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F_8BINOL, an Electronically Perturbed Version of BINOL with Remarkable Configurational Stability

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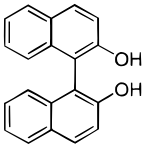
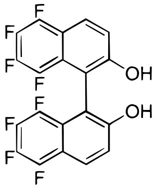
ABSTRACT



BINOL (1)



F_8BINOL (2)

Substitution of hydrogens by fluorines at the 5, 5′, 6, 6′, 7, 7′, 8, and 8′ positions of BINOL strongly affects distribution of electron density within the biaryl skeleton but has a very small influence on the torsion angle. The most important consequence of this structural alteration is the dramatic increase in configurational stability of homochiral F_8BINOL.

Modern asymmetric synthesis demands new and improved catalytic transformations. While many important discoveries in this area are due to serendipity, understanding the balance of steric and electronic factors is required in order to fine tune a catalyst to achieve optimal rate and selectivity in a particular reaction. A lot of research in recent years has been devoted to the development of chiral ligands. Among these, BINOL (**1**) and related molecules with axial chirality have found wide utility in asymmetric catalysis.[1] Over the years, several modifications of the BINOL skeleton aimed at changing its steric as well as electronic properties have been reported.[2] Thus, partially hydrogenated BINOL was used in enantioselective alkylation of aldehydes,[2a] conjugate addition of diethylzinc to cyclic enones,[2b] and ring opening of epoxides.[2c] Incorporation of bromine atoms at the 6 and 6′ positions of **1**, rather remote from the catalytic site, was shown to increase the enantioselectivity of the corresponding titanium catalysts in glyoxolate−ene reactions.[2d] Bulky triarylsilyl groups at the 3 and 3′ positions of **1** led to increased levels of enantiofacial discrimination of prochiral aldehydes in asymmetric Diels−Alder reactions.[2e] 3,3′-Dinitrooctahydrobinaphthol was applied in titanium-catalyzed asymmetric oxidation of methyl *p*-tolyl sulfide.[2f]

In this Letter we report our efforts in designing a new class of chiral polyfluoroaryl ligands based on **1**. We reasoned that substitution of hydrogens by fluorines at the 5, 5′, 6, 6′, 7, 7′, 8, and 8′ positions of **1** should induce considerable electronic perturbation of the aromatic system in the resulting 5,5′,6,6′,7,7′,8,8′-octafluoro-2,2′-dihydroxy-1,1′-binaphthyl (F_8BINOL, **2**). Figure 1 features a comparison of electrostatic potential surfaces (AM1) of **1** and **2** and reveals a noticeable difference in the distribution of electron density. The electron-deficient nature of the aromatic rings should raise the oxidative stability of **2** compared to **1** as

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(1) Noyori, R *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(2) (a) Chan, A. S. C.; Zhang, F. Y.; Yip, C. W. *J. Am. Chem. Soc.* **1997**, *119*, 4080. (b) Zhang, F. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179. (c) Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H. G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223. (d) Terada, M.; Motoyama, Y.; Mikami, K. *Tetrahedron Lett.* **1994**, *35*, 6693. (e) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (f) Reetz, M. T.; Merk, C.; Naberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5273.

