JOC*Note*

Synthesis, Structure, and Metal Complexation Behavior of a New Type of Functionalized Chiral Phenanthroline Derivative

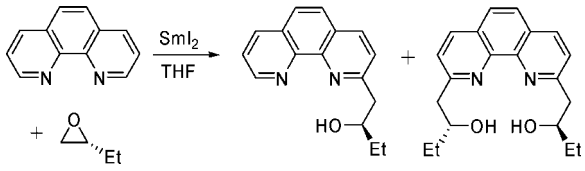
Jacob M. Plummer,[†] Jeremy A. Weitgenant,[†] Bruce C. Noll,[†] Joseph W. Lauher,[‡] Olaf Wiest,[†] and Paul Helquist*,[†]

Department of Chemistry and Biochemistry and the Notre Dame Cancer Center, 251 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556, and Department of Chemistry, State University of New York, Stony Brook, New York 11794

phelquis@nd.edu

Received December 11, 2007

SmI_2 serves as an effective promoter for the coupling of 1,10-



phenanthroline with an epoxide to generate a new class of chiral, functionalized ligands that readily form complexes with metals. Structural studies of the resulting phenanthroline derivative and two of its metal complexes are reported.

The development of new chiral ligands for use in metal-catalyzed enantioselective reactions remains an important need in synthetic organic chemistry. Among the many classes of well-established ligands are those that provide two nitrogen atoms for coordination to a variety of metals.[1] Examples are numerous, a few of which include 2,2′-bipyridines, 1,10-phenanthrolines, and bis(oxazolines). However, in many cases, the nitrogen atoms are complemented by additional coordinating sites such as hydroxyl groups. Specific examples include the popular salens (e.g., **1**),[2] bis(hydroxyalkyloxazoline) **2**,[3] functionalized bipyridine **3**,[4,5] and Schiff base **4** (Figure 1).[6]

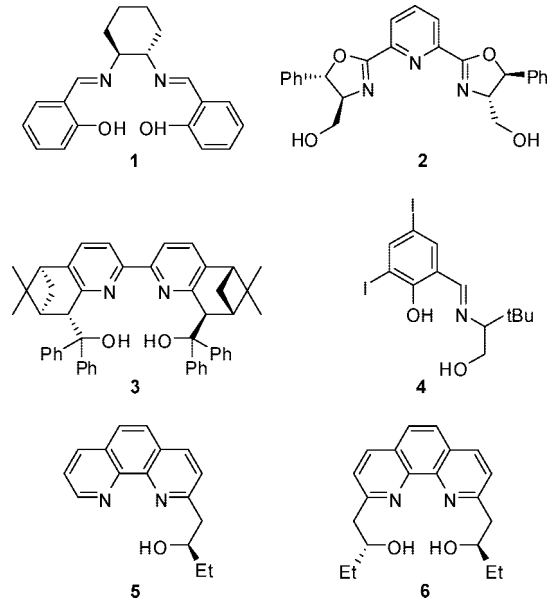


FIGURE 1. Examples of nitrogen ligands containing hydroxy groups as additional coordinating sites.

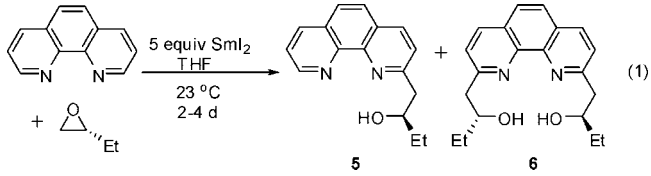
1,10-Phenanthrolines are well-known for their ability to form many useful metal complexes,[7] and their chiral derivatives have proven roles in enantioselective reactions that include ketone reductions,[8] enolate allylations,[9] oxidations,[10] and cyclopropanations[11] among others.[12] A potentially important modification of phenanthrolines to extend their utility would be the incorporation of additional coordination sites analogous to those in the previous examples **1**-**4**. However, the corresponding (hydroxyalkyl)phenanthrolines (e.g., **5** or **6**) have not seen significant previous development. Compared to some of the previous ligands, **5** or **6** would have chirality in a different proximity to the coordination sites, which may be important for designing new enantioselective catalysts. An earlier preparation of a few analogues of **5** required a multistep route.[13] We were therefore interested in developing a more direct synthesis of this new class of ligands. In this note, we are pleased to report a one-step method for the synthesis of this ligand class and structural studies of both a free ligand and two of its metal complexes to lay the groundwork for further studies of their applications.

