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A convenient route towards novel H_8-1,1′-bis-(dibenzofuran-2-ol) derivatives and evaluation of their use as chiral auxiliaries

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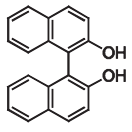
ABSTRACT

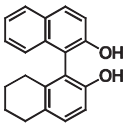
A novel bidentate ligand, H_8-BIFOL, was successfully prepared and resolved starting from readily available reagents. The reactivity and selectivity was evaluated in the alkynylation of benzaldehyde, resulting in ee's up to 56%.

1. Introduction

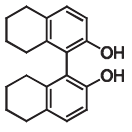
After the introduction of 1,1′-binaphthyl-2,2′-diol (BINOL) as a chiral agent in asymmetric synthesis, numerous publications appeared reporting new or more efficient synthetic routes using this ligand.[1] The excellent ee's and yields of many reactions using BINOL led to the development of a broad selection of new, substituted chiral auxiliaries, which dramatically improved the enantioselectivity of certain reactions.[2] A common modification of the classic binaphthyl structure is made by partial hydrogenation of the naphthalene units, providing the corresponding H_4- and H_8-BINOL ligands.[3] Their increased bulkiness and dihedral angle often give improved results regarding the selectivity of several asymmetric reactions.[4]



BINOL



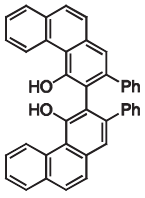
H_4-BINOL



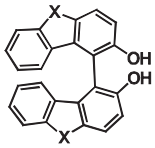
H_8-BINOL

Besides altering the structure of the naphthyl skeleton, it is also possible to vary the building block itself. A well known example of these kind of ligands is 2,2′-diphenyl-(3,3′-biphenanthrene)-4,4′-diol (VAPOL), which is for instance capable of providing previously unseen enantioselectivities in the synthesis or ring-opening of aziridines.[5]

Another class of C_2-symmetric bidentate ligands based on the dibenzofuran (BIFOL) or carbazole (BICOL) unit was introduced by Hiemstra et al.[6] Despite their promising activity in asymmetric catalysis, no other reports appeared using these new auxiliaries, which is probably caused by the rather tedious and lengthy synthetic route needed towards them.[7] Nevertheless, the presence of the electron-donating heteroatoms, which allow a more direct functionalization, and the different bite-angle due to the increased steric hindrance, are advantages that motivated us to look for another synthetic approach allowing to further explore the scope and applicability of these interesting ligands.



VAPOL



BIFOL (X=O)
BICOL (X=NH)

Keeping in mind further derivatization of the 3- and 3′-positions and the increased solubility in common organic solvents, we decided to investigate the synthesis of the previous unknown hydrogenated derivative of 1,1′-bis-(dibenzofuran-2-ol) (BIFOL).[8] Thus, in this paper we wish to present an efficient and large-scale synthesis of a novel C_2-symmetric bidentate ligand; 1,1′-bis-(6,7,8,9-tetrahydro-dibenzofuran-2-ol) or H_8-BIFOL **2**, and its application in the asymmetric alkynylation of aromatic aldehydes.

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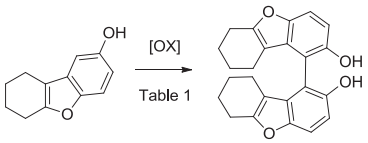
2. Discussion and results

2.1. Synthesis

The field of the BINOL based ligands has been studied extensively, resulting in numerous amounts of synthetic approaches. The best known route is the oxidative coupling of 2-naphthol, which is based on the dimerization of two radical species produced by the one electron oxidation under the influence of an oxidant. Recently, increased attraction has gone out to copper[9] or vanadium[10] mediated dimerizations as they allow the use of chiral inducers, resulting in an enantiomeric excess of one of the two possible isomers. As these methodologies are the most straightforward approach towards C_2-symmetric biphenols, we envisioned to apply these to the known compound 6,7,8,9-tetrahydro-dibenzofuran-2-ol **1**, which was prepared on a large scale according to a slightly modified literature procedure.[11] In order to find the appropriate conditions for the dimerization of **1**, a variety of commonly employed oxidants was screened (Table 1).

