ORGANIC LETTERS

1999
Vol. 1, No. 10
1659−1662

# Facile Synthesis of Substituted Phenanthroline Ligands by Samarium-Promoted Coupling of Phenanthroline with Ketones

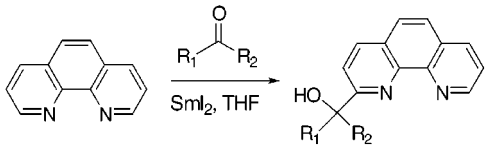
**David J. O'Neill and Paul Helquist***

*Department of Chemistry and Biochemistry, 251 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556*

*paul.helquist.1@nd.edu*

**Received September 14, 1999**

## ABSTRACT




**1,10-Phenanthroline undergoes coupling with ketones promoted by samarium diiodide to produce 2-(1-hydroxyalkyl)-1,10-phenanthrolines. *O*-Methylation of these derivatives provides the corresponding 2-(1-methoxyalkyl)phenanthrolines. Demethoxylation with samarium diiodide then affords 2-alkylphenanthrolines. This process may be repeated to obtain 2,9-disubstituted phenanthrolines. A variety of new, substituted phenanthrolines are thus obtained. These compounds have numerous potential applications as ligands in metal-promoted reactions, including asymmetric catalysis.**

Several approaches have been developed for the asymmetric synthesis of nonracemic organic compounds. An especially important strategy is the use of metal catalysts containing a number of types of chiral ligands.[1] 1,10-Phenanthroline has long been known as a commonly used, nearly universal ligand that forms complexes with a wide range of metals.[2] Chiral derivatives of phenanthroline may therefore be expected to have many applications as ligands in asymmetric catalysis employing any of several metals. In fact, uses of chiral phenanthrolines have been limited,[3] due in part to the small number of methods that have been reported previously for the synthesis of these ligands.[3,4] Nonetheless, we have recently demonstrated the usefulness of substituted phenanthrolines in asymmetric, palladium-catalyzed reactions.[5] The rational design of these ligands was guided by the use of specially parametrized molecular mechanics calculations for

(1) (a) Kagan, H. B. In *Comprehensive Organometallic Chemistry. The Synthesis, Reactions and Structures of Organometallic Compounds*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, Chapter 53. (b) *Asymmetric Synthesis. Chiral Catalysis*; Morrison, H., Ed.; Academic Press: New York, 1985; Vol. 5. (c) *Asymmetric Catalysis*; Bosnich, B., Ed.; Martinus Nijhoff: Dordrecht, 1986. (d) *Handbook of Enantioselective Catalysis with Transition Metal Compounds*; Brunner, H., Zettlmeier, W., Eds.; VCH: New York, 1993; Vol. I and II. (e) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (f) Shibasaki, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1996; Chapter 3. (g) Procter, G. *Asymmetric Synthesis*; Oxford University Press: New York, 1996.

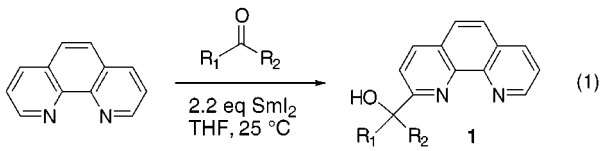
(2) (a) Holyer, R. H.; Hubbard, C. D.; Kettle, S. F. A.; Wilkins, R. G. *Inorg. Chem.* **1965**, *4*, 929−935. (b) McWhinnie, W. R.; Miller, J. D. In *Advances in Inorganic and Radiochemistry*; Emeléus, H. J., Sharpe, A. G., Eds.; Academic Press: New York, 1969; pp 135−215. (c) McBryde, W. A. E. *A Critical Review of Equilibrium Data for Proton- and Metal Complexes of 1,10-Phenanthroline, 2,2′-Bipyridyl and Related Compounds*; Pergamon Press: Oxford, 1978.

