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Regioselective Substitution of Fluorine in F_8BINOL as a Versatile Route to New Ligands with Axial Chirality

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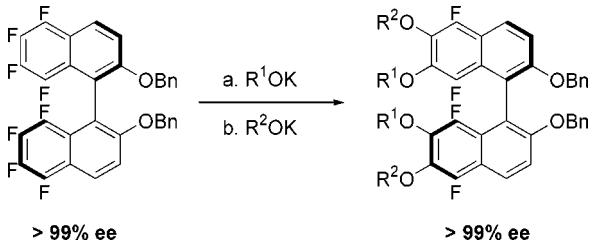
ABSTRACT



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Nucleophilic substitution of aromatic fluorine in F_8BINOL offers the possibility of selectively introducing a variety of substituents at the 6, 6′, 7, and 7′ positions. The configurational integrity of the homochiral precursors is maintained under the conditions described, allowing one to carry out these modification protocols on a microscale without the need for subsequent resolution steps. The resulting chiral ligands have been investigated as precursors to new asymmetric catalysts.

Parallel synthesis and combinatorial chemistry have had a major impact on homogeneous catalysis.[1] In particular, the structural variation of chiral ligands using high-throughput methods provides a means to efficiently fine-tune the rate and selectivity of the corresponding asymmetric catalysts.[2] This is commonly achieved by generating libraries of structurally related ligands using either solution- or solid-phase synthesis methods followed by screening of the derived catalysts.[2] The ligands that are prepared from several components offer the possibility of straightforward introduction of diverse substituents by choosing different building blocks at the synthesis stage. Alternatively, direct modification of the ligand can introduce elements of chemical diversity into its scaffold. The latter approach has not been widely utilized in parallel synthesis. In this regard, mild and high-yielding reactions that install substituents into selected positions of valuable chiral ligands are in high demand.

Derivatives of 2,2′-binaphthol (BINOL, **1**) are among the most widely used chiral ligands in asymmetric catalysis.[3] A

(1) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2494.

(2) For examples, see: (a) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712. (b) Gilbertson, S. R.; Wang, X. *Tetrahedron Lett.* **1996**, *37*, 6475. (c) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 220. (d) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668. (e) VidalFerran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970. (f) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885. (g) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1988**, *110*, 4901. (h) Gao, X.; Kagan, H. B. *Chirality* **1998**, *10*, 120. (i) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63*, 5312. (j) Taylor, S. J.; Morken, J. P. *Science* **1998**, *280*, 267. (k) Boussie, T. R.; Coutard, C.; Turner, H. W.; Murphy, V.; Powers, T. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3272. (l) Burgess, K.; Porte, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 2465. (m) Reetz, M. T.; Becker, M. H.; Kuhling, K. M.; Holzwarth, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2647. (n) Porte, A. M.; Reibenspiess, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180. (o) Matsuo, J.; Odashima, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 345. (p) Reetz, M. T.; Becker, M. H.; Klein, H. W.; Stockigt, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1758. (q) Francis, M. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 937. (r) LaPointe, A. M. *J. Comb. Chem.* **1999**, *1*, 101. (s) Kobayashi, S.; Kusakabe, K.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225. (t) Kobayashi, S. *Curr. Opin. Chem. Biol.* **2000**, *4*, 338. (u) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279.