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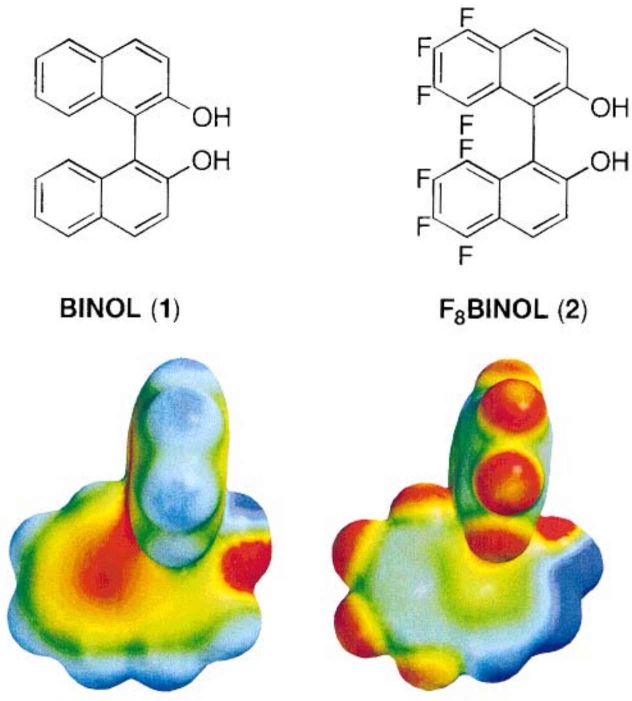
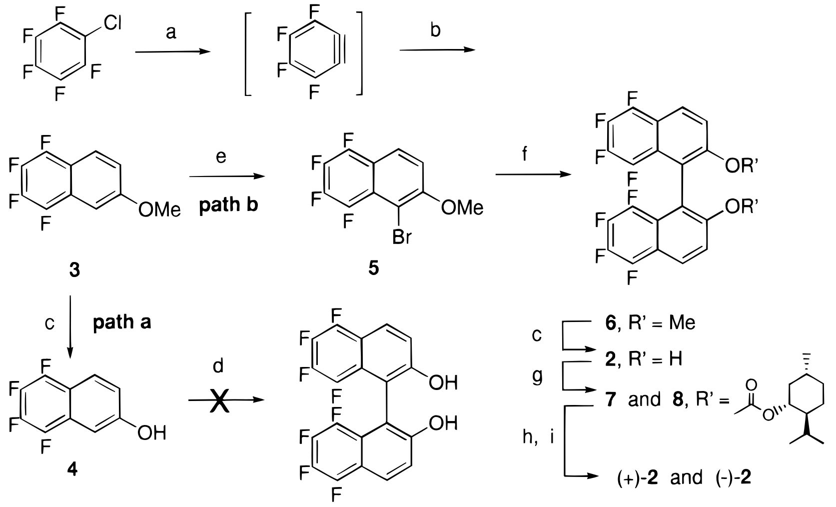


Figure 1. Electrostatic potential surfaces (AM1) of BINOL (**1**) and F$_8$BINOL (**2**) obtained with Spartan Pro. The color code spans from −20 (red) to +20 kcal/mol (blue).

well as increase the acidity of the ring-bound hydroxyl groups. This could translate into modulated binding to metals as well as reactants in the F$_8$BINOL-mediated processes. Furthermore, since the fluorine atom is only 0.27 Å larger than the hydrogen atom,[3] one could anticipate a small increase in the barrier to axial torsion upon octafluorination.[4] We have found that such a combination of steric and electronic alterations in fact leads to a *dramatic* increase in configurational stability of homochiral **2** with electronic effects playing a decisive role.

The racemic form of **2** was prepared according to Scheme 1. Tetrafluorobenzyne, generated by treating a hexane solution of chloropentafluorobenzene with *n*-butyllithium at −15 °C, was reacted with 3-methoxythiophene[5] in a Diels−Alder reaction. Upon in situ extrusion of sulfur, 2-methoxy-5,6,7,8-tetrafluoronaphthalene (**3**) was obtained in 52% yield.[6] 5,6,7,8-Tetrafluoro-2-naphthol (**4**), prepared from **3** by demethylation with BBr_3 in dichloromethane, did not undergo the $FeCl_3$-catalyzed oxidative coupling (Scheme 1, path a) commonly used for the preparation of **1** from 2-naphthol.[7] The relatively high oxidation potential of **4** (1.84 V vs Ag/AgCl) is a likely reason for the observed lack of reactivity. Therefore, we chose a reductive route (Scheme 1, path b) through the intermediacy of the 1-brominated derivative **5**, prepared in 88% yield by treating **3** with *N*-bromosuccinimide in acetonitrile. The Ullmann coupling of **5**, facilitated by the presence of aromatic fluorines, gave the desired bis(methoxy) product **6** in 85% yield. Demethylation of **6** with BBr_3 furnished **2** in 90% yield. Following recrystallization from methanol/water, pure **2** was obtained as white solid (mp 235 °C), soluble in common organic solvents. After several unsuccessful attempts to resolve **2**, we were able to fractionally crystallize the diastereomeric bis[(−)-menthoxycarbonyl] derivatives **7** and **8**, obtained by reacting racemic **2** with excess (−)-menthyl chloroformate in quantitative yield.[8] Saponification of each diastereomer with LiOH in THF followed by extraction with diethyl ether afforded (−)-F$_8$BINOL ($[\alpha]^{25}_D$ −40°, c = 1, THF) and (+)-F$_8$BINOL ($[\alpha]^{21}_D$ +39°, c = 1, THF), respectively. The enantiomeric excess, determined by chiral HPLC (Chiralpak AD column, hexane/2-propanol 9:1, 1 mL/min), was found

Scheme 1[a]