(3) (a) Gladiali, S.; Chelucci, G.; Chessa, G.; Delogu, G.; Soccolini, F. *J. Organomet. Chem.* **1987**, *327*, C15−C17. (b) Schionato, A.; Paganelli, S.; Botteghi, C.; Chelucci, G. *J. Mol. Catal.* **1989**, *50*, 11−18. (c) Gladiali, S.; Chelucci, G.; Soccolini, F.; Delogu, G.; Chessa, G. *J. Organomet. Chem.* **1989**, *370*, 285−294. (d) Gladiali, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G.; Mestroni, G. *Tetrahedron: Asymmetry* **1990**, *1*, 635−648. (e) Gladiali, S.; Pinna, L.; Delogu, G.; Graf, E.; Brunner, H. *Tetrahedron: Asymmetry* **1990**, *1*, 937−942. (f) Chelucci, G. *Gazz. Chim. Ital.* **1992**, *122*, 89−98. (g) Weijnen, J. G. J.; Koudijs, A.; Engbersen, J. F. J. *J. Mol. Catal.* **1992**, *73*, L5−L9. (h) Weijnen, J. G. J.; Koudijs, A.; Engbersen, J. F. J. *J. Org. Chem.* **1992**, *57*, 7258−7265. (i) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1992**, *48*, 3653−3658. (j) Kandzia, C.; Steckhan E.; Knoch, F. *Tetrahedron: Asymmetry* **1993**, *4*, 39−42. (k) Riesgo, E. C.; Credi, A.; De Cola, L.; Thummel, R. P. *Inorg. Chem.* **1998**, *37*, 2145−2149.

10.1021/ol990284w CCC: $18.00 
**Published on Web 10/10/1999**

the prediction of structures of ground-state complexes and reaction transition states.[5,6] However, the extension of these studies to the wealth of reactions in which chiral phenanthroline ligands may potentially be employed is dependent upon more general methods for the synthesis of substituted phenanthrolines. The availability of additional methods would also have an impact on other numerous uses of phenanthrolines and their metal complexes.[7] Herein we report a very simple method for the synthesis of substituted phenanthrolines by the straightforward samarium-promoted coupling of ketones with the parent compound, 1,10-phenanthroline.

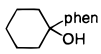
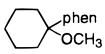
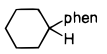
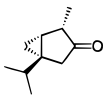
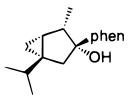
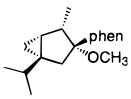
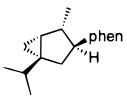
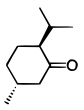
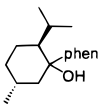
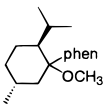
One possible strategy for the generation of substituted phenanthrolines would be the metal−halogen exchange reaction of 2-halophenanthrolines[4i,8] followed by addition of the resulting 2-metalated derivatives to carbonyl compounds to give 2-(1-hydroxyalkyl)phenanthrolines (**1**). However, attempted exchange reactions of 2-halophenanthrolines with typical alkyllithium reagents result mainly in addition/substitution of the alkyllithiums on the phenanthroline nucleus. Reaction of 2-halophenanthrolines with active metals and metalation of 1,10-phenanthroline with strong bases also fail to give useful intermediates for carbonyl addition reactions. A much simpler variation of this strategy which would give the desired substituted ligands more directly from 1,10-phenanthroline itself would be pinacol-like coupling of this parent compound with ketones. These types of couplings are well-known for carbonyl compounds, imines, oximes, nitriles, amides, indoles, and related substrates employing various reducing agents. Especially prominent in recent years has been the use of samarium diiodide.[9,10] Indeed, when 1,10-phenanthroline and ketones are allowed to react with a THF solution of freshly prepared samarium diiodide,[11] the desired substituted phenanthrolines **1** are obtained (eq 1).[12] The scope of the reaction is indicated by



(1)

the examples in Table 1 whereby aliphatic ketones may be employed in general, but aromatic ketones and aldehydes are not useful substrates due to other competing reductive processes such as self-couplings and carbonyl reductions. The racemic products from the use of prochiral ketones (entries c, d, and e) are potentially resolvable, but alternatively, chiral ketones such as thujone (entry f) and menthone (entry g) can be employed to give chiral, nonracemic products directly.[13]

**Table 1.** Samarium Diiodide-Promoted Coupling of Ketones with 1,10-Phenanthroline and Subsequent *O*-Methylation and Demethoxylation

| starting materials | | products and yields (%) | | |
|---|---|---|---|---|
| entry | ketone | **1** | **3** | **4** |
| a |  |  88 |  90 |  66 |
| b |  |  89 |  66 | -- |
| c |  |  73 |  72 |  45 |
| d |  |  71 |  70 |  58 |
| e |  |  40 |  55 | -- |
| f |  |  45[a] |  75[a] |  68[a] |
| g |  |  54[a,b] |  88[a,b] | -- |

[a] Stereochemical assignments tentatively assigned on the basis of $^1$H and $^{13}$C NMR data. [b] Racemic menthone was used in this series.

