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THE OXIDATIVE CROSS-COUPLING OF SUBSTITUTED 2-NAPHTHOLS, PART I: THE SCOPE AND LIMITATIONS[1]

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ABSTRACT: *Highly selective oxidative cross-coupling of differently substituted 2-naphthols mediated by Cu(II)-tert-butyl amine complexes is described. The "cross"-products are obtained in good to excellent yields and the selectivity up to >90% is observed depending on the substitution of naphthol nuclei. The alternative procedures - the cross-coupling of free naphthols with CuCl(OMe) as well as the coupling of sodium naphtholates with anhydrous copper(II) chloride - were also studied. All these methods enable a simple and high-yield access to the unsymmetrically substituted binaphthols. A successful optical resolution of methyl 2,2'-dihydroxy-1,1'-binaphthalene-3-carboxylate by means of liquid chromatography on triacetylcellulose and the subsequent configurational correlation with a binaphthol derivative of known absolute configuration is reported.*

During past two decades many communications have appeared describing the use of chiral 1,1'-binaphthalene-2,2'-diol [*binaphthol*] derivatives in various stereoselective processes.[3] The rigid binaphthol skeleton was successfully utilized in numerous ways being incorporated into reactants,[3c,4] reagents[3a,b,5] or catalysts,[3d-k,6] immobilized onto stationary phases for chromatographic resolution,[7] built into macrocyclic polyethers,[8] as well as used as a chiral shift agent.[9] The formation of diastereomeric covalent compounds,[10] complexes[11] and/or clathrates[12] of optically active binaphthols with racemic substances led often to an efficient optical resolution.

Synthetic strategy toward the binaphthol-derived systems mostly involves a direct oxidative coupling of appropriately substituted 2-naphthols as a key step (*Scheme 1*). Many oxidizing agents have so far been investigated

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Scheme 1

to promote this reaction, however, a literature search discloses that at present there are no general rules allowing to predict which oxidant would work best for a given substrate.[13] Nevertheless, some redox-active metal salts and/or complexes proved to be efficient for an acceptably broad range of phenolic substrates. Besides Fe(III)[14] and Mn(III),[15] Cu(II)-derived oxidants are of particular interest in this respect.

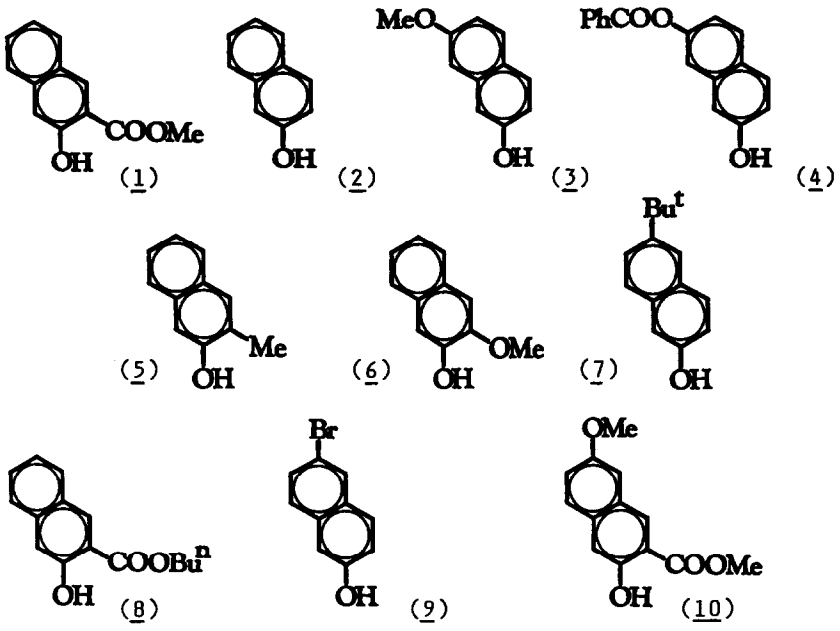
Cupric salts readily form complexes with amine ligands which are subsequently able to couple 2-naphtholic substrates in high yields.[16] The synthetic protocol given by Brussee for the 1,1'-binaphthalene-2,2'-diol preparation may serve as a valuable starting point for related syntheses.[16a]

Most of the work on the oxidative coupling of phenolic substrates reported to date concentrates on the ***self-coupling*** reactions affording the ***symmetrical*** binaphthols. However, in 1987, Yamamoto and co-workers described the first two examples of a ***cross-coupling*** reaction giving ***unsymmetrical*** biaryls in reasonable yield.[17] These findings stimulated our research aimed to elucidate the two particular questions: (**1**) Can the *cross*-coupling reaction of two differently substituted 2-naphthols be performed selectively to afford an ***unsymmetrical*** binaphthol as the major product, and (**2**) if so, is it possible to explain the selectivity in terms of available mechanistic schemes? This and the following communication will attempt to provide a solution.

