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A new route to 2,2′,3,3′-tetrasubstituted binaphthyls

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ABSTRACT

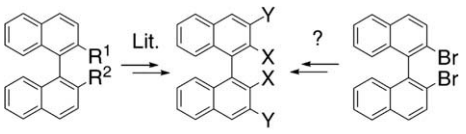
Based on an *ortho*-lithiation protocol of 2,2′-dibromo-1,1′-binaphthyl four tetrasubstituted binaphthyls, 2,2′-dibromo-3,3′-diiodo-, 3,3′-dibromo-2,2′-diiodo-, 2,2′,3,3′-tetrabromo-, and 2,2′,3,3′-tetraiodo-1,1′-binaphthyls have been prepared in excellent yield which in turn proved to be versatile key intermediates in the synthesis of various 2,2′,3,3′-tetrasubstituted 1,1′-binaphthyl derivatives.

The inherently chiral 1,1′-binaphthyl fragment is probably the best known atropisomeric unit and a motif frequently found in those auxiliaries and ligands which are not derived from the chiral pool (Fig. 1).[1] Since their broad range of applicability often with excellent asymmetric induction in numerous asymmetric transformations has been discovered, methods for economic and selective access were desired and numerous strategies have been worked out.[2]

The introduction of at least one substituent in position 2 is obligatory to sufficiently hinder biaryl rotation and to enable configurative stability at room temperature.[3] Typically symmetrically or unsymmetrically 2,2′-disubstituted binaphthyls have been synthesized with potential of forming substrate-reagent complexes or chelates with transition metals. In the majority of cases their synthesis is based on three chiral key intermediates **1**–**3**, easily resolvable into enantiomers which are subsequently transformed into the desired derivatives.[4] Alternatively, enantioselective or diastereoselective oxidative coupling or cross-coupling protocols of achiral or chirally modified precursors using substoichiometric (chiral) copper, palladium, and nickel complexes, respectively have been performed.[5] Moreover, optical resolution procedures for the final products have been reported (Scheme 1).[6,2]

Further substituents have been introduced in pos. 3 and 3′ when either extended chiral environment or improved conformative stability through a buttressing effect was desired. Since *ortho*-metallation of O-protected binaphthol derivatives is readily performed, 2,2′-OR-3,3′′-X substituted binaphthyls are accessible in excellent yield from binaphthol in few steps.[7] More difficult is the preparation of binaphthyls with 2,2′-substituents other than OR, since this requires either (a) a stereoconservative exchange of two OR, both di-*ortho* substituted; which may be difficult from steric reasons and reduced racemization barrier of intermediates,[8] (b) the use of other ortho-directing groups,[9] (c) a diastereoselective binaphthyl coupling of suitable substituted naphthalene precursors or (d) an optical resolution step of the final product.[10]

Examples for the first route have been published by Maruoka's group to obtain tetrasubstituted binaphthyls with carbon substituents in pos. 2, 2′, 3, and 3′ from binaphthol (7–10 steps, 50–65% overall yield).[11] Similar compounds were also accessible via an *ortho*-magnesation of 1,1′-binaphthyl-2,2′-dicarboxylic acid diisopropylester as the key step (5 steps, 74% overall yield)[12] and *ortho*-lithiation of the free diacid followed by bromination with 2,4,4,6-tetrabromo-2,5-hexadien-1-on.[13,14] To the best of our knowledge no attempt has been made to find routes to 2,2′,3,3′-substituted binaphthyls via *ortho*-metallation of 2,2′-dibromo-1,1′-binaphthyl **4** although various bromoarenes have been frequently *ortho*-metallated with lithium dialkylamides.[15]



$R^1 = R^2 =$
OH **1**
NH_2 **2**
COOH **3**

4

Scheme 1.