(4) (a) Graham, B. In *The Chemistry of Heterocyclic Compounds: Six-Membered Heterocyclic Nitrogen Compounds with Three Condensed Rings*; Allen, C. F. H., Ed.; Interscience Publishers: New York, 1958; Chapter 6, pp 386-409. (b) Corey, E. J.; Borror, A. L.; Foglia, T. *J. Org. Chem.* **1965**, *30*, 288−290. (c) Dietrich-Buchecker, C. O.; Marnot, P. A.; Sauvage, J. P. *Tetrahedron Lett.* **1982**, *23*, 5291−5294. (d) Newkome, G. R.; Theriot, K. J.; Gupta, V. K.; Fronczek, F. R.; Baker, G. R. *J. Org. Chem.* **1989**, *54*, 1766−1769. (e) Beer, R. H.; Jimenez, J.; Drago, R. S. *J. Org. Chem.* **1993**, *58*, 1746−1747. (f) Goodman, M. S.; Hamilton, A. D.; Weiss, J. *J. Am. Chem. Soc.* **1995**, *117*, 8447−8455. (g) Lam F.; Chan, K. S.; Liu, B.-J. *Tetrahedron Lett.* **1995**, *36*, 6261−6262. (h) Riesgo, E. C.; Jin, X.; Thummel, R. P. *J. Org. Chem.* **1996**, *61*, 3017−3022. (i) Toyota, S.; Woods, C. R.; Benaglia, M.; Siegel, J. S. *Tetrahedron Lett.* **1998**, *39*, 2697−2700. (j) Dietrich-Buchecker, C.; Jiménez, M. C.; Sauvage, J.-P. *Tetrahedron Lett.* **1999**, *40*, 3395−3396.

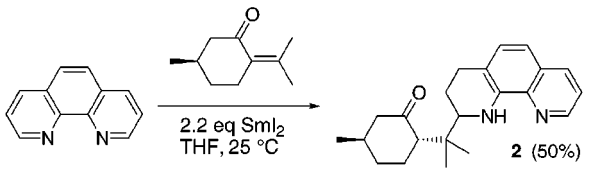
(5) (a) Peña-Cabrera, E.; Norrby, P.-O.; Sjögren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299−4313. For related studies of palladium complexes of substituted phenanthrolines, see: (b) Åkermark, B.; Hansson, S.; Vitagliano, A. *J. Am. Chem. Soc.* **1990**, *112*, 4587−4588. (c) Sjögren, M.; Hansson, S.; Norrby, P.-O.; Åkermark, B.; Cucciolito, M. E.; Vitagliano, A. *Organometallics* **1992**, *11*, 3954−3964. (d) Hansson, S.; Norrby, P.-O.; Sjögren, M.; Åkermark, B.; Cucciolito, M. E.; Giordano, F.; Vitagliano, A. *Organometallics* **1993**, *12*, 4940−4948. (e) Sjögren, M.; Hansson, S.; Åkermark, B.; Vitagliano, A. *Organometallics* **1994**, *13*, 1963−1971.

(6) (a) Norrby, P.-O.; Åkermark, B.; Hæffner, F.; Hansson, S.; Blomberg, M. *J. Am. Chem. Soc.* **1993**, *115*, 4859−4867. (b) Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16*, 3015−3021.