OXIDATIVE CROSS-COUPLING OF SUBSTITUTED 2-NAPHTHOLS MEDIATED BY Cu(II)-AMINE COMPLEXES

The oxidative cross-coupling of differently substituted 2-naphthols was investigated using the substrates depicted in ***Table 1***. The cross-couplings were performed with an excess of *in situ* formed copper(II) chloride-*tert*-butyl (or ethyl) amine complex in methanolic media under strictly anaerobic conditions. The results summarized in ***Table 2*** demonstrate well that under comparable oxidative conditions the selectivity of the cross-coupling is dramatically influenced by the substitution of aromatic rings. In one extreme (e.g. **Entry** I to VII) the selectivity is excellent (86-92% of the cross-product) while in the second extreme (**Entry XII**) the selectivity does not exceed limits of statistical distribution (47% of the crossed product). All the reactions given in **Entries** I-X are of considerable preparative value as they represent an easy and direct access to unsymmetrically substituted binaphthols.[2] In some instances a single recrystallization yields a pure product. The reactions in **Entries XI** and **XII** are not selective and thus of a less value. Moreover, we did not succeed to purify

Table 1



completely the cross-coupled products (31) and (32) and their identity was deduced from GC-MS measurements.

The coupling reactions of 7-benzoyloxy-2-naphthol (4) deserve special comment. All efforts to perform a *self*-coupling reaction of this compound proved to be unsuccessful. In a striking contrast, however, (4) couples with (1) efficiently, giving the cross-product (16) in high yield [***Table 2***, **Entry III**].

Using methyl 3-hydroxy-2-naphthoate (1) and 2-naphthol (2), the influence of the reaction variables on the selectivity of *cross*-coupling reaction was next examined. The results shown in ***Table 3*** indicate that neither variation of the temperature and the solvent, nor the structure of amine ligand have a significant effect.

Attempts have been made to extend the cross-coupling methodology to other phenolic as well as non-phenolic substrates, however, serious limitations were observed under the conditions examined. The amides derived from the ester (1) proved to be completely inert under the oxidative cross-coupling conditions using 2-naphthol (2) as the second component. The same was true for methyl 5-*tert*-butyl salicylate, 4-methyl umbelliferone and also for non-phenolic derivatives, such as 2-methoxynaphthalene, 2-acetylnaphthalene and 2,4-pentanedione.

Table 2

Entry	Substrates (i)	Substrates (j)	Temp. (°C)	Time (min)	Yield[e] (%)	Products Ratio [%rel.] % (ii)	% (ij)	% (jj)
I	(1)	(2)	50	30	97	5 (11)	91 (12)	4 (13)
II	(1)	(3)	50	110	95	5 (11)	92 (14)	3 (15)
III[a]	(1)	(4)	41	120	93	12 (11)	88 (16)	0 (17)
IV	(1)	(5)	50	60	90	6 (11)	93 (18)	1 (19)
V	(1)	(6)	23	5	85	5 (11)	89 (20)	6 (21)
VI	(1)	(7)	20	100	85	5 (11)	92 (22)	3 (23)
VII	(8)	(2)	50	120	85	12 (24)	86 (25)	2 (13)
VIII	(1)	(9)	50	120	86	25 (11)	72 (26)	3 (27)
IX[b]	(10)	(2)	23	150	75	34 (28)	64 (29)	2 (13)
X	(10)	(3)	50	30	85	22 (28)	75 (30)	3 (15)
XI[c]	(1)	(10)	50	120	70	17 (11)	57 (31)	26 (28)
XII[d]	(2)	(3)	23	1440	80	26 (13)	47 (32)	27 (15)

[e] *Isolated yields of unsymmetrical binaphthols are: (12):86%; (14):76%; (16):79%; (18):78%; (20):74%; (22):77%; (25): 71%; (26): 46%; (29):47%; (30):61%.*
[a] *5% of (4) recovered;* [b] *15% of (2) recovered;* [c] *24% of (1) recovered;* [d] *ethylamine used as a ligand*

OXIDATIVE CROSS-COUPLING OF SUBSTITUTED 2-NAPHTHOLS MEDIATED BY Cu(II) SALTS IN THE PRESENCE OF SODIUM METHOXIDE

Copper(II) chloride reacts with 1 equivalent of sodium methoxide in methanolic solution to give a yellow-green precipitate of copper(II) chloride-methoxide[18] *CuCl(OMe)*. This compound was used alone or as a complex with pyridine to couple 2,6-disubstituted phenols efficiently to polyaryl ethers and diphenoquinones.[19] We wish to report that *CuCl(OMe)* is also very effective when taken as the oxidant for the cross-coupling reactions of substituted 2-naphthols. Thus, methyl 3-hydroxy-2-naphthoate (1) and 2-naphthol (2) are coupled quickly and selectively to give 86% yield of isolated (12) (***Scheme 2/A***).