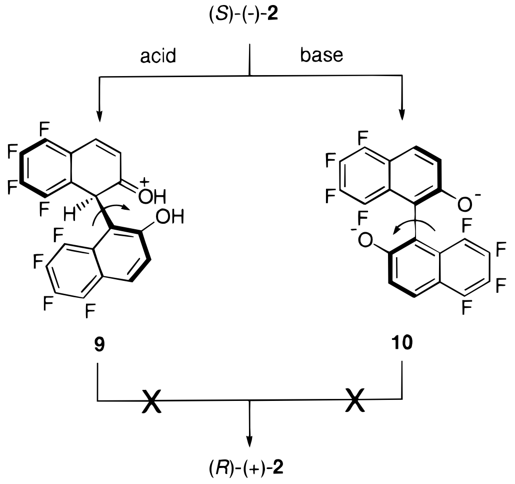


[a] Key: (a) *n*-BuLi, hexanes, −15 °C; (b) 3-methoxythiophene, −15 °C to rt, 12 h; (c) BBr_3, CH_2Cl_2, rt, 10 h; (d) $FeCl_3$, H_2O, reflux; (e) NBS, CH_3CN, rt, 1 h; (f) Cu°, 175 °C, 24 h; (g) (−)-menthyl chloroformate, pyridine, CH_2Cl_2, rt, 2 h; (h) fractional crystallization (MeOH); (i) LiOH, THF/H_2O, rt, 2 h.

to be >99% in each case. The (*S*)-absolute configuration of the (−) enantiomer was determined by the X-ray analysis of its bis[(−)-menthoxycarbonyl] derivative. Notably, the same relationship exists between the absolute configuration and the sign of optical rotation of **1**.[8]

To elucidate the effect of fluorine substitution on atropisomerism and configurational stability of **2**, we investigated racemization of its *S*-enantiomer. The racemization of homochiral **1** in both acidic and basic media is well known.[9] The acid-promoted process is believed to proceed through protonation of the C(1) carbon atom of the binaphthyl ring followed by rotation of the naphthyl moiety around the resulting C(sp^2)−C(sp^3) bond. Besides the steric influence on the rotation barrier,[4] fluorine substitution was found to minimize the acid-promoted racemization, presumably due to destabilization of the cationic intermediate **9** (Scheme 2).

Scheme 2



We have observed a dramatic increase in configurational stability of (−)-**2** under acidic conditions: when subjected to reflux in a 1:1 mixture of THF and 13% aqueous HCl, *no racemization* was detected by chiral HPLC after 24 h. In comparison, (−)-**1** was racemized under these conditions (from 99% to 13% ee, determined using Chiralpak AS column, hexane/2-propanol 9:1, 1 mL/min).

In the case of base-induced racemization, the enantiomeric excess of (−)-**1** decreased from 99% to 0% after 12 h in boiling 5% aqueous NaOH. It was proposed earlier that this path proceeds through deprotonation of the hydroxyl groups leading to an anionic intermediate that undergoes rotation around the C(1)−C(1′) bond.[9] We have found that the pK_a' of the hydroxyl group in **1** decreases by 1 unit upon fluorine substitution of the aromatic scaffold (**1**, pK_a' 10.28; **2**, pK_a' 9.29). Thus, we expected (−)-**2** to racemize at least as readily as (−)-**1** under basic conditions. However, (−)-**2** dissolved in aqueous NaOH solution and remained configurationally stable at room temperature. When the temperature was raised to 100 °C, *no racemization* was observed after 24 h, once again indicating configurational stability.[10]

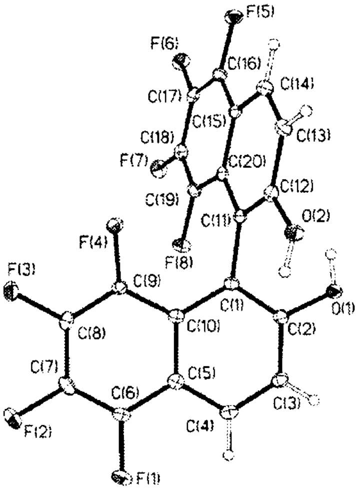


Figure 2. ORTEP diagram of *R*-(+)-**2**.