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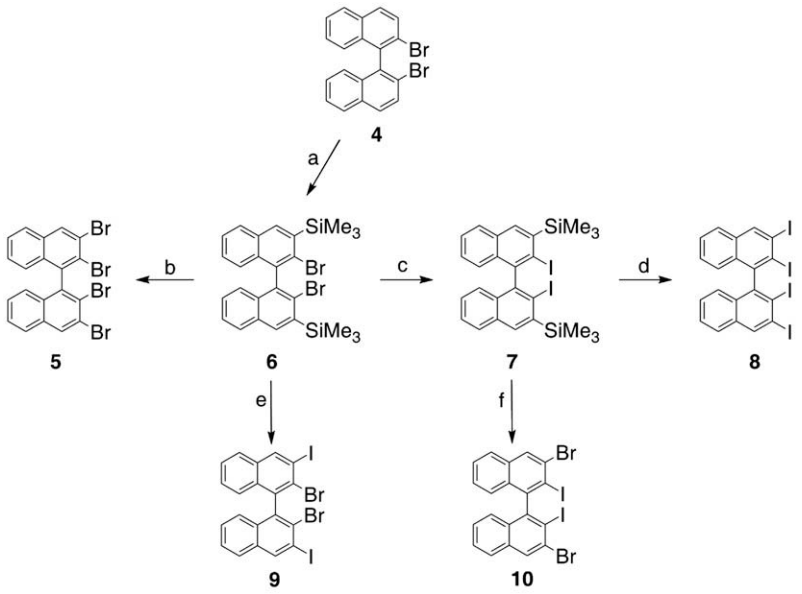
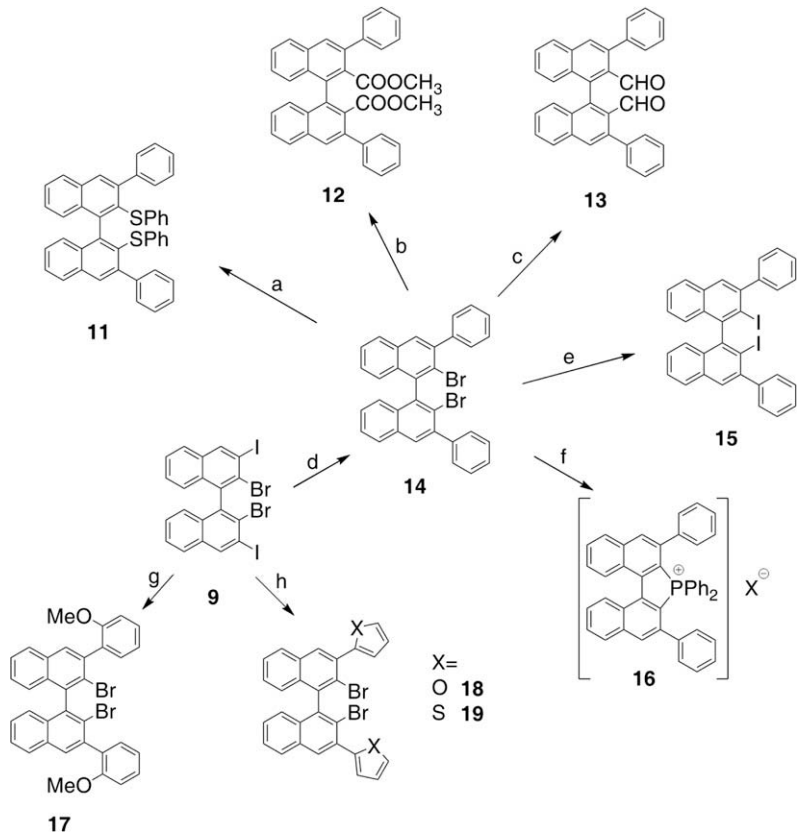
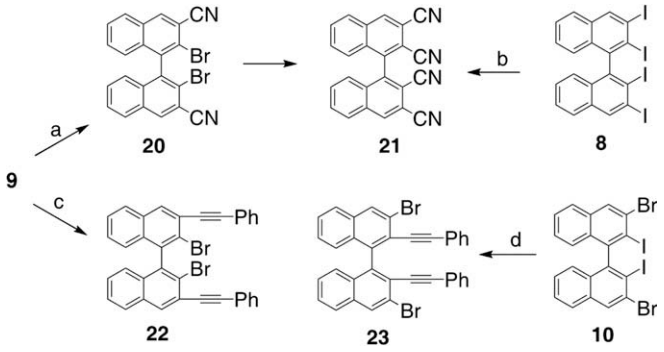