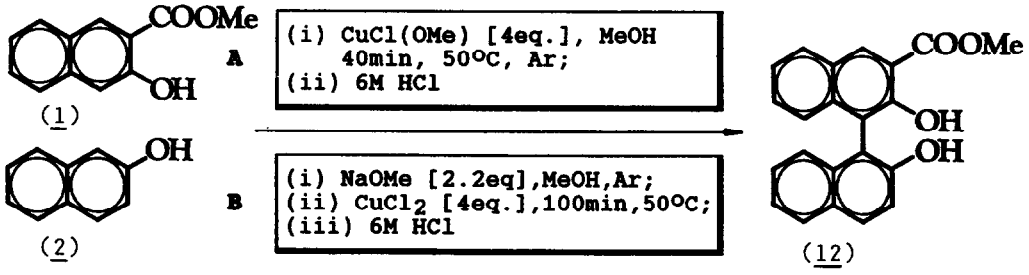
In ***Scheme 2/A***, the Cu(II) oxidant containing basic methoxide ligand was preformed in the reaction mixture and then a solution of naphthols was added. This order, however, can be reversed without any change of selectivity

Table 3

Entry	Amine[a]	Solvent	Temp.(°C)	time(min)	Yield(%)	%(11)	%(12)	%(13)
I	*tert*-BuNH$_2$	MeOH	50	30	97	5	91	4
II			20	180	92	8	88	4
III			5	360	88	1	90	9
IV			20[b]	130	85	7	88	5
V		iPrOH	20	180	95	7	89	4
VI		acetone		3600	c	6	84	10
VII	1-amino adamantane	MeOH	50	70	70	5	93	2
VIII	Pyridine			180	75	7	93	0

[a]Copper(II) chloride/amine complexes (1:4) [with pyridine 1:2 ratio was used] were preformed.
[b]200% excess of Cu(II) complex used. [c]34% of (1) and 12% of (2) were recovered.

Scheme 2



and chemical yield when sodium naphtholates were first preformed and then a solution of dry copper(II) chloride was added (*Scheme 2/B*).
The main advantage of this coupling protocol consists in its simplicity: the amine which has to be used in excess [Cu(II)/amine ratio being 1/4] is not needed and, moreover, the formation of a voluminous precipitate of the Cu(II)-amine complex is avoided. Substantial reduction of the reaction volumes is thus possible.
The scope of the reactions performed in the presence of methoxide anions seem to be limited by the structure of starting phenolic substrates analogously as noted above for Cu(II)/amine-mediated couplings.

OPTICAL RESOLUTION OF METHYL 2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE

The racemic *cross*-product (12) was successfully resolved on a *semi*-preparative scale using low-pressure liquid chromatography on triacetylcelul-

lose (***Figure 1***). Moreover, a simple assignment of absolute configuration is possible by comparison with CD spectrum of the optically pure dimethyl 2,2'-dihydroxy-1,1'-binaphthalene-3,3'-dicarboxylate (33) of a known absolute configuration[20] (***Figure 2***). Thus, (+)-(12) can be assigned the (R)-configuration.

Figure 1

Triacetylcellulose MERCK 15-25µm; column 3x60cm, eluted with 96% EtOH. Eluent flow rate 3mL/min, UV detection at 254nm. Single injection of 150mg of the racemic (12) in 8mL of EtOH. Chart speed 0.15cm/min. (-)-(12) is eluted first.

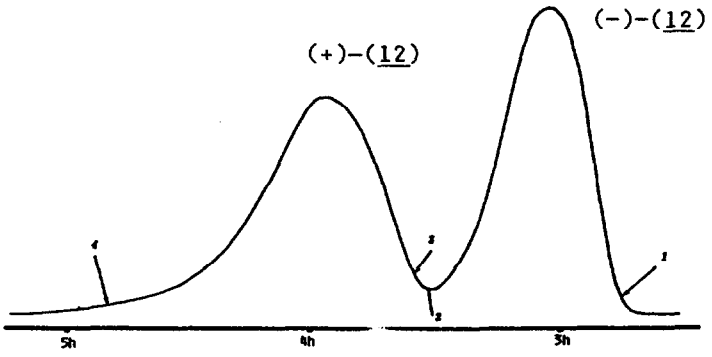
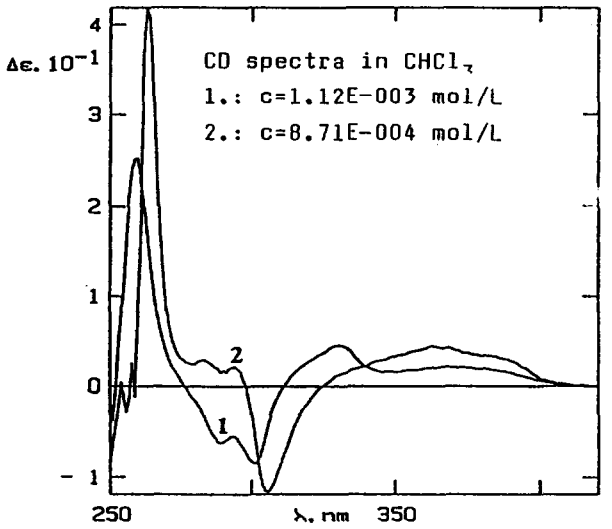
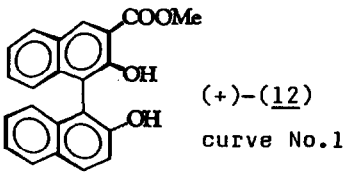
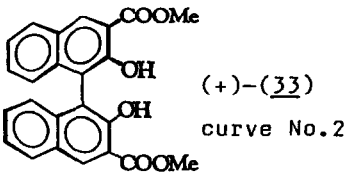