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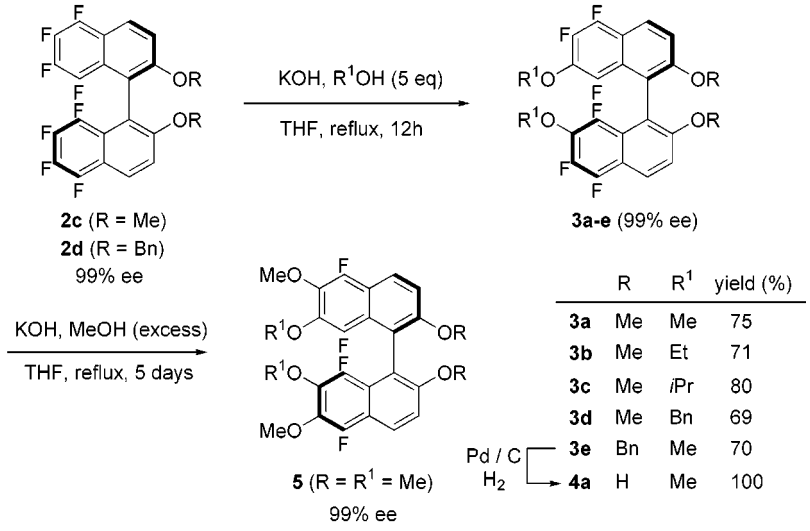
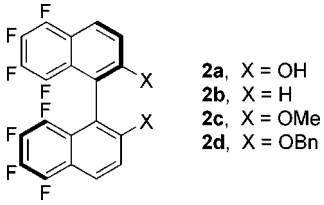
Scheme 1



number of modifications of the BINOL scaffold aimed at improving catalytic performance have been documented.[3] We recently reported the synthesis and first catalytic applications of F_8BINOL (**2a**), an isostere of BINOL with modulated



coordination preferences and remarkable configurational stability under a wide range of reaction conditions.[4] The application of **2a** in titanium-catalyzed asymmetric sulfide oxidation with organic hydroperoxides revealed increased activity of the derived catalyst compared to that of BINOL.[5] The opposite sense of chiral induction in asymmetric sulfoxidation was observed for BINOL and F_8BINOL of the same absolute configuration, indicating significant difference in the nature of the catalytically active species obtained from these two ligands. A related goal of our research is to develop mild routes to diversely functionalized ligands with axial chirality based on the electronically perturbed polyfluorobinaphthol scaffold. The challenge of improving catalytic efficiency can be approached by a ligand modification reaction that proceeds in high yield on a sub-millimole scale without concomitant racemization. A useful process should accomplish one (or both) of the following goals: (a) introduce substituents into positions that have electronic influence over the hydroxyl groups (e.g., 6 and 6′) or (b) introduce substituents into the positions that modulate steric effects (e.g., 7,7′ or 3,3′). If these requirements are met, rapid generation of diverse catalyst libraries should become straightforward. The present Letter highlights the possibility of selective introduction of a variety of substituents at the 7 and 7′ positions via nucleophilic substitution of fluorine. The resulting chiral ligands have been investigated as precursors to new titanium-based catalysts. Worthy of note, the 7 and 7′ positions cannot be accessed through direct electrophilic modification routes that are commonly used in order to modify BINOL. Most importantly, the configurational integrity of the homochiral precursors is not perturbed under the conditions described herein. More forceful conditions allow one to introduce substituents into the 6 and 6′ positions.

Nucleophilic displacement of aromatic fluorine is a well-known reaction with a wide scope and utility.[6] A variety of nucleophiles are known to participate in this chemistry. When 5,5′,6,6′,7,7′,8,8′-octafluoro-1,1′-binaphthyl (**2b**) was subjected to the substitution protocol with sodium methoxide, the nucleophilic displacement of fluorine did take place but a complicated mixture of poly(methoxylated) products signaled lack of regioselectivity. Gratifyingly, the presence of the methoxy substituents at the 2 and 2′ positions in bis(methyl) ether **2c** was sufficient to secure high regioselectivity of the methoxylation reaction (Scheme 1). Double substitution resulted in the 7,7′-bis(methoxy) product **3a** in

(3) For representative applications of BINOL derivatives in asymmetric catalysis, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (c) Rosini, C.; Franzini, L.; Rafaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (d) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (e) Kitajima, H.; Katsuki, T. *Synlett* **1996**, 568. (f) Reetz, M. T.; Merk, C.; Naberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5273. (g) Chan, A. S. C.; Zhang, F. Y.; Yip, C. W. *J. Am. Chem. Soc.* **1997**, *119*, 4080. (h) Morita, T.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1445. (i) Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223. (j) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220. (k) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2000**, *56*, 351. (l) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403.