Scheme 2. 2,2′,3,3′-Tetrahalo-1,1′-binaphthyls. Reagents and conditions: (a) LiTMP/$ClSiMe_3$, −78 °C→rt (81%); (b) NBS, acetonitrile, rt (quant.); (c) *n*-BuLi/THF/−78/−40/−78 °C, ICH_2CH_2I (94%); (d) ICl, DCM, −40 °C (93%); (e) ICl, DCM, −40 °C (92%); (f) NBS, acetonitrile, rt (85%).

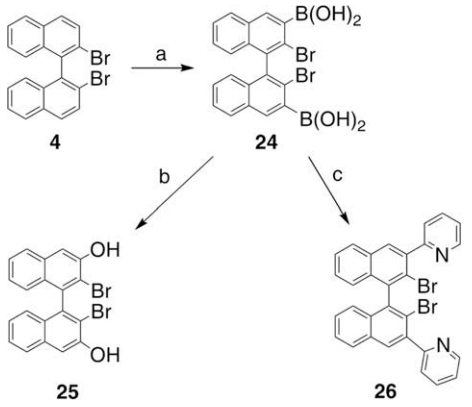


Scheme 3. 2,2′,3,3′-Tetrasubstituted binaphthyl derivatives accessible from **9**. Reagents and conditions: (a) *n*-BuLi/THF/−78/−40/−78 °C, PhSSPh (73%); (b) *n*-BuLi/THF/−78/−40/−78 °C, CO_2(s), CH_2N_2, MeOH (75%); (c) *n*-BuLi/THF/−78/−40/−78 °C, DMF (74%); (d) $PhB(OH)_2$, $Pd(PPh_3)_4$, toluene, reflux (92%); (e) *n*-BuLi/THF/−78/−40/−78 °C, ICH_2CH_2I (87%); (f) *n*-BuLi/THF/−78/−40/−78 °C, Ph_2PCl (89%); (g) 2-MeO–C_6H_4–$B(OH)_2$, $Pd(PPh_3)_4$, toluene, reflux (75%); (h) 2-furyl-$B(OH)_2$ or 2-thienyl-$B(OH)_2$, respectively, $Pd(PPh_3)_4$, DME, 120 °C (MW) (12% and 61%, respectively).

Such binaphthyl precursors with two pairs of independently transformable substituents in pos. 2 and 2′ as well as in 3 and 3′ would offer improved synthetic flexibility particularly in the field of ligand design for asymmetric catalysis. In classical biaryl ligands or auxiliaries bearing exclusively 2,2′ substituents, these are responsible for both, kinetic stability of the chelate and catalytic activity as a consequence of electron density and orbital geometries, but also for the chirality transfer from the chiral backbone



Scheme 4. 2,2′,3,3′-Tetrasubstituted binaphthyl derivatives with cyano and ethynyl substituents from **8**, **9**, and **10**. Reagents and conditions: (a) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 110 °C, 5 h (67%); (b) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 110 °C, 20 h (74%); (c) PhC≡CZnCl, $Pd(PPh_3)_4$, THF, reflux, 1 h (85%); (d) PhC≡CZnCl, THF, reflux, 1 h (7%).



Scheme 5. Reagents and conditions: (a) LiTMP/B(*i*-PrO)$_3$, −78 °C→rt (90%); (b) H_2O_2, MeOH, rt (76%); (c) 2-bromopyridine, $Pd(PPh_3)_4$, DME, 110 °C (MW) (43%).

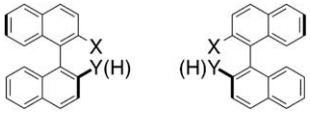


Figure 1. Atropisomeric 1,1′-binaphthyls.