Table 1
Study towards dimerization of H_4-dibenzofuranol. TMEDA=*N*,*N*,*N*,*N*-tetramethyl-ethylenediamine



1 *(rac)*-**2**

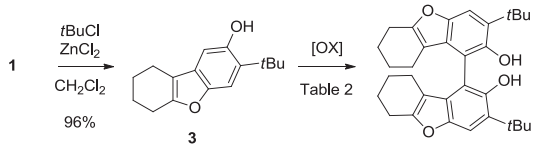
Entry[a]	Oxidant/Ligand	Solvent	Time (h)	Yield (%)
1	$K_3[Fe(CN)_6]$, KOH	CH_2Cl_2	20	—[b]
2	$Cu(NO_3)_2$ (10 mol %)/ Benzylamine (20 mol %), O_2	CH_2Cl_2	115	16
3	CuCl (100 mol %)/ Benzylamine (200 mol %)	CH_2Cl_2	67	—
4	$CuCl_2$ (100 mol %)/ Benzylamine (200 mol %)	CH_2Cl_2	67	—
5[c]	$FeCl_3/Al_2O_3$	Toluene	17	—[d]
6	$VO(acac)_2$ (10 mol %), O_2	CH_2Cl_2	70	Traces [b]
7	CuCl (100 mol %)/TMEDA (200 mol %)	CH_2Cl_2	140	31
8[e]	$Mn(acac)_3$	MeCN	24	Traces

[a] All reactions were carried out at room temperature with 1.0 mmol of **1** in 10 mL degassed solvent under an atmosphere of N_2 (unless otherwise mentioned).
[b] Starting material was recovered.
[c] Reaction carried out at 70 °C.
[d] Traces of product were detected by MS.
[e] Reaction carried out at reflux temperature.

Unfortunately, none of the conditions provided satisfactory results, mostly due to the formation of over-oxidized compounds or to unreacted starting material. Noteworthy however is the use of copper (II) nitrate/benzylamine (Table 1, entry 2), which yielded the targeted compound **2**, albeit in low yield. Somewhat better results were observed with CuCl/TMEDA, but prolonged reaction times were necessary. As these findings were not very promising for the further development of the ligand, we were obliged to modify our approach.

Preliminary research in our laboratory has showed that the oxidative coupling can be significantly improved by the introduction of a *tert*-butyl substituent at the *ortho*-position. This bulky alkyl-group prevents the formation of the unwanted 1,3′ and 3,3′ dimerization products and stabilizes the radical intermediates that are present during the reaction. Also it has been showed by Schrock et al. that the presence of these sterically demanding substituents on bidentate ligands can, for example, improve the selectivity of enantioselective olefin metathesis.[12] Thus, the alkylated H_4-dibenzofuranol **3** was prepared in an almost quantitative yield starting from **1** under general Friedel–Crafts conditions. Since the copper-mediated dimerizations provided the best results until now, further optimalizations were carried out using similar conditions (Table 2).

Table 2
Optimalization of the oxidative coupling of **3**. DACH=*rac*(-*trans*)diaminocyclohexane, TMEDA=*N*,*N*,*N*,*N*-tetramethylethylenediamine, MBA=(*rac*)-α-methylbenzylamine