The molecular structure of homochiral **2**, determined by X-ray analysis, is shown in Figure 2.[11] The torsion angle between the tetrafluoronaphthol planes in *R*-(−)-**2** (79.7°) is only 1.4° larger than in the parent protio derivative *R*-(−)-**1** (78.3°).[12] Thus, fluorination appears to have a fairly insignificant steric influence on the torsion angle and the observed effect on the structural integrity of **2** must be primarily electronic in nature. The desired conformational flexibility,

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(3) Smart, B. E. In *Organofluorine compounds: Principles and Commercial Applications*; Banks, R. E., Ed.; Plenum Press: New York, 1994; Chapter 3.

(4) (a) Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99 and references therein. (b) Soloshonok, V. A. *Enantiocontrolled Synthesis of Fluoroorganic Compounds*; Wiley: New York, 1999. (c) García Martínez, A.; Osío Barcina, J.; de Fresno Cerezo, A.; Rivas, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 673. (d) Tang, T.-H.; Nowakowska, M.; Guillet, J. E.; Csizmadia, I. G. *J. Mol. Struct.* **1991**, *232*, 133.

(5) Gronowitz, S. *Ark. Kemi* **1958**, *12*, 239.

(6) The side reaction between tetrafluorobenzyne (2 equiv) and sulfur to give octafluorodibenzothiophene accounts for the moderate yield.

(7) Pummerer, R.; Prell, E.; Rieche, A. *Ber.* **1926**, *59B*, 2159.

(8) For resolution of BINOL through separation of the bis[(−)-menthoxycarbonyl] derivatives, see: Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.* **1995**, *60*, 6599.

(9) Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173.

(10) Partial decomposition due to nucleophilic aromatic substitution of fluorines by hydroxyl groups was observed under these conditions: Yudin, A. K.; Martyn, L. J. P. Unpublished data.

(11) Crystal data: **2** $C_{20}H_6F_8O_2$, $M_r = 430.25$, orthorhombic, $C222_1$, $a = 7.9676(2)$, $b = 13.3257(4)$, and $c = 29.0028(7)$ Å, $V = 3079.34(14)$ Å^3, $Z = 8$, $D_x = 1.856$ g cm^{-3}, λ(Mo Kα) = 0.71073 Å, μ(Mo Kα) = 0.185 mm^{-1}, $F(000) = 1712$, $T = 100.0(1)$ K, 11618 reflections collected, $R(F) = 0.0564$, $R(wF^2) = 0.0749$ for all 3508 independent reflections, [$R(F) = 0.0353$, $R(wF^2) = 0.0707$ for 2644 data with $F > 4\sigma(F_o)$]. Data were collected on a Nonius Kappa-CCD. Data were integrated and scaled using the Denzo-SMN package (Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307). The structure was solved and refined using SHELXTL V5.0. (Sheldrick, G. M. SHELXTL/PC V5.1 Users Manual (1997), Bruker Analytical X-ray Systems, Madison, WI) All non-hydrogen atoms were refined with anisotropic parameters. Hydrogen atoms were included in geometric positions and treated as riding atoms.

(12) Toda, F.; Tanaka, K.; Miyamoto, H.; Koshima, H.; Miyahara, I.; Hirotsu, K. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1877.

one of the most important characteristics of BINOL allowing it to coordinate a wide variety of metals,[1] should be preserved in **2**.

In summary, fluorine substitution confers remarkable configurational stability on homochiral 5,5′,6,6′,7,7′,8,8′-octafluoro-2,2′-dihydroxy-1,1′-binaphthyl. At the same time, a 10-fold increase in acidity of the ring-bound hydroxyl groups takes place. Similar trends should operate for other substituents at the 2 and 2′ positions, eventually providing robust catalysts with modulated reactivities. Reactions that involve highly acidic and/or oxidative conditions[13] under which **1** is configurationally or structurally unstable seem to be particularly attractive. Most importantly, both enantiomers of **2** can be readily prepared from commercially available starting materials. The documented minimal steric influence of fluorine substitution coupled with its significant electronic effect on axial chirality may become a general paradigm for the design of new and improved ligands.[14,15] We are currently exploring the scope of the F_8BINOL-derived asymmetric catalysts as well as other applications of the octafluorobinaphthyl scaffold.

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Supporting Information Available: Experimental procedures and full characterization of compounds **2**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] The oxidation potential of F_8BINOL (2.07V vs Ag/AgCl) is 0.6 V more positive than that of BINOL (1.47 V vs Ag/AgCl).

[14] For studies related to electronic effects of substituents on chiral ligands in asymmetric catalysis, see: (a) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948. (b) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325. (c) Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 931.

[15] Jendralla, H.; Li, C. H.; Paulus, E. *Tetrahedron: Asymmetry* **1994**, *5*, 1297.