(7) (a) Sigman, D. S. *Biochemistry* **1990**, *29*, 9097−9105. (b) Engbersen, J. F. J.; Koudijs, A.; van der Plas, H. C. *J. Org. Chem.* **1990**, *55*, 3647−3654. (c) Bodige, S.; Torres, A. S.; Maloney, D. J.; Tate, D.; Kinsel, G. R.; Walker, A. K.; MacDonnell, F. M. *J. Am. Chem. Soc.* **1997**, *119*, 10364−10369. (d) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346−355. (e) Miller, M. T.; Gantzel, P. K.; Karpishin, T. B. *J. Am. Chem. Soc.* **1999**, *121*, 4292−4293. (f) Goodbrand, H. B.; Hu, Nan-Xing *J. Org. Chem.* **1999**, *64*, 670−674. (g) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433−2439. (h) Stengone, C. N.; Widenhoefer, R. A. *Tetrahedron Lett.* **1999**, *40*, 1451−1454. (i) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2660. (j) Tzalis, D.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 3685−3688.

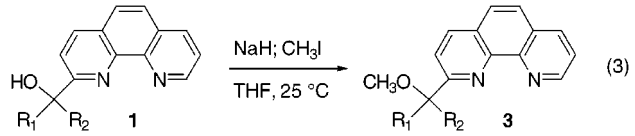
(8) Ogawa, S.; Yamaguchi, T.; Gotoh, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 976−978.

Attempts were made without success to extend this reaction to other, related substrates such as pyridine and isoquinoline in place of phenanthroline. Likewise, α,β-unsaturated ketones, in place of saturated ketones, do not generally give useful results, but in the case of pulegone, product **2** is obtained which results from conjugate addition and reduction of the phenanthroline nucleus (eq 2).



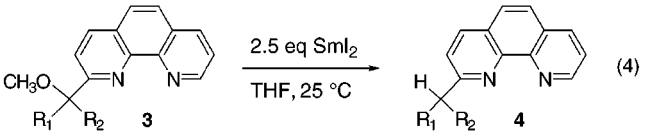
(2)

The substituted phenanthrolines **1** may be employed in further reactions for the purpose of obtaining modified ligands. For example, *O*-alkylations may be effected straightforwardly as exemplified by methylation with methyl iodide to give the 2-(1-methoxyalkyl)phenanthrolines **3** (eq 3). In



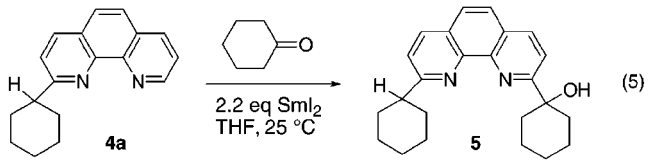
(3)

turn, the alkoxyalkyl derivatives **3** may be subjected to reductive cleavage, again with samarium diodide,[9] to give the simpler 2-alkylphenanthrolines **4** (eq 4). The results of these further modifications are included in Table 1.



(4)

The potential exists for introducing another group at C(9) of these phenanthroline derivatives by a second samarium diiodide-promoted coupling of a ketone with a product of the preceding sequence of reactions. This approach to obtaining 2,9-disubstituted phenanthrolines is illustrated with the formation of cyclohexanone-derived product **5** (eq 5).



(5)

Our preliminary results have shown that the reaction of 1,10-phenanthroline with ketones and samarium diiodide provides a simple method for the synthesis of substituted phenanthroline ligands. The possibility exists of extending these preparations to the use of other reducing agents and to additional classes of substrates. Also, *O*-alkylations and *O*-acylations beyond the simple methylations reported here may be employed to introduce additional stereochemical features and other metal-coordinating groups based upon oxygen, nitrogen, sulfur, phosphorus, unsaturated functional groups, heterocycles, and even additional phenanthroline moieties. The further enhancement of these preparations and the use of the resulting ligands in asymmetric catalysis are subjects of further investigations in our laboratory.

**Acknowledgment.** We thank Professors Per-Ola Norrby (Royal Danish School of Pharmacy, Copenhagen), Björn Åkermark (Royal Institute of Technology, Stockholm), and Jan Bäckvall (University of Stockholm) for valuable

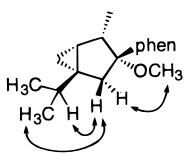
(9) For reviews, see: (a) Molander, G. A. In *The Chemistry of the Metal−Carbon Bond*; Hartley, F. R., Ed.; Wiley: New York, 1990; Vol. 5, Chapter 8. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. (c) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: London, 1994. (d) Molander, G. A. *Org. React.* **1995**, *46*, 211−368. (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (f) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609.