Figure 2





(+)-(12)
curve No.1



(+)-(33)
curve No.2

EXPERIMENTAL

Melting points were determined using Kofler hot stage and are uncorrected. Binaphthol products tend to hold up various solvents [especially water] very tightly and therefore the analytical samples were dried

carefully in vacuo [10Pa]. ^{1}H-NMR spectra were recorded with TMS as an internal standard at 200 and 400MHz on a Varian XL 200 and Bruker 400 AT instrument, respectively. MS spectra were measured with ZAB EQ (VG Analytical) and Jeol DX 303 instrument in EI mode. The GC-MS measurements were performed using tandems of these spectrometers with Hewlett-Packard 5890 A gas chromatograph. GC was carried out on Hewlett-Packard 5890 gas chromatograph [methylsilicone, 5m wide-bore capillary column] with FID detection. HPLC analyses were performed using reverse phase, methanol-water eluent and UV detection at 254 nm. The reactions were routinely monitored by TLC on POLYGRAM SIL G/UV254 and POLYGRAM ALOX N254 [Macherey-Nagel, Duren]. For the preparative TLC separations KIESEGEL 60 F 254 plates [Merck, 20x20cm, 2mm layer of sorbent] were used. Column flash chromatography was performed with SEPARON SGX [TESSEK Prague] silica gel. For radial chromatography rotating pre-coated disks [1-2mm of Merck H silica gel] and UV detection were used. The disks were activated for 4 hours at 100°C prior to chromatography. For short-path distillation ALDRICH-Kugelrohr apparatus was used.

2-Naphthol, 2,3-dihydroxynaphthalene, 3-hydroxy-2-naphthoic acid, 6-bromo-2-naphthol, 3,7-dihydroxy-2-naphthoic acid, tert-butyl amine, 2-acetylnaphthalene and 2,4-pentanedione were purchased from ALDRICH and used without any purification. The solvents were distilled prior to use, dry methanol was obtained by the routine procedure. Dry copper(II) chloride was prepared by dehydration of its dihydrate by careful heating in a ceramic dish.

Methyl 3-hydroxy-2-naphthoate,[20] 7-methoxy-2-naphthol,[21] 7-benzoyloxy-2-naphthol,[22] 6-tert-butyl-2-naphthol[23] and 3-methyl-2-naphthol[20] were prepared as described in the literature.

n-BUTYL 3-HYDROXY-2-NAPHTHOATE (9): 3-Hydroxy-2-naphthoic acid [18.8g, 0.1mol] was suspended in 300mL of benzene, 50mL of 1-butanol and 0.5g of p-toluensulphonic acid monohydrate were added and the mixture was refluxed using Dean-Stark water collector until the separation of water phase ceased (approx. 24 hours). The homogeneous solution was cooled down, washed with water, 10%aq. $NaHCO_3$ and dried with $MgSO_4$. Evaporation of the solvent left 23.0g of yellow oil which was finally purified by filtration through a short column of silica gel (elution with toluene). 20.0g (82%) of (9) were obtained as a yellow viscose liquid.

MS: m/z=244 ($M^{+\cdot}$). ^{1}H-NMR(200MHz,$CDCl_3$,ppm): 1.04(t,J=7.4Hz,3H,-CH_3); 1.36--1.66 (m,2H,-CH_2-); 1.71-1.94(m,2H,-CH_2-); 4.40(t,J=6.9Hz,2H,-CH_2-O-); 7.25--7.33(m,2H,arom.); 7.43-7.51(m,1H,arom.); 7.65(dd,J_1=0.7Hz,J_2=8.0Hz,1H, arom.); 7.78(dd,J_1=0.7Hz,J_2=8.0Hz,1H,arom.); 8.43(s,1H,C^1-H); 10.59(s,1H, exchanged with CD_3COOD,-OH). Anal. Calc. for $C_{15}H_{16}O_3$ (244.28): C 73.75; H 6.60. Found C 73.50; H 6.49.

METHYL 7-METHOXY-3-HYDROXY-2-NAPHTHOATE (10): 3,7-Dihydroxy-2-naphthoic acid [10.2g, 50mmol] was suspended in 100mL of dry methanol and 93% H_2SO_4 [5mL] was slowly added to a stirred mixture. The resulting dark-brown solution was refluxed for 48 hours under argon atmosphere. On cooling the bright-yellow precipitate separated. The reaction mixture was concentrated to 50mL and the precipitate isolated by suction. The crude product was recrystallized from methanol; yield 5.0g (43%) of bright-yellow crystalline (10), mp 134-5°C.

MS: m/z=232 ($M^{+\cdot}$). ^{1}H-NMR(200MHz,$CDCl_3$,ppm): 3.88(s,3H,-OCH_3); 4.01(s,3H,

-$COOCH_3$); 6.95-7.26(m,3H,arom.); 7.60(d,J=9Hz,1H,arom.); 8.36(s,1H,C^1-H); 10.25(s,1H,exchanged with CD_3COOD,-OH). IR(CCl_4, c 0.0015mol/l) 3280cm^{-1}. Anal. Calc. for $C_{13}H_{12}O_4$ (232.23): C 67.23; H 5.21. Found C 67.45; H 5.40.