[†] University of Notre Dame.
[‡] State University of New York.

(1) (a) Belda, O.; Moberg, C. *Coord. Chem. Rev.* **2005**, *249*, 727. (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497.
(2) (a) Baleizão, C.; Garcia, H. *Chem. Rev.* **2006**, *106*, 3987. (b) Venkataramanan, N. S.; Kuppuraj, G.; Rajagopal, S. *Coord. Chem. Rev.* **2005**, *249*, 1249. (c) Achard, T. R. J.; Clutterbuck, L. A.; North, M. *Synlett* **2005**, *12*, 1828. (d) Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6*, 123.
(3) Desimoni, G.; Faita, G.; Guala, M.; Laurenti, A.; Mella, M. *Chem.−Eur. J.* **2005**, *11*, 3816.
(4) Chen, Y.-J.; Lin, R.-X.; Chen, C. *Tetrahedron: Asymmetry* **2004**, *15*, 3561.
(5) For related bipyridines, see: (a) Ogawa, C.; Wang, N.; Boudou, M.; Azoulay, S.; Manabe, K.; Kobayashi, S. *Heterocycles* **2007**, *72*, 589. (b) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. *Org. Lett.* **2005**, *7*, 4729.
(6) Legros, J.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4225.
(7) (a) Chelucci, G.; Addis, D.; Baldino, S. *Tetrahedron Lett.* **2007**, *48*, 3359. (b) Luman, C. R.; Castellano, F. N. In *Comprehensive Coordination Chemistry II*; McCleverty, J. A., Meyer, T. J., Eds.; Elsevier: Oxford, 2004; Vol. 1, pp 25−39.
(8) Gladiali, S.; Pinna, L.; Delogu, G.; Graf, E.; Brunner, H. *Tetrahedron: Asymmetry* **1990**, *1*, 937.
(9) (a) Chelucci, G.; Pinna, G. A.; Saba, A.; Sanna, G. *J. Mol. Catal. A* **2000**, *159*, 423. (b) Meynhardt, B.; Lüning, U.; Wolff, C.; Näther, C. *Eur. J. Org. Chem.* **1999**, 2327. (c) Peña-Cabrera, E.; Norrby, P.-O.; Sjögren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299.
(10) Chelucci, G.; Loriga, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron Lett.* **2002**, *43*, 3601.
(11) Chelucci, G.; Gladiali, S.; Sanna, M. G.; Brunner, H. *Tetrahedron: Asymmetry* **2000**, *11*, 3419.
(12) (a) Schulz, E. In *Chiral Diazaligands for Asymmetric Synthesis*; Lemaire, M., Mangeney, P., Eds.; Springer: Berlin, 2005; pp 94–148. (b) Schoffers, E. *Eur. J. Org. Chem.* **2003**, 1145. (c) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129.
(13) Weitgenant, J. A.; Mortison, J. D.; Helquist, P. *Org. Lett.* **2005**, *7*, 3609.

10.1021/jo702566m CCC: $40.75
Published on Web 04/10/2008

We and others have previously demonstrated the utility of samarium diiodide[14] for effecting coupling reactions of phenanthrolines and related substrates with aldehydes and ketones.[13,15,16] On the basis of this prior experience, we hypothesized that an approach for obtaining both mono- (**5**) and bis-2-(2-hydroxyalkyl) (**6**) derivatives would be the coupling between 1,10-phenanthroline and epoxides.[17,18] To test this idea for the purpose of this initial study, we have focused on the use of readily available (*R*)-1,2-epoxybutane. The reaction was performed by combining 1,10-phenanthroline with the epoxide and SmI_2 in THF at 23 °C for between 2 and 4 d to provide both **5** and **6** (eq 1). The isolated yields varied in different runs with up to 13% of **5** as the minor product and up to 42% of **6** as the major product as one pure diastereomer. Longer run times resulted in no additional product formation as the SmI_2 appeared to be completely consumed after 4 days. Analysis of the crude products by ^{1}H NMR typically showed nearly total conversion of the 1,10-phenanthroline to **6**. Significant material loss occurred in the purification process needed to isolate pure samples of the products. To date, all attempts to employ SmI_2 catalytically by using an excess of a reducing agent such as Mischmetall[19] resulted in no product formation.