Entry[a]	Oxidant/Ligand	Solvent	Time (h)	Yield (%)[b]
1	$CuCl_2$ (100 mol %), Benzylamine (200 mol %)	CH_2Cl_2	24	62
2	$CuCl_2$ (100 mol %), Benzylamine (200 mol %)	MeCN	42	63
3	CuI (100 mol %), Benzylamine (200 mol %)	MeCN	20	—[c]
4	CuCl (100 mol %), Benzylamine (200 mol %)	CH_2Cl_2	22	33
5	CuCl (100 mol %), TMEDA (200 mol %)	CH_2Cl_2	0.75	33
6	$CuSO_4$ (100 mol %), Benzylamine (200 mol %)	CH_2Cl_2	163	66
7	$Cu(NO_3)_2$ (100 mol %), Benzylamine (200 mol %)	CH_2Cl_2	24	82
8	$Cu(NO_3)_2$ (10 mol %), Benzylamine (20 mol %), O_2	CH_2Cl_2	17	93 (84)[d]
9	$Cu(NO_3)_2$ (10 mol %), Benzylamine (20 mol %), O_2	MeCN	50	56
10	$Cu(NO_3)_2$ (10 mol %), DACH (10 mol %), O_2	CH_2Cl_2	26	—[c]
11	$Cu(NO_3)_2$ (10 mol %), MBA (10 mol %), O_2	CH_2Cl_2	18	86

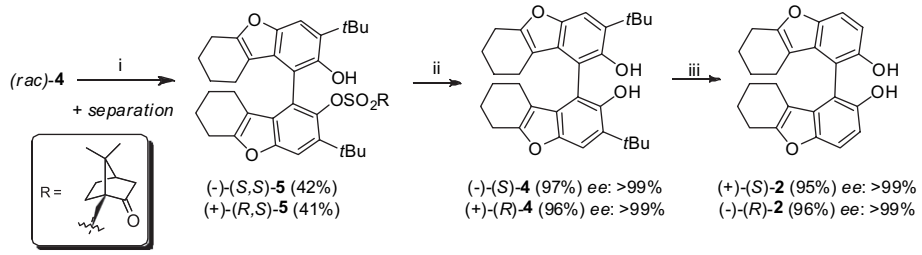
[a] Reactions were carried out at room temperature with 0.5 mmol of **3** in 5 mL solvent under N_2 atmosphere (unless otherwise mentioned).
[b] Isolated yields.
[c] Starting material was recovered.
[d] Yield in parentheses is after recrystallization (EtOH).

This time we were pleased to see that ^{t}Bu$_2$-H$_8$-BIFOL **4** was formed in moderate to excellent yields. Several copper sources were examined of which copper(II) nitrate seemed to be the best choice (Table 2, entry 7). Lowering the amount of copper by using oxygen as the stoichiometric oxidant resulted in higher yields, which made it feasible to scale up the reaction. Changing the solvent to acetonitrile (MeCN) did not improve the reaction, nor did the use of other amines. Notable was the use of the CuCl/TMEDA reagent (Table 2, entry 5), which decreased the reaction time significantly, however at the cost of inferior yield.

2.2. Resolution

In order to be useful as a chiral auxiliary, the separation (or enantioselective synthesis) of the two isomers is essential. Several methods, including oxidative coupling with chiral amines and inclusion crystallization using *N*-benzylcinchoninium chloride[13] were examined, however, none resulted in a notable enantiomeric excess of the ligand (according to HPLC analysis).

More satisfactory results were obtained with the formation of diastereoisomers by employing 1-(*S*)-camphorsulfonyl chloride as chiral substrate, allowing near quantative separation by means of standard column chromatography followed by alkaline hydrolysis. All efforts to obtain the two diastereoisomers (*S*,*S*)-**5** or (*R*,*S*)-**5** by crystallization were unsuccessful. Finally, the alkyl substituents were removed to obtain H$_8$-BIFOL **2** in excellent yields without any measurable racemization (Scheme 1).



Scheme 1. Resolution of the enantiomers using camphorsulfonyl chloride. (i) 1-(*S*)-camphorsulfonyl chloride, Et_3N, DMF. (ii) NaOH (3 M), THF/MeOH (3:1). (iii) $AlCl_3$, PhOH, Toluene. Enantiomeric excess was calculated using HPLC analysis (Chiralpak IB). The absolute configuration was determined using X-ray analysis.

Suitable crystals for X-ray analysis of **4** were obtained via slow evaporation out of methanol and showed (*S*)-configuration for the first fraction (Fig. 1).