OXIDATIVE CROSS-COUPLINGS MEDIATED BY COPPER(II)/AMINE COMPLEXES: A GENERAL PROCEDURE [See *Table 1 and 2*]

All the reactions were performed under strictly anaerobic conditions. Prior to addition of amine, the reaction mixture was treated as follows:
A solution of naphthols and Cu(II) salt in alcoholic solvent was brought to a gentle boil by connection to a water pump for approx. 2 minutes. The source of vacuum was disconnected and the apparatus was filled with argon. This operation was repeated four times and will hereafter be referred to as "deoxygenation".
The isolation of symmetrical binaphthols is not described here. Their structure was proved by the comparison with authentic samples.
Hereafter, the isolated mixture of binaphthols (before separating them) is called a "crude" product. It does not contain any starting material. The yields given for crude products are related to the theoretical amount of cross-coupled substances.

A vigorously stirred solution of an equimolar mixture of naphthols (i) and (j) (1 mmol of each) and $CuCl_2$ (4mmol, 538mg) in alcoholic solvent [for type and volume see below] was deoxygenated and then *tert*-butylamine (16mmol, 16mL of a 1M solution in the corresponding degassed alcohol) was slowly added by syringe through a septum. The heterogeneous reaction mixture was heated as indicated in *Table 1*. After the completion the reaction mixture was cooled down to approx. 10°C and decomposed by addition of 6M HCl [or aq.AcOH (1:1) in **Entry III**] to pH~4. The solvent was removed on an evaporator and the products were partitioned between water and chloroform. The organic phase was washed with water, 10%aq.$NaHCO_3$ and dried with $MgSO_4$. The crude products obtained after evaporation of chloroform were purified either by crystallization or by chromatography on silica gel.

METHYL 2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (12): The starting components [202mg of (1), 144mg of (2)] were dissolved in 80mL of MeOH. The crude product [333mg (97%)] was analyzed by GC [(11)/(12)/(13) = 5/91/4] and purified by flash chromatography (elution with toluene to toluene-5%EtOAc) to give 295mg (86%) of pale-yellow crystalline (12), mp 182-3°C.
MS: m/z=344 ($M^{+\cdot}$). ^{1}H-NMR(200MHz,$CDCl_3$,ppm): 4.07(s,3H,-$COOCH_3$); 4.97(s,1H,exchanged with CD_3COOD,$C^{2'}$-OH); 7.01-7.44(m,7H,arom.); 7.85-7.99(m,3H,arom.); 8.73(s,1H,C^4-H); 10.84(s,1H,exchanged with CD_3COOD,C^2-OH). IR(CCl_4,c 0.0015 mol/l,cm^{-1}): 3232[C^2O-H, H-bridge to sp^2 oxygen]; 3552[$C^{2'}$O-H, H-bridge to sp^3 oxygen]; 3604[very weak, free O-H]. Anal. Calc. for $C_{22}H_{16}O_4$ (344.35): C 76.73; H 4.68. Found C 76.78; H 4.74.

METHYL 2,2'-DIHYDROXY-7'-METHOXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (14): The starting components [202mg of (1), 174mg of (3)] were dissolved in 80mL of MeOH. The crude product [355mg (95%)] was analyzed by GC [(11)/(14)/(15) = 5/92/3] and purified by repeated flash chromatography (in the first run elution with chloroform, in the second with toluene-2%acetone) to give 284mg

(76%) of pale-yellow crystalline (14), mp 207°C.
MS: m/z=374 ($M^{+\cdot}$). ^{1}H-NMR(400MHz,$CDCl_3$,ppm): 3.50(s,3H,$-OCH_3$); 4.07(s,3H, $-COOCH_3$); 4.94(s,1H,exchanged with CD_3COOD,$C^{2'}$-OH); 6.37(d,J=2.5Hz,1H,$C^{8'}$-H); 6.99(dd,J_1=8.9Hz,J_2=2.5Hz,1H,arom.); 7.20-7.26(m,2H,arom.); 7.38-7.40(m,2H, arom.); 7.77(d,J=8.9Hz,1H,arom.); 7.84(d,J=8.9Hz,1H,arom.); 7.91-7.95(m,1H, arom.); 8.74(s,1H,C^4-H); 10.87(s,1H,exchanged with CD_3COOD,C^2-OH). Anal. Calc. for $C_{23}H_{18}O_5$ (374.37): C 73.79; H 4.85. Found C 73.82; H 4.91.

METHYL 7'-BENZOYLOXY-2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (16): The starting components [202mg of (1), 264mg of (4)] were dissolved in 80mL of MeOH. The reaction mixture was quenched with 50% AcOH to give 431mg (93%) of crude product the composition of which was determined by HPLC on reverse phase [(11)/(16)/(17) = 12/88/0]. As much as 5% of starting (4) were recovered from the reaction mixture. Preparative radial chromatography (elution with chloroform) afforded 365mg (79%) of light-yellow crystalline (16), mp 207-8°C.
MS: m/z=464 ($M^{+\cdot}$). ^{1}H-NMR(200MHz,$CDCl_3$,ppm): 4.04(s,3H,$-COOCH_3$); 5.00(s,1H, exchanged with CD_3COOD,$C^{2'}$-OH); 6.83(d,J=2.0Hz,1H,$C^{8'}$-H); 7.19-7.59(m,7H, arom.); 7.77-8.12(m,5H,arom.); 8.71(s,1H,C^4-H); 10.94(s,1H,exchanged with CD_3COOD,C^2-OH). Anal. Calc. for $C_{29}H_{20}O_6$ (464.45): C 74.99; H 4.34. Found C 75.13; H 4.40.