(usually through a propeller-shaped arrangement of phenyl rings). Ligands with additional substituents in pos. 3,3′ should better match these twofold requirements. While alkyl or aryl groups of proper size and shape in pos. 3 and 3′ will influence the coordination mode of substrate, donor groups in pos. 2 and 2′ can be rather optimized for stability of the (chelate) complex. Further benefits of this concept could be a buttressing effect increasing the racemization barrier in 2,2′-dilithio intermediates and facilitating a stereoconservative transformation.

Treatment of **4** with excess of Li-2,2,6,6-tetramethylpiperidid (LiTMP) at −78 °C and in situ trapping with trimethylchlorosilane[16] afforded **6** in 81% yield which could be further converted to **7** under standard conditions (*n*-BuLi, −78 °C, ICH_2CH_2I). From each of these intermediates two tetra-halo binaphthyls, **5** and **9** from **6**, as well as **8** and **10** from **7** could be synthesized as outlined in Scheme 2. While for a $Me_3Si{\rightarrow}I$ exchange[17] a standard protocol was applied the corresponding $Me_3Si{\rightarrow}Br$ transformation was best performed with NBS in acetonitrile (Scheme 2).[18]

To demonstrate the versatility of tetrahalogenids as synthetic key intermediates some subsequent transformations were performed as outlined in Schemes 3 and 4. The Suzuki–Miyaura coupling[19] of **9** with phenyl boronic acid afforded selectively **14** while arylation with 2-bromoanisole yielded a mixture of three interconverting rotamers of **17** in fair yield (coalescence of OMe groups in ^{1}H NMR, 400 MHz at ca. 315 K). No coupling products **18** and **19** were isolated with 2-bromo-furane and 2-bromo-thiophene boronic acid under similar conditions. Only when applying more harsh conditions (microwave heating, 120 °C, 3 days) **18** and **19** were formed in low yield (12% and 61%, respectively). Subsequent bromide-lithio exchange in **9** and treatment with PhSSPh, CO_2, DMF, and ICH_2CH_2I led to **11**, **12** (isolated as methylester), **13**, and **15**, respectively.

Palladium-catalyzed cyanation (Scheme 4) gave the dicyano compound **20** while enforcing conditions furnished 2,2′,3,3′-tetracyano-1,1′-binaphthyl **21** albeit in moderate yield. More straightforward was the reaction from tetraiodide **8** (74% of **21**). Regioisomers **9** and **10** were also found to be suitable substrates for a site selective Sonogashira coupling with phenylacetylene to give **22** and **23** although in very different yields (85% vs 7%) reflecting the steric congestion in **23**. An attempted introduction of diphenylphosphino groups into **14** failed (*n*-BuLi, −78 °C, $ClPPh_2$). As the only isolable product the yellow tetraarylphosphonium salt **16** was obtained (89%) as a crystalline compound with intensive green-yellow fluorescence. Its solid-state structure was determined.

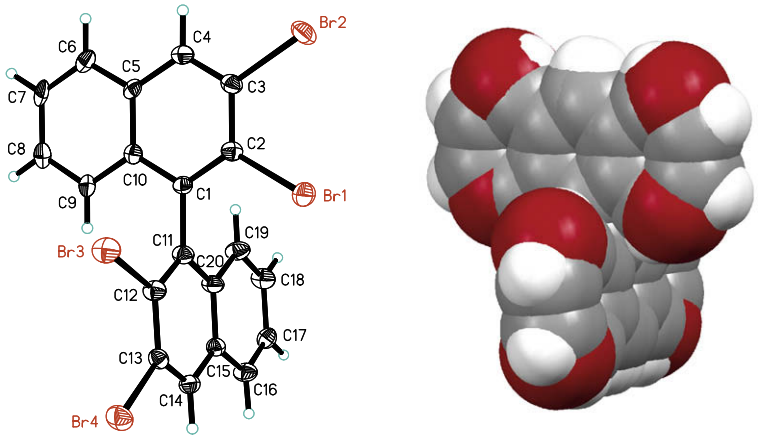


Figure 2. Molecular structure of **5** in solid state. Left: ORTEP representation of a molecule with 50% displacement ellipsoids. Right: Superposition of an *R*-configured molecule and a *S*-configured molecule in space filling representation was encountered statistically in solid state due to the partial orientation disorder of the naphthyl moieties; Br red, C grey, H white; a related situation was encountered with the 2,2′-dibromo-3,3′-dicyano-compound **20**, see text.