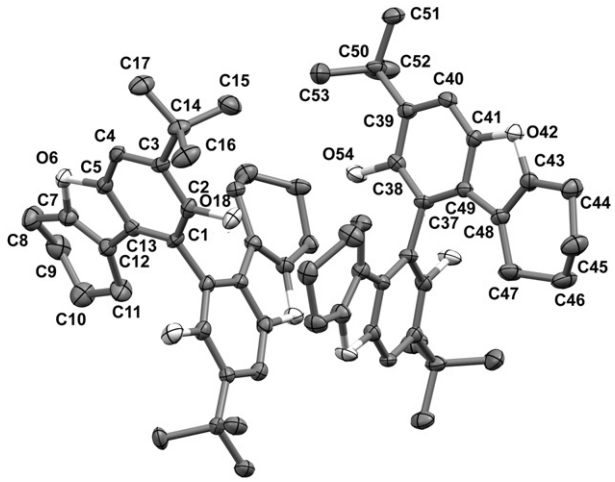


Fig. 1. Representation of two independent molecules in the asymmetric unit with partial atom labelling and 50% probability displacement ellipsoids; H-atoms as well as disorder on the cyclohexene rings are omitted for clarity.

2.3. Screening of the catalyst activity

Since several years now, the well established procedure for the alkynylation of aromatic or aliphatic aldehydes using titanium-binolate species has become a benchmark system for the evaluation of newly synthesized bidentate ligands.[14] Different parameters were evaluated using (−)-(*R*)-H_8-BIFOL, however, the average enantiomeric excess of **10** remained moderate (Table 3). Lowering the temperate to 0 °C increased the selectivity to 56% (Table 3, entry 2). Changing the amount of ligand did not have any substantial influence on the enantiomeric excess.

3. Conclusion

In summary, we reported a novel up scalable route towards a new bidentate ligand starting from cheap, commercially available reagents. A copper catalyzed oxidative coupling was used as the key-step in the synthesis. The resolution was achieved by separation of diastereoisomers, which were prepared using (1)-(*S*)-camphorsulfonyl chloride as a chiral substrate. The usefulness of the new ligands as chiral auxiliary was screened through the alkynylation of benzaldehyde, resulting in moderate ee's up to 56%. Although similar experiments using BINOL resulted in a higher selectivity, optimalization studies regarding this reaction will be continued. Further investigation of the use of H_8-BIFOL or its derivatives in other asymmetric reactions is currently ongoing and will be reported in due course.

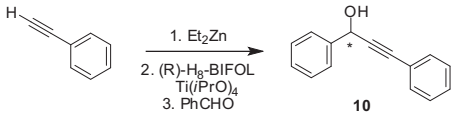
4. Experimental section

4.1. General

All commercial products were used without further purification. All solvents that were used were stored on oven dried molecular sieves (4 Å). All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. ^1H and ^{13}C NMR spectra are recorded on a 300 or 400 MHz (75 MHz and 100 MHz for ^{13}C, respectively) Bruker Avance spectrometer with $CDCl_3$ as solvent and TMS as internal standard. Melting points are uncorrected. HRMS spectra were recorded on a Kratos HRMS system, EI and CI spectra were recorded on an HP system. For the resolution on chiral HPLC a Chiralpak IB column (kept at 20 °C) was used. All chromatographic separations were performed on a Buchi MPLC system.

*4.1.1. 6,7,8,9-Tetrahydro-2-hydroxydibenzofuran (**1**).* *N*-Morpholino-1-cyclohexene (56.48 g, 0.338 mol) was added dropwise over a 1 h period to a solution of benzoquinone (33.21 g, 0.307 mol) in toluene

Table 3
Screening of the new ligands in alkynylation of benzaldehyde



Entry	Ligand (mol %)	Alkyne (mol %)	Et_2Zn (mol %)	$Ti(^iPrO)_4$ (mol %)	T (°C)	Solvent	Time (h)	Yield (%)	ee (%)[a]
1	10	2	2	0.25	RT	THF	20	69	42
2	10	2	2	0.25	0	THF	19	67	56
3	5	2	2	0.25	0	THF	21	50	52
4[b]	10	2	2	0.25	0	THF	20	53	50
5	10	2	2	0.50	0	THF	20	71	46
6	20	2	2	0.25	0	THF	22	66	52
7	10	2	2	0.25	RT	Toluene	19	63	24

[a] Enantiomeric excess was calculated using HPLC analysis (Chiralpak IB). The main isomer of **10** was determined to be (*S*).
[b] Benzaldehyde was dissolved in 1 mL THF.

