Compound **5** was obtained in 60% yield (0.47 g) as a colorless solid. M.p. 200 °C; $[\alpha]_D = +80$ ($c = 1$, $CHCl_3$); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -12.9$ and -14.8 ($J_{PP} = 15.9$ Hz); ^1H NMR (400 MHz, $CDCl_3$, selected data): $\delta = 3.10$ (s; OMe), 6.84 (d, $J = 7.8$ Hz, 1H), 6.94 (dd, $J = 7.2$, 2.8 Hz, 1H), …7.34 (ddd, $J = 8.1$, 6.2, 1.9 Hz, 1H), 7.38 (t, $J = 8.0$ Hz, 1H), 7.78 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, selected data): $\delta = 54.6$ (OMe), 110.6, … 158.0 ppm (d, $J = 10.6$ Hz, C–O); HRMS (DCI): m/z: $(M+1)$ calcd 603.2007; found 603.2001.

Asymmetric hydrogenation: typical procedure: Hydrogenation experiments were performed at a 1 mmol scale, with a 1% ruthenium catalyst which was prepared from [(cod)Ru(2-methylallyl)$_2$] (3.2 mg) and the chiral diphosphine **5** (7.2 mg), by addition of 2.2 equivalents of aqueous HBr (0.16 – 0.18 M) in acetone.[6b] After evaporation of the solvent, the crude residue was taken up in degassed MeOH (2 mL) or EtOH (2 mL), substrate was added, and the reactor was placed under H_2 at a given pressure and temperature (see Table 1). All conversions were quantitative. Enantiomeric excesses and absolute configurations were determined by chiral GC (Entry 1: Lipodex A, flow 1 mL min^{-1}, initial temperature 35 °C (30 min), rate 1 °C min^{-1}, final temperature 70 °C, retention times 45 (*S*) and 48 (*R*). Entry 2: Lipodex A, flow 1 mL min^{-1}, initial temperature 50 °C (5 min), rate 0.5 °C min^{-1}, final temperature 70 °C, retention times 48.6 (*S*) and 49.2 (*R*)) or by GC on a DB1701 column, after formation of the Mosher ester (entry 3: initial temperature 150 °C (60 min), rate 1 °C min^{-1}, final temperature 180 °C, retention times 88.6 (*R*) and 89.7 (*S*). Entry 4: initial temperature 200 °C (10 min), rate 5 °C min^{-1}, final temperature 250 °C, retention times 18.2 (*R,R*), 18.7 (*S,S*), and 19.7 (*syn* isomer) min) by comparison with known compounds.

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