METHYL 3'-METHYL-2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (18): The starting components [202mg of (1), 158mg of (5)] were dissolved in 80mL of MeOH. The crude product [315mg (88%)] was analyzed by GC [(11)/(18)/(19) = 5/94/1] and purified by flash chromatography (elution with toluene) to give 280mg (78%) of pale-yellow crystalline (18), mp 236°C.
MS: m/z=358 ($M^{+\cdot}$). ^{1}H-NMR(400MHz,$CDCl_3$,ppm): 2.52(s,3H,$-CH_3$); 4.07(s,3H, $-COOCH_3$); 5.00(s,1H,exchanged with CD_3COOD,$C^{2'}$-OH); 6.99(d,J=8.3Hz,1H,arom.); 7.15-7.19(m,2H,arom.); 7.25-7.39(m,3H,arom.); 7.76-7.80(m,2H,arom.); 7.90--7.95(m,1H,arom.); 8.74(s,1H,C^4-H); 10.83(s,1H,exchanged with CD_3COOD,C^2-OH). Anal. Calc. for $C_{23}H_{18}O_4$ (358.37): C 77.08; H 5.06. Found C 77.30; H 5.12.

METHYL 3'-METHOXY-2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (20): The starting components [202mg of (1), 174mg of (6)] were dissolved in 80mL of MeOH. The crude product [318mg (85%)] was analyzed by GC [(11)/(20)/(21) = 5/89/6] and purified by flash chromatography (elution with toluene-2%acetone) to give 277mg (74%) of pale-yellow crystalline (20), mp 290-1°C.
MS: m/z=374 ($M^{+\cdot}$). ^{1}H-NMR(400MHz,DMSO-d_6,ppm): 4.02(s,6H,$-COOCH_3$+$-CH_3$); 6.84(d,J=8.0Hz,1H,$C^{4'}$-H); 6.97-6.99(m,1H,arom.); 7.04-7.09(m,1H,arom.); 7.23--7.27(m,1H,arom.); 7.34-7.39(m,2H,arom.); 7.45(s,1H,arom.); 7.82(d,J=8.0Hz, 1H,arom.); 8.09-8.11(m,1H,arom.); 8.73(s,1H,C^4-H); 8.80(bs,1H,exchanged with CD_3COOD,$C^{2'}$-OH); 10.35(bs,1H,exchanged with CD_3COOD,C^2-OH). Anal. Calc. for $C_{23}H_{18}O_5$ (374.37): C 73.79; H 4.85. Found C 73.90; H 4.90.

METHYL 6'-tert-BUTYL-2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (22): The starting components [202mg of (1), 200mg of (7)] were dissolved in 80mL of MeOH. The crude product [360mg (90%)] was analyzed by reverse phase HPLC

[(11)/(22)/(23) = 5/92/3] and purified by flash chromatography (elution with toluene-2%acetone) to give after careful drying [(22) forms stable 1:1 solvates with acetone, benzene, alcohols etc.] 306mg (77%) of pale-yellow crystalline (22), mp 267-70°C.
MS: m/z=400 ($M^{+\cdot}$). ^{1}H-NMR(400MHz,$CDCl_3$,ppm): 1.36(s,9H,*tert*-butyl); 4.07(s, 3H,$-COOCH_3$); 4.88(s,1H,exchanged with CD_3COOD,$C^{2'}$-OH); 7.02(d,J=8.9Hz,1H, arom.); 7.20-7.23(m,1H,arom.); 7.32-7.35(m,2H,arom.); 7.37-7.39(m,2H,arom.); 7.79(d,J=1.5Hz,1H,arom.); 7.89(d,J=8.9Hz,1H,arom.); 7.93-7.95(m,1H,arom.); 8.73(s,1H,C^4-H); 10.83(s,1H,exchanged with CD_3COOD,C^2-OH).
Anal. Calc. for $C_{26}H_{24}O_4$ (400.48) C 77.98; H 6.04. Found C 78.10; H 6.10.