(10) For related coupling reactions, see: (a) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141−1142. (b) Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1991**, *31*, 3555−3556. (c) Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729−8730. (d) Akane, N.; Hatano, T.; Kusui, H.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 7902−7907. (e) Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. *Tetrahedron Lett.* **1996**, *37*, 7755−7756. (f) Marco-Contelles, J.; Gallego, P.; Rodriguez-Fernandez, M.; Khiar, N.; Destabel, C.; Bernabe, M.; Martinez-Grau, A.; Chiara, J. L. *J. Org. Chem.* **1997**, *62*, 7397−7412. (g) Molander, G. A.; Wolfe, C. N. *J. Org. Chem.* **1998**, *63*, 9031−9036. (h) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1998**, *39*, 3333−3336. (i) Lin, S.-C.; Yang, F.-D.; Shiue, J.-S.; Yang, S.-M.; Fang, J.-M. *J. Org. Chem.* **1998**, *63*, 2909−2917. (j) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397−4407. (k) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877−5882. (l) Zhou, L. H.; Zhang, Y. M.; Shi, D. Q. *Tetrahedron Lett.* **1998**, *39*, 8491−8494. (m) Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315−1318. (n) Yang, S.-M.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 394−399.

(11) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.

(12) A representative procedure is given for use of cyclohexanone. To a stirred solution of 1,10-phenanthroline (0.1 g, 0.55 mmol) in THF (5 mL) was added a freshly prepared 0.1 M solution of $SmI_2$ in THF (12.2 mL, 1.22 mmol)[11] at 25 °C. After 5 min, cyclohexanone (0.120 g, 1.22 mmol) was added, and the resulting mixture was stirred for 12 h at 25 °C. Saturated aqueous $NH_4Cl$ was added, and the mixture was extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography (alumina, ethyl acetate/hexane gradient) to give 0.134 g (88%) of 2-(1-hydroxycyclohexyl)-1,10-phenanthroline (**1a**) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.18 (dd, $J$ = 4.20, 1.80 Hz, $H_{P9}$), 8.28 (d, $J$ = 8.40 Hz, $H_{P4}$), 8.27 (dd, $J$ = 8.40, 1.80 Hz, $H_{P7}$), 7.82 and 7.79 (two d, $J$ = 8.80 Hz, $H_{P5}$ and $H_{P6}$), 7.76 (d, $J$ = 8.40 Hz, $H_{P3}$), 7.65 (dd, $J$ = 8.10, 4.50 Hz, $H_{P8}$), 2.08−1.71 (m, 10H, cyclohexyl); $^{13}$C NMR (75 MHz) $\delta$ 166.52, 150.31, 145.81, 143.96, 137.15, 136.06, 129.00, 127.46, 126.28, 126.20, 122.93, 119.21, 73.50, 38.63, 23.70, 22.15; IR ($CHCl_3$) 3352 (OH), 3048 (C−H Ar), 2928 (CH), 909 (C−H Ar) cm$^{-1}$; HRMS *m/e* calcd for $C_{18}H_{19}N_2O$ ($MH^+$) 279.1497, found 279.1490.

(13) In this initial survey of the reactivity of various types of ketones, the stereochemistry of the products from addition to chiral ketones has not been rigorously established. Only single stereoisomers of the products **1f** and **1g** from the reactions of (−)-thujone and DL-menthone were detected in the crude reaction mixtures. For the (−)-thujone-derived series of products, a NOESY NMR study of the methoxy derivative **3f** provided the cross-correlations shown below in support of the assigned stereochemistry.



discussions, Donald Schifferl and Dr. Jaroslav Zajicek for NMR assistance, and Dr. William Bogess and Nonka Sevova for mass spectrometry assistance. We are grateful for financial support from the National Science Foundation, the National Institutes of Health, and the University of Notre Dame. D.J.O. is grateful for a Reilly Fellowship.

**Supporting Information Available:** Experimental procedures and NMR spectra for the substituted phenanthrolines **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990284W