The absolute configuration of **6** follows from the X-ray studies reported below. On the other hand, when racemic 1,2-epoxybutane was employed as the substrate, the expected mixture of diastereomers was obtained in a 3:2 ratio favoring the racemic diastereomer over the meso form.

As an initial exploration of coordination properties using metals that are especially relevant for later studies of applications in catalytic reactions, the complexes **6(Cu)** and **6(Zn)** were obtained by straightforward reactions of the free ligand with $Cu(OTf)_2$and $Zn(OTf)_2$, respectively.

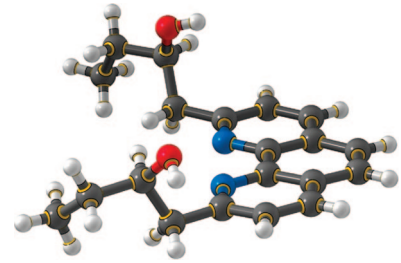


FIGURE 2. Monomer crystal structure of **6**.

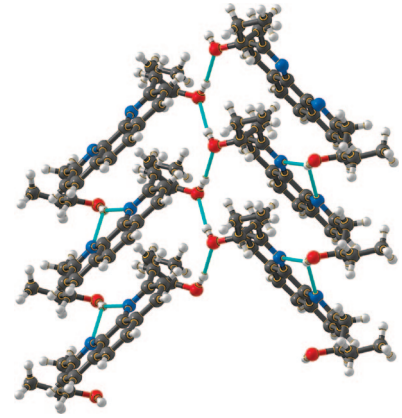


FIGURE 3. Hydroxyl group chain in **6**.

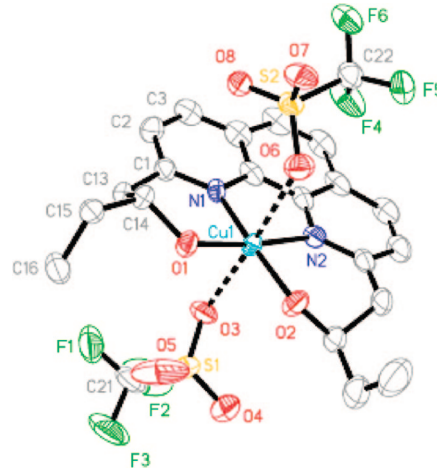


FIGURE 4. Thermal ellipsoid plot for **6(Cu)**. H-atoms and second molecule of asymmetric unit omitted for clarity. Ellipsoids drawn at 50% probability.

X-ray quality crystals were readily obtained for the free ligand and for each of these complexes. The structure solution for the ligand **6** (Figure 2) was in chiral space group $P2_12_12_1$ (No. 19). The absolute configuration could not be determined reliably. The ligand exists in the solid state as a one-dimensional α-network formed by a chain of hydrogen bonded hydroxy groups (Figure 3).

The structure solution of **6(Cu)** (Figure 4) was in chiral space group $P2_1$ (No. 4). The absolute configuration was determined from the Flack test, $x = 0.078(18)$. The asymmetric unit is comprised of two independent molecules. Pseudoinversion symmetry is broken by the pendant groups of the phenanthroline ligands. The Cu of each molecule lies in the planes of the chelating atoms. Each Cu is also coordinated to two triflates; distances are 2.442(5), Cu1−O3; 2.454(6), Cu1−O6; 2.390(5); Cu2−O11; 2.461(5), Cu2−O14.

(14) (a) Kagan, H. B. *Chem. Rev.* **2002**, *102*, 1805. (b) Williams, D. B. G.; Caddy, J.; Blann, K. *Org. Prep. Proc. Int.* **2003**, *35*, 307. (c) Berndt, M.; Gross, S.; Hoelemann, A.; Reissig, H.-U. *Synlett* **2004**, 422. (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.