BUTYL 2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (24): The starting components [244mg of (8), 144mg of (2)] were dissolved in 80mL of iPrOH. The crude product [328mg (85%)] was analyzed by GC [(24)/(25)/(13) = 12/86/2] and purified by flash chromatography (elution with chloroform) to give 275mg (71%) of (24) as a white-yellow glassy solid.
MS: m/z=386 ($M^{+\cdot}$). ^{1}H-NMR(400MHz,$CDCl_3$,ppm): 1.035(t,J=7.4Hz,3H,$-CH_3$); 1.50--1.60(m,2H,$-CH_2$-); 1.82-11.89(m,2H,$-CH_2$-); 4.46(t,J=6.7Hz,2H,$-CH_2$-); 5.00(s,1H,exchanged with CD_3COOD,$C^{2'}$-OH); 7.08(dd,J_1=8.4Hz,J_2=0.6Hz,1H,arom.); 7.16-7.19(m,1H,arom.); 7.21-7.25(m,1H,arom.); 7.29-7.33(m,1H,arom.); 7.29--7.33(m,1H,arom.); 7.34-7.39(m,3H,arom.); 7.86(d,J=7.9Hz,1H,arom.); 7.91--7.96(m,2H,arom.); 8.73(s,1H,C^4-H); 10.95(s,1H,exchanged with CD_3COOD,C^2-OH).
Anal. Calc. for $C_{25}H_{22}O_4$ (386.43) C 77.70; H 5.74. Found C 77.89; H 5.84.

METHYL 6'-BROMO-2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (26): The starting components [202mg of (1), 223mg of (9)] were dissolved in 50mL of MeOH. The crude product [364mg (86%)] was analyzed by reverse phase HPLC [(11)/(26)/(27) = 25/72/3] and purified by flash chromatography (elution with toluene) followed by recrystallization from toluene to give 196mg (46%) of white crystalline (26), mp 234°C.
MS: m/z=423 ($M^{+\cdot}$). ^{1}H-NMR(400MHz,$CDCl_3$,ppm): 4.05(s,3H,$-COOCH_3$); 5.05(s,1H, exchangeable with CD_3COOD,$C^{2'}$-OH); 6.94(d,J=9.0Hz,1H,arom.); 7.13(m,1H,arom.); 7.29(dd,J_1=9.0Hz,J_2=2.0Hz,1H,arom.); 7.36-7.40(m,3H,arom.); 7.82(d,J=7.8Hz, 1H,arom.); 7.93(m,1H,arom.); 8.01(d,J=2.0Hz,1H,arom.); 8.73(s,1H,C^4-H); 10.87(s,1H,exchangeable with CD_3COOD,C^2-OH). Anal. Calc. for $C_{22}H_{15}BrO_4$ (423.26): C 62.43; H 3.57; Br 18.88. Found C 62.19; H 3.50; Br 18.65.

METHYL 6-METHOXY-2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (29): The starting components [232mg of (10), 144mg of (2)] were dissolved in 200mL of MeOH. The crude binaphthol mixture [281mg (75%)] was analyzed by GC [(28)/(29)/(13) = 34/64/2]. Some starting (2) (15%) was recovered from the reaction mixture. Flash chromatography (elution with toluene to toluene-5%acetone) followed by preparative TLC (eluted twice in toluene-4%acetone) afforded 177mg (47%) of (29) as a yellow crystalline solid, mp 211°C.
MS: m/z=374 ($M^{+\cdot}$). ^{1}H-NMR(400MHz,$CDCl_3$,ppm): 3.90(s,3H,$-OCH_3$); 4.01(s,3H, $-COOCH_3$); 5.00(s,1H,exchanged with CD_3COOD,$C^{2'}$-OH); 7.03-7.10(m,3H,arom.); 7.21-7.25(m,2H,arom.); 7.31(dt,J_1=7.5Hz,J_2=1.0Hz,1H,arom.); 7.36(d,J=8.9Hz, 1H,arom.); 7.86(d,J=8.1Hz,1H,arom.); 7.91(d,J=8.9Hz,1H,arom.); 8.61(s,1H,

C^4-H); 10.66(s,1H,exchanged with CD_3COOD,-C^2-OH). Anal. Calc. for $C_{23}H_{18}O_5$ (374.37): C 73.79; H 4.85. Found C 73.87; H 4.90.

METHYL 6,7'-DIMETHOXY-2,2'-DIHYDROXY-1,1'-BINAPHTHALENE-3-CARBOXYLATE (30): The starting components [232mg of (10), 174mg of (3)] were dissolved in 200mL of MeOH. The crude product [343mg (85%)] was analyzed by GC [(28)/(30)/(15) = 22/75/3] and purified by flash chromatography (elution with chloroform) to give a bright-yellow solid which was shortly boiled with 25mL of MeOH, cooled down to 5°C and isolated by suction. Yield 247mg (61%) of yellow crystalline (30), mp 215°C.
MS: m/z=404 ($M^{+\cdot}$). ^{1}H-NMR(400MHz,$CDCl_3$,ppm): 3.52(s,3H,$C^{7'}$-OCH_3); 3.89(s,3H, C^6-OCH_3); 4.04(s,3H,-$COOCH_3$); 4.95(s,1H,exchanged with CD_3COOD,$C^{2'}$-OH); 6.36(d,J=2.5Hz,1H,$C^{8'}$-H); 6.99(dd,J_1=8.9Hz,J_2=2.5Hz,1H,arom.); 7.06(dd, J_1=9.3Hz,J_2=2.6Hz,1H,arom.); 7.13(d,J=9.3Hz,1H,arom.); 7.19-7.22(m,2H,arom.); 7.76(d,J=8.9Hz,1H,arom.); 7.83(d,J=8.9Hz,1H,arom.); 8.62(s,1H,C^4-H); 10.70(s,1H,exchanged with CD_3COOD,C^2-OH). Anal. Calc. for $C_{24}H_{20}O_6$ (404.40): C 71.28; H 4.99. Found C 71.46; H 5.08.