(4) Yudin, A. K.; Martyn, L. J. P.; Pandiaraju, S.; Zheng, J.; Lough, A. *Org. Lett.* **2000**, *2*, 41.

(5) Martyn, L. J. P.; Pandiaraju, S.; Yudin, A. K. *J. Organomet. Chem.* **2000**, *603*, 98.

(6) Welch, J. T.; Peters, D.; Miethchen, R.; Il'chenko, A. Y.; Rüdiger, S.; Podlech, J. In *Organo-fluorine Compounds*, 4th ed.; Baasner, B., Hagemann, H., Tatlow, J. C., Eds.; Georg Thieme Verlag: Stuttgart, 2000; Vol. E10b/Part 2, pp 293−459.

good chemical yield and with high regioselectivity which was elucidated by single-crystal X-ray analysis (Figure 1).[7]

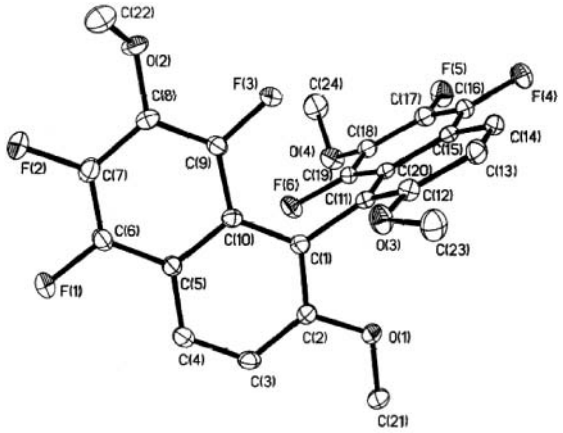


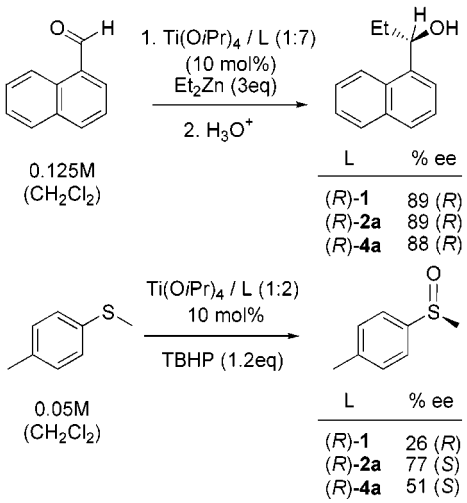
Figure 1. Molecular structure of **3a**.

This process should enable one to select appropriate nucleophiles in order to modulate steric requirements of the F_nBINOL system by remote substitution. The major byproduct of this process is the 6,6′,7,7′-tetramethoxylated derivative. In fact, subjecting **3a** to further methoxylation afforded compound **5** in 32% yield. This reaction was slower than the first one and required 5 days to completion. Preliminary results indicate that sulfur- and nitrogen-based nucleophiles also participate in this substitution chemistry, albeit in lower yields.

Other alkoxy nucleophiles behaved in a manner similar to that of sodium methoxide (Scheme 1). However, subsequent demethylation with boron tribromide suffered from poor chemoselectivity despite the anticipated reactivity difference between the two halves of the aromatic system in **3a** due to the electron-poor character of the fluorinated ring. Thus, it is essential to use the bis(benzyl) ether **2d** which benefits from selective deprotection via hydrogenation and leads to ligand **4a** via **3e**. The 7,7′-bis(ethoxy) and 7,7′-bis(isopropoxy) ligands **4b** and **4c** were obtained from **2d** in 79% and 77% yields, respectively (see Supporting Information). Most importantly, no racemization was observed in the course of any of these substitution processes (monitored by chiral HPLC) when enantiomerically pure precursors were used in the alkoxylation reaction. Similar to the case of **2a**, we attribute this configurational stability to the electronic effect of aromatic fluorine.[4]