(800 mL) at 0 °C. After addition, stirring at 0 °C was continued for another 7 h. The precipitate was collected by filtration, washed thoroughly with toluene and dried overnight in vacuo. The resulting white, beige solid was mixed well with water (600 mL) and under mechanical stirring, HCl (100 mL, 5 M) was added dropwise (30 min). After 6 h the precipitate was collected again, washed well with water and dried. The obtained slightly red solid was purified by filtration over silica (CH_2Cl_2) yielding the pure compound as a white solid (29.43 g, 51%). Using enamine of lesser quality resulted in lower yields and required more purification. Mp 103–104 °C (Lit:[11] 104 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, 1H, J=9.1 Hz), δ 6.82 (d, 1H, J=1.8 Hz), δ 6.69 (dd, 1H, J_1=8.2 Hz, J_2=2.7 Hz), δ 4.64 (s, 1H), δ 2.71 (m, 2H), δ 2.56 (m, 2H), δ 1.87 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4, δ 151.2, δ 149.4, δ 129.9, δ 112.9, δ 111.2, δ 104.1, δ 23.67, δ 23.0, δ 22.8, δ 20.6 ppm; MS (CI) m/z (MH^+) 189.

*4.1.2. 6,7,8,9-Tetrahydro-2-hydroxy-3-tert-butyldibenzofuran (**3**).* A mixture of **1** (18.8 g, 0.1 mol), *tert*-butylchloride (27.77 g, 32.67 mL, 0.3 mol) and $ZnCl_2$ (34.07 g, 0.25 mol) in CH_2Cl_2 (200 mL) was refluxed for 9 h (after about 20 min the product started to precipitate). The reaction mixture was then hydrolyzed in water (200 mL) and extracted with CH_2Cl_2. The organic layer was separated, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure, yielding 23.4 g (96%) of pure compound as a white solid. If necessary, the product can be recrystallized from chloroform to remove small impurities. Mp 201–202 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 1H), δ 6.67 (s, 1H), δ 4.65 (s, 1H), δ 2.69 (m, 2H), δ 2.53 (m, 2H), δ 1.85 (m, 4H), δ 1.44 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, δ 150.3, δ 149.6, δ 132.6, δ 127.0, δ 112.3, δ 109.0, δ 105.0, δ 35.1, δ 30.0, δ 23.7, δ 23.1, δ 22.9, δ 20.7 ppm; MS (EI) m/z (M^+) 244, ($-CH_3$) 229; HRMS calcd for [$C_{16}H_{20}O_2$] 244.14633, found 244.14606.