(15) (a) Aulenta, F.; Berndt, M.; Brüdgam, I.; Hartl, H.; Sörgel, S.; Reißig, H.-U. *Chem.−Eur. J.* **2007**, *13*, 6047. (b) Reißig, H.-U.; Khan, F. A.; Czerwonka, R.; Dinesh, C. U.; Shaikh, A. L.; Zimmer, R. *Eur. J. Org. Chem.* **2006**, 4419. (c) Bolt, V.; Reißig, H.-U. *Eur. J. Org. Chem.* **2006**, 4989. (d) Berndt, M.; Hlobilová, I.; Reissig, H.-U. *Org. Lett.* **2004**, *6*, 957. (e) Ohno, H.; Wakayama, R.; Maeda, S.-i.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909. (f) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190. (g) Gross, S.; Reissig, H.-U. *Org. Lett.* **2003**, *5*, 4305.

(16) (a) Weitgenant, J. A.; Mortison, J. D.; O'Neill, D. J.; Mowery, B.; Puranen, A.; Helquist, P. *J. Org. Chem.* **2004**, *69*, 2809. (b) O'Neill, D. J.; Helquist, P. *Org. Lett.* **1999**, *1*, 1659.

(17) For Ti-promoted reductive couplings of epoxides, see (a) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359. (b) Chakraborty, T. K.; Samanta, R.; Das, S. *J. Org. Chem.* **2006**, *71*, 3321. (c) Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Org. Lett.* **2006**, *8*, 669. (d) Fernández-Mateos, A.; de la Nava, E. M.; Coca, G. P.; Silvo, A. R.; González, R. R. *Org. Lett.* **1999**, *1*, 607. (e) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

(18) For Sm-promoted reactions of epoxides, see: (a) Aurrecoechea, J. M.; Pérez, E. *Tetrahedron Lett.* **2003**, *44*, 3263. (b) Aurrecoechea, J. M.; Pérez, E.; Solay, M. *J. Org. Chem.* **2001**, *66*, 564. (c) Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1996**, *61*, 5885. (d) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596.

(19) Lannou, M.-I.; Hélion, F.; Namy, J.-L. *Tetrahedron* **2003**, *59*, 10551.

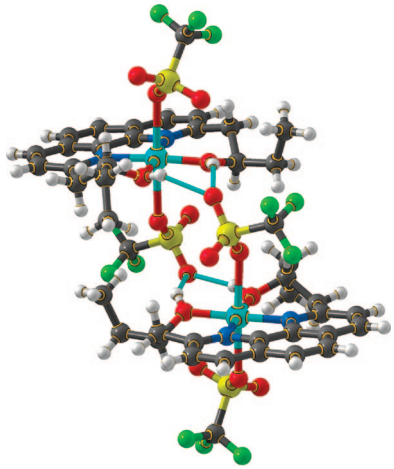


FIGURE 5. Copper H-bonded dimer **6(Cu)**.

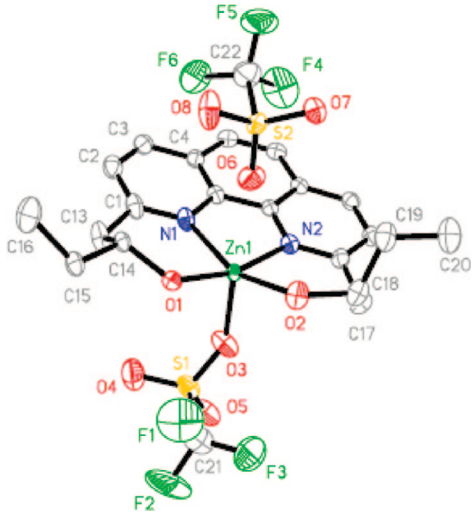


FIGURE 6. Thermal ellipsoid plot for **6(Zn)**. H-atoms and minor parts of disorder omitted for clarity. Only one of two molecules of asymmetric unit shown. Ellipsoids drawn at 50% probability.

The supramolecular chemistry of the $Cu(OTf)_2$ complex is dominated by hydrogen bonds from the coordinated hydroxyl groups to a single oxygen atom of one of the axial triflate ligands of a neighboring Cu complex (Figure 5).