OXIDATIVE CROSS-COUPLING OF METHYL 3-HYDROXY-2-NAPHTHOATE (1) WITH METHYL 7-METHOXY-3-HYDROXY-2-NAPHTHOATE (10): The starting components [202mg of (1), 232mg of (10)] were dissolved in 200mL of MeOH. The crude binaphthol mixture [302mg (70%)] was analyzed by GC-MS to give (11)[$M^{+\cdot}$402]/(31)[$M^{+\cdot}$432]/(28)[$M^{+\cdot}$462] = 17/57/26. As much as 24% of starting (1) were recovered from the reaction.

OXIDATIVE CROSS-COUPLING OF 2-NAPHTHOL (2) with 7-METHOXY-2-NAPHTHOL (3): The starting components [144mg of (2), 174mg of (3)] were dissolved in 80mL of MeOH, ethylamine (16mL of 1M solution in MeOH) was used in place of tert-butyl amine. The crude product [253mg (80%)] was analyzed by GC-MS to give (13)[$M^{+\cdot}$286]/(32)[$M^{+\cdot}$316]/(15)[$M^{+\cdot}$346] = 26/47/27].

THE INFLUENCE OF REACTION VARIABLES ON THE SELECTIVITY OF CROSS-COUPLING REACTION

202mg (1mmol) of (1) and 144mg (1mmol) of (2) were coupled under the conditions given in *Table 3*:

Entry I-III: 538mg (4mmol) of $CuCl_2$, 16mL of 1M *tert*-butyl amine in MeOH, 80mL of MeOH,
IV: 807mg (6mmol) of $CuCl_2$, 24mL of 1M *tert*-butyl amine in MeOH, 80mL of MeOH,
V: 538mg (4mmol) of $CuCl_2$, 16mL of 1M *tert*-butyl amine in iPrOH, 80mL of iPrOH,
VI: 538mg (4mmol) of $CuCl_2$, 1.7mL (1.2g, 16mmol) of *tert*-butyl amine, 100mL of acetone,
VII: 538mg (4mmol) of $CuCl_2$, 2.42g (16mmol) of 1-adamantyl amine, 80mL of MeOH,
VIII: 538mg (4mmol) of $CuCl_2$, 1.3g (16mmol) of pyridine, 80mL of MeOH.

CuCl(OMe) **AS AN OXIDANT: SELECTIVE FORMATION OF (12)**

To a solution of 538mg (4mmol) of $CuCl_2$ in 40mL of dry MeOH 1M NaOMe in MeOH (4mL) was slowly added and the resulting heterogeneous mixture was stirred for 15 minutes during which the colour turned to yellow-green. The suspension was deoxygenated and finally, a solution of 202mg (1mmol) of (1) and 144mg (1mmol) of (2) in 40mL of dry, deoxygenated MeOH was added in one portion. The dark-brown mixture was heated at 50°C for 40 minutes, cooled and quenched with 6M HCl. The workup was performed as described for **Entry** I in ***Table 2*** affording 294mg (86%) of (12) after chromatographic separation.

CROSS-COUPLING OF SODIUM NAPHTHOLATES: AN OPTIMIZED PROCEDURE FOR (12)

In a 500mL flask a solution of NaOMe was prepared by dissolution of sodium [4.83g, 210mmol] in dry deoxygenated MeOH (100mL). This solution was carefuly transfered via cannula to a 2L three-necked flask [equipped with mechanical stirrer, argon inlet and Dimroth condenser] containing a rapidly stirred solution of 20.2g (100mmol) of (1) and 14.4g (100mmol) of (2) in 500mL of deoxygenated MeOH. The resulting yellow solution was stirred for 10 minutes and finally, a solution of 53.8g (400mmol) of $CuCl_2$ in 200mL of deoxygenated MeOH was added within 5 minutes with cannula. After 100 minutes at 50°C, the reaction mixture was cooled down and quenched with 6M HCl to pH~3. Methanol was evaporated and the residue partitioned between 400mL of chloroform and 200mL of water. After washing with water and 10%aq. $NaHCO_3$, the solution was dried over $MgSO_4$. Chloroform was evaporated and the dirty-yellow solid was recrystallized from toluene (200mL). The isolated (12) [26.2g] was found (GC) to be at least 99.5% pure. Further 4.2g of (12) were isolated by column chromatography, the overall yield being thus 88.5%.

OPTICAL RESOLUTION OF (12) BY CHROMATOGRAPHY ON TRIACETYL CELLULOSE

The resolution was carried out on a 3 x 60cm column filled with triacetyl celullose [MERCK 15-25μm]; elution with 96%EtOH, eluent flow rate 3mL/min, single injection of 150mg of *rac.*(12) in 8mL of EtOH, UV detection at 254nm. The *(-)*-enantiomer was eluted first. $[\alpha]^{D}_{20}$ = -31.0° (chloroform,c=0.4840) for (-)-(12) and $[\alpha]^{D}_{20}$ = +30.5° (chloroform,c=0.4988) for (+)-(12).

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