*4.1.3. Large scale preparation of 1,1′-bis-(6,7,8,9-tetrahydro-2-hydroxy-3-tert-butyldibenzofuran) (rac-**4**).* To a mixture of **3** (10.02 g, 0.0411 mol) and $Cu(NO_3)_2.3H_2O$ (0.993 g, 0.0041 mol) in CH_2Cl_2 (200 mL), benzylamine (0.881 g, 0.899 mL, 0.0082 mol) was added. The resulting solution was stirred at room temperature under O_2 atmosphere (ambient pressure) during 17 h after which it was poured into water (300 mL), acidified with HCl and finally extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo, yielding a dark red solid, which was dissolved in refluxing EtOH (230 mL) and stored overnight at −18 °C. The precipitate was collected by filtration, washed with cold ethanol and dried, yielding a slightly pink solid (7.62 g, 76%), which was pure enough for further reactions according to ^{1}H NMR and TLC analysis. The coloured impurities (*o*-quinone-like compounds) can be removed if necessary by flash column chromatography (9/1: C_7H_{16}/CH_2Cl_2). The filtrate after crystallization was concentrated in vacuo and purified by column chromatography (9/1: C_7H_{16}/CH_2Cl_2), yielding another 0.760 g (8%) of pure 4. Mp 194–195 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.44 (s, 2H), δ 5.08 (s, 2H), δ 2.67 (m, 4H), δ 2.02 (m, 2H), δ 1.78 (m, 4H), δ 1.58 (m, br, 6H), δ 1.47 (s, 18H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, δ 149.2, δ 148.8, δ 132.6, δ 126.4, δ 112.8, δ 109.9, δ 109.1, δ 35.3, δ 29.9, δ 23.8, δ 22.7, δ 22.7, δ 20.1 ppm; MS (EI) m/z (M^+) 486, (−CH3) 471, 415 ($-C_5H_{12}$); HRMS calcd for [$C_{32}H_{38}O_4$] 486.27701, found 486.27799.

4.1.4. Esterification and resolution of 1,1′-bis-(6,7,8,9-tetrahydro-2-hydroxy-3-tert-butyldibenzofuran). To a solution of *rac*-**4** (4.86 g, 10 mmol) and 1(*S*)-camphorsulfonyl chloride (4.518 g, 18 mmol) in dry DMF (60 mL) at 0 °C, Et_3N (10 mL) was added dropwise. After the addition was complete the mixture was allowed to heat up to room temperature and stirred for 3 h. The resulting suspension was poured into water (400 mL) after which the precipitate was collected by filtration, washed well with water and saturated NH_4Cl and finally dried in vacuo, yielding 7.35 g as a 1:1 mixture of the two diastereoisomers. The separation was performed using column chromatography (8/2:CH_2Cl_2/C_7H_{16}).

*4.1.5. Fraction 1 (R_f=0.29): (S)-2′-(((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonyloxy)-1,1′-bis-(6,7,8,9-tetrahydro-3-tert-butyldibenzofuran-2-ol) ((S,S)-**5**).* Yield 2.95 g, 42%; mp 83 °C; $[\alpha]_D^{20}$ −85 (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 1H), δ 7.42 (s, 1H), δ 5.19 (s, 1H), δ 2.63 (m, 4H), δ 2.33–δ 2.08 (m, 4H), δ 1.96–δ 1.63 (m, 13H), δ 1.58 (s, 9H), δ 1.48 (s, 9H), δ 1.31 (m, 1H), δ 0.98–δ 0.80 (m, 3H), δ 0.74 (s, 3H), δ 0.54 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.9, δ 156.1, δ 154.9, δ 152.1, δ 149.2, δ 148.5, δ 144.6, δ 139.6, δ 133.8, δ 128.0, δ 126.7, δ 121.2, δ 115.3, δ 113.9, δ 113.2, δ 110.5, δ 109.6, δ 58.4, δ 50.8, δ 47.9, δ 43.2, δ 42.5, δ 35.7, δ 35.6, δ 35.3, δ 31.5, δ 30.0, δ 26.9, δ 26.6, δ 26.1, δ 23.8, δ 22.7, δ 22.6, δ 22.8, δ 20.3, δ 20.1, δ 19.7, δ 19.3 ppm; MS (EI) m/z (M^+) 700; HRMS calcd for [$C_{42}H_{52}O_7S$] 700.34338, found 700.34234.