Another key intermediate was diboronic acid **24** that was similarly synthesized as **6** from **4** (71% yield, Scheme 5). Oxidation of **24** with H_2O_2 furnished diphenol **25** (76%), Suzuki–Miyaura coupling with 2-bromopyridine yielded **26** in moderate yield (43%).

Crystallographic investigations: Simple 1,1′-binaphthyl derivatives other than those based on 2,2′-dihydroxy-1,1′-binaphthyl have been explored scarcely by crystallography. Therefore it was considered rewarding to study some representatives of the new compound library by X-ray crystal structure determinations. The selection of compounds for this purpose was in part dictated by crystallization behavior. Thus, the key compound **14** resisted all efforts to obtain crystals of sufficient size. Finally following compounds were studied: **5**, **20**, **11**, **22**, and the phosphonium salt **16**. Crystallographic details are reported in the Supplementary data. The 2,2′,3,3′-tetrabromo-compound **5** crystallized from DMF as a solvate of monoclinic symmetry, space group $P2_1/n$, with the 1,1′-binaphthyl moiety in general position (Fig. 2) showing normal bond lengths and angles and a naphthyl–naphthyl angle of 88.1(1)° (defined as interplanar angle between the least-squares planes of the two naphthyl moieties). Interestingly, the structure determination revealed the presence of significant disorder by which the Br atoms and the terminal benzenes of the naphthyl groups interchanged positions for about 10% of all molecules (1st naphthyl 13%, 2nd naphthyl 7% orientation reversal). As shown in Figure ure 2, the two Br atoms of each naphthyl moiety have a similar space requirement as the terminal benzene ring at the opposite side. In the lack of strongly directing intermolecular forces such as hydrogen bonds, the crystal lattice of **5** is partly tolerant and can take up a certain amount of *S*-configured molecules in sites designed for *R*-configured molecules and vice versa.[20]

This conclusion is supported by the observation that also 2,2′-dibromo-3,3′-dicyano-compound **20**, which crystallized without solvent in a lattice of monoclinic symmetry, space group $C2/c$ (different from **5**), showed the same kind of *R*/*S*-tolerance, albeit at a lower level: only 8.8% of one naphthyl moiety is in reverse orientation, whereas the second naphthyl moiety is practically ordered (misorientation < 2%). This situation changes of course as soon as substituents in the 2,2′- and/or 3,3′-positions of the binaphthyl core become large enough to inhibit false naphthyl orientation, as is the case with the phenylsulfanyl-phenyl compound **11** or the bromo phenylethinyl compound **22** (Fig. 3). In compound **11**, which crystallizes in the triclinic space group $P\bar{1}$, the molecule adopts a conformation that is nearly C_2-symmetric and shows a naphthyl–naphthyl angle of 73.89(2)°. In compound **22**, which crystallizes in the monoclinic space group $P2_1/n$, the binaphthyl moiety exhibits a naphthyl–naphthyl angle of 89.79(5)° and an intramolecular Br···Br distance of 3.973(1) Å, by 0.3 Å larger than two van der Waals radii of Br (Fig. 3).

The phosphonium bromide **16**, which crystallized as the monoclinic solvate **16**·2$CHCl_3$, deviates most significantly in geometry from all previous compounds (Fig. 4). Because of the bridging phosphorus the naphthyl–naphthyl angle is low, 42.0(1)°, and both naphthyl moieties are very distinctly bent and twisted in order to achieve an acceptable peri-hydrogen contact (H9···H19 = 2.32 Å). Therefore, the torsion angle C2–C1–C11–C12 = 24.0(4)° differs considerably from the naphthyl-naphthyl interplanar angle. Because of a sterical congestion between the four phenyl substituents of **16** the bond angles around phosphorus deviate distinctly from those of an ideal tetrahedron (C–P–C angles from 94.1° to 118.8°), but the molecule of **16** approaches a non-crystallographic C_2-symmetry quite well.