The utility of the poly(alkoxylated) ligands in asymmetric catalysis was examined using diethylzinc addition to aldehydes (Scheme 2).[8] We have observed high levels of

Scheme 2



enantioselectivity in titanium-catalyzed addition of diethylzinc to aldehydes using the hexafluoro derivative **4a** under the conditions where formation of the monomeric catalyst precursors of 1:1 composition is favored (7:1 Ti/L ratio).[8c] The enantioselectivity of this process was found to be the same as in the case of F_8BINOL, indicating that steric effects at remote positions are relatively insignificant in this case. On the other hand, catalytic asymmetric oxidation of methyl *p*-tolyl sulfide revealed a significant difference between **2a** and **4a**. The enantioselectivity with the **4a**/Ti catalyst was only 51% (F_8BINOL: 77%ee) with the same sense of chiral induction.[9] Despite this unsatisfactory result, it is clear that bis-substitution may lead to *different* catalytic activity, which is in fact encouraging and warrants the need for high-throughput reaction screening protocols with the catalysts produced using the outlined chemistry. Our current efforts are directed toward other catalyst systems which are sensitive to steric effects at remote positions.

In summary, the outlined chemistry should provide a convenient method for introducing diverse substituents into the 7 and 7′ positions which should in turn facilitate positional scanning protocols for F_8BINOL as well as help place a binding site in that region. It should now become possible to "fine-tune" sterics through 7 and 7′ substitution. Another potentially useful extension of this methodology is

(7) Crystal Data for **1** $C_{24}H_{16}O_4F_6$, M = 482.37, orthorhombic, space group *Pbca*, (No. 61) T = 100(1) K, a = 8.3124(2), b = 16.8836(3), c = 28.9812(6) Å, V = 4067.32(15)(2) Å^3, Z = 8, D_c = 1.575 g cm^{-3}, μ(Mo Kα) = 0.143 mm^{-1}, 31743 reflections collected, R1 = 0.0696, wR2 = 0.1187 for all 3584 independent reflections, [R1 = 0.0461, wR2 = 0.1074 for 2694 data with $F > 4\sigma(F_o)$]. The data that were collected on a Nonius Kappa-CCD were integrated and scaled using the DENZO-SMN package (Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307−326). The structures were solved and refined using SHELXTL V5.0 (Sheldrick, G. M. SHELXTL\PC V5.1, Bruker Analytical X-ray Systems, Madison, WI, 1997).

(8) For examples, see: (a) Chow, H. F.; Ng, M. K. *Tetrahedron: Asymmetry* **1996**, *7*, 2251. (b) Ng, M.-K.; Chow, H.-F. *Tetrahedron Lett.* **1996**, *37*, 2979. (c) Zhang, F. Y.; Yip, C. W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585. (d) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233. (e) Yang, X. W.; Sheng, J. H.; Da, C. S.; Wang, H. S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295. (f) Yang, X. W.; Su, W.; Liu, D. X.; Wang, H. S.; Shen, J. H.; Da, C. S.; Wang, R.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 3511. (g) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **2000**, *41*, 57.

(9) Studies aimed at understanding the effect of remote substitution on kinetic resolution of sulfoxides in this system are in progress.

straightforward attachment of F_8BINOL-derived catalysts to solid support using the bis(nucleophile) linker strategy. Screening of a variety of metals should enable one to rigorously and quickly establish the structure/reactivity relationships for the resulting catalyst libraries. Configurational integrity of the ligand core in the course of the substitution process is the key advantage that enables one to run these reactions on a sub-millimole scale with no requirement for a subsequent resolution step, impossible to carry out in a high-throughput fashion. The outlined chemistry should also find use in "noncatalytic" applications of the binaphthol scaffold, such as molecular recognition and design of novel materials.[7b]

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Supporting Information Available: Experimental procedures and characterization of compounds **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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