*4.1.6. Fraction 2 (R_f=0.19): (R)-2′-(((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonyloxy)-1,1′-bis-(6,7,8,9-tetrahydro-3-tert-butyldibenzofuran-2-ol) ((R,S)-**5**).* Yield 2.85 g, 41%; mp 81 °C; $[\alpha]_D^{20}$ +85 (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 1H), δ 7.41 (s, 1H), δ 5.34 (s, 1H), δ 2.65 (m, 5H), δ 2.23 (m, 1H), δ 2.17–δ 1.66 (m, 13H), δ 1.55 (s, 9H), δ 1.48 (s, 9H), δ 1.40–δ 0.79 (m, 6H), δ 0.50 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.1, δ 156.2, δ 154.6, δ 152.1, δ 149.1, δ 148.5, δ 144.4, δ 139.5, δ 134.5, δ 128.3, δ 126.5, δ 121.5, δ 115.3, δ 113.9, δ 113.2, δ 110.6, δ 109.7, δ 58.4, δ 50.5, δ 47.9, δ 42.9, δ 42.4, δ 35.8, δ 35.6, δ 35.4, δ 31.6, δ 29.9, δ 27.00, δ 26.6, δ 25.3, δ 23.8, δ 22.9, δ 22.8, δ 22.6, δ 22.5, δ 20.5, δ 20.1, δ 19.3, δ 18.5 ppm; MS (EI) m/z (M^+) 700; HRMS calcd for [$C_{42}H_{52}O_7S$] 700.34338, found 700.34446.

4.2. General procedure for the hydrolysis of the sulfonate esters

A mixture of (*S*,*S*)-**5** or (*R*,*S*)-**5** (0.700 g, 1 mmol), NaOH (10 mL, 3 M) in THF/MeOH (30 mL:10 mL) was refluxed during 22 h. After this period, the reaction mixture was cooled down to room temperature, poured into water and neutralized (HCl). The organic fraction was extracted using CH_2Cl_2, washed with brine and finally dried over $MgSO_4$. The resulting red oil after evaporation was purified using flash chromatography (7/3:C_7H_{16}/CH_2Cl_2) yielding the ligands as a white solid.

*4.2.1. (S)-1,1′-Bis-(6,7,8,9-tetrahydro-2-hydroxy-3-tert-butyldibenzofuran) ((S)-**4**).* Yield 97%, mp 259 °C; $[\alpha]_D^{20}$ −158 (*c* 0.5, CH_2Cl_2), spectroscopic data were identical with that of *rac*-(**4**); ee >99% (Chiralpak IB, hexane, flow rate=0.5 mL/min, retention time=11.9).

*4.2.2. (R)-1,1′-Bis-(6,7,8,9-tetrahydro-2-hydroxy-3-tert-butyldibenzofuran) ((R)-**4**).* Yield 96%, mp 257 °C; $[\alpha]_D^{20}$ +158 (*c* 0.5, CH_2Cl_2), spectroscopic data were identical with that of *rac*-(**4**); ee >99% (Chiralpak IB, hexane, flow rate=0.5 mL/min, retention time=11.5).

4.3. General procedure for the de-*tert*-butylation of (4)

To a solution of (*S*)-**4** or (*R*)-**4** (0.265 g, 0.545 mmol) and phenol (0.359 g, 3.816 mmol) in toluene (10 mL), $AlCl_3$ (0.218 g, 1.636 mmol) was added at room temperature. Stirring was continued under ambient temperature during 4 h, after which the reaction mixture was hydrolyzed in water. The organic fractions were extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and finally dried over $MgSO_4$. After evaporation and purification using column chromatography (CH_2Cl_2), the compound was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, 2H, J=8.8 Hz), δ 6.92 (d, 2H, J=8.6 Hz), δ 4.75 (s, 2H), δ 2.69 (m, 4H), δ 2.01 (m, 2H), δ 1.79 (m, 6H),

δ 1.57 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0, δ 150.1, δ 148.9, δ 129.2, δ 113.3, δ 112.4, δ 111.1, δ 109.1, δ 23.8, δ 22.7, δ 22.6, δ 20.3 ppm; MS (EI) *m*/*z* (M^+) 374; HRMS calcd for [$C_{24}H_{22}O_4$] 374.15449, found 374.15371.