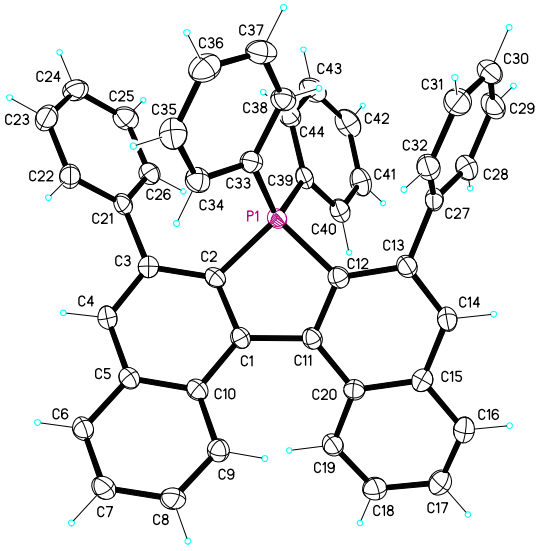


Figure 4. Molecular structure of **16**·2$CHCl_3$ in the solid state showing 50% displacement ellipsoids. Bromide and $CHCl_3$ omitted for clarity. Selected bond distances and angles (Å, °): P1–C1 1.797(2), P1–C11 1.794(2), P1–C33 1.793(3), P1–C39 1.791(2); C2–P1–C12 94.1(1), P1–C2–C1 107.6(2), P1–C12–C11 107.9(2), C2–C1–C11 113.4(2), C12–C11–C1 112.6(2), C2–P1–C33 107.9(1), C2–P1–C39 118.8(1), C12–P1–C33 117.6(1), C12–P1–C39 106.0(1), C33–P1–C39 111.7(1).

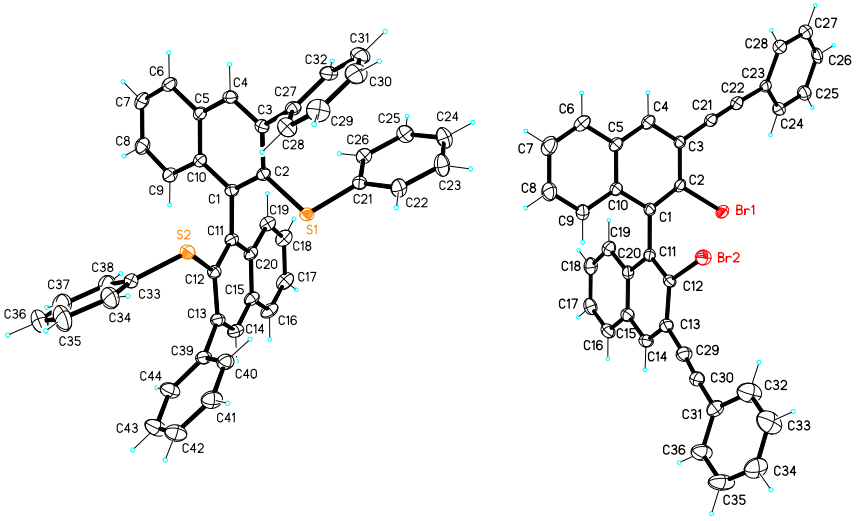


Figure 3. Molecular structure of **11** (left) and **22** (right) in the solid state showing 50% displacement ellipsoids.

In summary we developed a short and high yielding path to four 2,2′,3,3′-tetrahalo-1,1′-binaphthyls and demonstrated their use as flexible precursors for regioselective access to various tetrasubstituted binaphthyl derivatives.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.008.

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20. *Note:* While all compounds of the present study were racemates, this observation has a consequence for enantiomerically enriched material, which cannot be expected to be efficiently purified from the subordinate enantiomer by fractional crystallization because of the partial tolerance against molecules of the antipode.