The structure solution for **6(Zn)** (Figure 6) was in chiral space group *P*1 (No. 1). The absolute configuration was determined from the Flack test, $x = -0.028(6)$. Two crystallographically independent molecules occupy the asymmetric unit and the unit cell. Pseudoinversion symmetry is broken by the pendant groups of the phenanthroline ligands. Zn1 and Zn2 are displaced from the plane of the coordinating atoms, 0.323 Å toward O3 for Zn1 and 0.204 Å toward O14 for Zn2. Some disorder is observed in the system. The triflate oxygen positions O11 to O13 show rotational disorder, evidenced by a second set of O sites. Site occupancies for the two groups were set to a sum of 1. No additional constraints were applied. The site occupancy for the primary set refined to 0.620(5). Additional disorder was seen in the position of Zn1. A second site for Zn1 was observed to lie nearly in the plane of the base of the square pyramid, 0.061 Å away from Zn1 and the coordinated triflate. As a result, distances to the triflate anions are almost identical, 2.247 Å to O6 and 2.279 Å to O3. Site occupancy for Zn1 refined to 0.658(10).

Details of the solid state structure of **6(Zn)** are shown in Figure 7. A more thorough discussion of the supramolecular

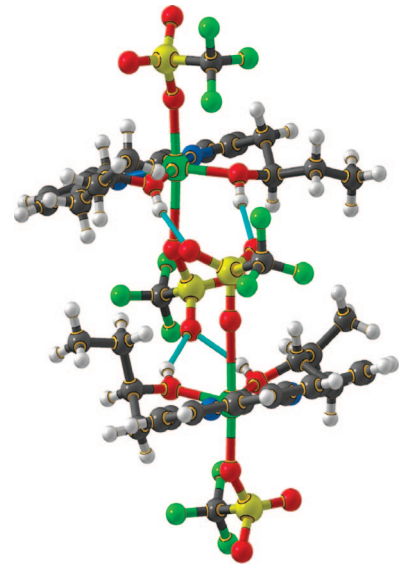


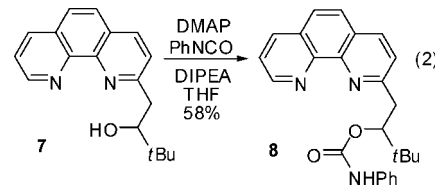
FIGURE 7. Zinc H-bonded dimer **6(Zn)**.

features of the free ligand **6** and its two metal complexes can be found in the Supporting Information.

We have studied a few additional cases of the ligand preparation to give an indication of potential generality. When racemic epoxypropane was used, both mono- and bis(hydroxyalkyl) adducts were formed in a 1.0:1.2 ratio (35% isolated yield). The bis adduct was isolated as a 2:1 mixture of diastereomers, which is similar to the previous result obtained using racemic 1,2-epoxybutane (vide supra). The racemic and meso diastereomers from epoxypropane were not specifically assigned in this mixture. When the more sterically hindered racemic 3,3-dimethyl-1,2-epoxybutane was employed, only the mono adduct **7** was formed (34% isolated yield).

Although we have not performed any mechanistic studies, it is reasonable to suggest that these reactions may occur by an initial electron transfer from samarium to the phenanthroline nucleus followed by nucleophilic attack of the reduced phenanthroline intermediate on the epoxide followed by aerobic rearomatization of the phenanthroline during product isolation. This scenario is consistent with the observed regioselectivity of the epoxide ring opening at C(1) and retention of configuration at C(2) of the epoxybutane. On the other hand, an alternative pathway involving initial electron transfer to the epoxide and ring cleavage[17] followed by attack of the resulting intermediate on the phenanthroline would appear to be inconsistent with the observed regio- and stereoselectivity.

As one example of further derivatization of these ligands to alter their potential coordination behavior, we have found that the mono(hydroxyalkyl)phenanthroline **7** reacts straightforwardly with phenylisocyanate to give the carbamate derivative **8** (eq 2).



In conclusion, the SmI_2-promoted coupling of epoxides with 1,10-phenanthroline provides a new class of functionalized ligands that form metal complexes having potential applications

in catalytic reactions. Although the coupling product yields are low to modest at this stage of development, the reaction nonetheless has the attractive feature of providing the ligands of interest in just one simple step from readily available starting materials. We are currently studying modified versions of these reactions to extend them to pyridines, bipyridines, and quinolines, to use aziridines as substrates, and to apply the resulting ligands in metal-promoted enantioselective reactions. Upon extension to other nitrogen heterocycles, the epoxide coupling reaction may also be useful in alkaloid synthesis.