*4.3.1. (S)-1,1′-Bis-(6,7,8,9-tetrahydro-2-hydroxy-dibenzofuran) ((S)-**2**).* Yield 95%, mp 57–61 °C; $[\alpha]_D^{20}$ +58 (*c* 1, CH_2Cl_2); ee >99% (Chiralpak IB, 50/50:CH_2Cl_2/hexane, flow rate=1.2 mL/min, retention time=7.1).

*4.3.2. (R)-1,1′-Bis-(6,7,8,9-tetrahydro-2-hydroxy-dibenzofuran) ((R)-**2**).* Yield 96%, mp 59–62 °C; $[\alpha]_D^{20}$ −58 (*c* 1, CH_2Cl_2); ee >99% (Chiralpak IB, 50/50:CH_2Cl_2/hexane, flow rate=1.2 mL/min, retention time=6.7).

4.4. General procedure for the alkynylation of benzaldehyde (10)

To a flame-dried flask containing THF (2 mL), phenylacetylene (0.204 g, 0.220 mL, 2 mmol) and Et_2Zn (2 mL, 1 M solution in hexane) were added dropwise. After refluxing for 1 h, the reaction mixture was cooled down to room temperature, and a solution containing the ligand (10 mol %) and Ti(O^iPr)$_4$ (25 mol %) in THF (2 mL) was added via cannula. The resulting yellow mixture was stirred for another hour at room temperature (reactions performed at 0 °C were cooled before addition of benzaldehyde) after which benzaldehyde (0.106 g, 0.101 mL, 1 mmol) was added. Stirring was continued during the times indicated in Table 3. After the reaction was complete (judged by TLC analysis), the solution was poured into saturated NH_4Cl, extracted with EtOAc and the organic fractions dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, compound **8** was obtained as a light yellow oil after using column chromatography (15/85:EtOAc/C_7H_{16}). Enantiomeric excess was determined by chiral HPLC using a Chiralpak IB column (5/5:CH_2Cl_2/C_7H_{16}, flowrate 0.75 mL/min). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47–δ 7.29 (m, br, 10H), δ 5.69 (d, 1H, *J*=6.0 Hz), δ 2.37 (d, 1H, *J*=6.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.8, δ 131.9, δ 128.8, δ 128.7, δ 128.6, δ 128.4, δ 126.9, δ 88.8, δ 86.8, δ 65.24 ppm.

*4.4.1. Crystal data for (S)-**4**.* $C_{32}H_{38}O_4$, *M*=486.62, colourless plate, 0.15×0.12×0.05 mm^3, monoclinic, space group $P2_1$ (No. 4), *a*=10.6393(8), *b*=21.6225(18), *c*=11.6943(9) Å, β=91.397(5)°, *V*=2689.5(4) Å^3, *Z*=4, D_c=1.202 g/cm^3, F_{000}=1048, Bruker SMART 6000, Cu Kα radiation, λ=1.54178 Å, *T*=100(2) K, $2\theta_{max}$=142.8°, 23,148 reflections collected, 9521 unique (R_{int}=0.0927). Final GooF=1.027, R_1=0.0647, wR_2=0.1340, *R* indices based on 7057 reflections with *I*>2sigma(*I*) (refinement on F^2), 713 parameters, 42 restraints. Lp and absorption corrections applied, μ=0.612 mm^{-1}. Absolute structure parameter=0.0(2).[15] The structure was solved and refined using the SHELX-97 suite of programs.[16] The program Mercury was used to prepare figures.[17] All hydrogen atoms were positioned geometrically and refined using a riding model with C–H=0.99–0.95 Å, O–H=0.84 Å and U_{iso}(H)=1.2 U_{equiv}(C, O), 1.5 U_{equiv} (methyl C). The cyclohexene rings C7–C12, C43–C48 and C61–C66 were partially disordered and modelled over two positions with site occupancy ratios of 71:29, 78:22 and 79:21, respectively. The C–C bonds in the disordered moieties and the displacement parameters were restrained to be approximately equal.

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Supplementary data

Copies of NMR spectra and chiral chromatograms. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.077. These data include MOL files and InChIKeys of the most important compounds described in this article.

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