Experimental Section

Synthesis of *R*-2-(2-Hydroxybutyl)-1,10-phenanthroline (5) and *R,R*-2,9-Bis(2-hydroxybutyl)-1,10-phenanthroline (6). In a flame-dried, 250-mL round-bottom flask, 361 mg (1.00 mmol) of 1,10-phenanthroline was dissolved in 10 mL of anhyd THF. To this solution was added 0.70 mL (8.00 mmol) of *R*-(+)-1,2-epoxybutane followed by 100 mL (10.0 mmol) of 1 M SmI_2 in THF. The solution was covered with aluminum foil and allowed to stir for 3.5 d at 23 °C. The reaction was quenched with satd NH_4Cl (100 mL). The layers were separated, and the aq layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by column chromatography (50:50, hexanes/EtOAc, basic alumina) followed by an additional column chromatography (1:19, concd NH_4OH/CH_3CN, silica) yielding 67 mg (13%) of **5** as an off-white solid. The remaining material was purified by repeating the previous two column chromatography systems and recrystallized from hot CH_3CN to yield 73 mg (11%) of **6** as a slightly yellow solid. Additionally, **6** could be isolated in up to 42% yield in other runs. X-ray quality crystals of **6** were obtained by recrystallization from a mixture of EtOAc and hexanes at –20 °C. **5**: mp = 69–114 °C (dec); TLC R_f = 0.30 (EtOAc, basic alumina); $[\alpha]^{20}{}_D$ = +18.4° (c = 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (dd, J = 4.3, 0.9 Hz, 1H), 8.24 (dd, J = 8.0, 1.0 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 9.4 Hz, 1H), 7.61 (dd, J = 8.0, 4.4 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 4.24 (m, 1H), 3.29 (m, J = 14.8, 2.8 Hz, 1H), 3.21 (dd, J = 15.0, 9.2 Hz, 1H), 1.70 (m, 2H), 1.08 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 150.4, 145.6, 145.0, 136.7, 136.2, 128.9, 127.1, 126.4, 126.0, 124.0, 123.1, 72.5, 44.1, 30.5, 10.3; IR (film) cm^{-1} 3340, 3047, 2962, 2925, 2875, 1507, 1499, 1394, 846, 736; HRMS (FAB$^+$, *m/*z) calcd for $C_{16}H_{16}N_2O$ (M + H$^+$) 253.1341, found 253.1348. **6**: mp = 123–126 °C; TLC R_f = 0.45 (EtOAc, basic alumina); $[\alpha]^{20}{}_D$ = –24.4° (c = 0.45, ethanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.2 Hz, 2H), 7.75 (s, 2H), 7.50 (d, J = 8.2 Hz, 2H), 4.26 (m, 2H), 3.25 (dd, J = 15.5, 2.5 Hz, 2H), 3.17 (dd, J = 15.5, 9.0 Hz, 2H), 1.76 (m, 2H), 1.65 (m, 2H), 1.07 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 144.6, 136.7, 127.3, 125.8, 124.0, 72.3, 43.5, 30.2, 10.4; IR (film) 3306, 2962, 1591, 1497, 1368, 1113, 980, 849 cm^{-1}; HRMS (FAB$^+$, *m/*z) calcd for $C_{20}H_{24}N_2O_2$ (M + H$^+$) 325.1916, found 325.1922.

Acknowledgment. We thank the University of Notre Dame, Proctor and Gamble Pharmaceuticals, and the Wolf Fellowship (J.M.P.) for financial support of this research. We also acknowledge NSF award CHE-0443233 for X-ray instrumentation and collaboration with the Walther Cancer Institute.

Note Added in Proof. After acceptance of this paper, a key report appeared of metal complexes and uses of additional hydroxyalkyl-functionalized nitrogen donor ligands related to those summarized in Figure 1: Montoya, V.; Pons, J.; Branchadell, V.; Garcia-Antón, J.; Solans, X.; Font-Bardía, M.; Ros, J. *Organometallics* **2008**, *27*, 1084.

Supporting Information Available: Additional experimental procedures, preparation of metal complexes, spectroscopic characterization data, and X-ray crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702566M