

# PINDY: A Novel, Pinene-Derived Bipyridine Ligand and Its Application in Asymmetric, Copper(I)-Catalyzed Allylic Oxidation<sup>†</sup>

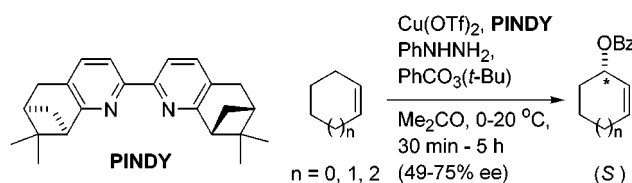
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Received May 26, 2000

## ABSTRACT



The title bipyridine ligand (+)-6(PINDY), prepared in five steps from (–)- $\beta$ -pinene, forms a stable complex with  $\text{CuCl}_2$  (8) that has been characterized by X-ray crystallography to reveal an unusual geometry at Cu. Triflate 9 proved to catalyze asymmetric allylic oxidation ( $10 \rightarrow 11$ ; rt, ~30 min, 49–75% ee).

Transition metal complexes with  $\text{sp}^2$ -nitrogen as the ligating atom(s) constitute an important class of chiral catalysts<sup>1</sup> in which substituted oxazolines and bisoxazolines play the prime role.<sup>2</sup> By contrast, 2,2'-bipyridyl and 1,10-phenanthroline<sup>3</sup> received much less attention in asymmetric catalysis owing to the difficulties associated with their conversion into chiral molecules.<sup>4–12</sup> Herein, we report on an expedient synthesis of the bipyridine ligand **6** (PINDY),<sup>13</sup> derived from

(–)- $\beta$ -pinene, and its application in asymmetric allylic oxidation.

The  $\text{C}_2$ -symmetrical ligand (+)-**6** was synthesized via annulation of the pyridine ring to a building block originating from the chiral pool (Scheme 1): (–)- $\beta$ -Pinene (–)-**1** was oxidized ( $\text{OsO}_4$ ,  $\text{NaIO}_4$ ,  $\text{Me}_3\text{NO}$ ,  $t$ -BuOH,  $\text{H}_2\text{O}$ , 80 °C, 2 h) to produce (+)-nopinone (+)-**2** (64%),<sup>14,15</sup> which was converted into oxime **3** ( $\text{NH}_2\text{OH}\cdot\text{HCl}$ , pyridine, ethanol).<sup>16</sup> Reduction of the latter oxime with powdered iron in the

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

(2) For a recent overview, see: Pfaltz, A. *Acta Chem. Scand.* **1996**, 50, 189.

(3) For the rich coordination chemistry of bipyridine and phenanthroline, see, e.g.: (a) Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Oxford, 1987; Vol 2, p 73. (b) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.

(4) (a) Ito, K.; Tabuchi, S.; Katsuki, T. *Synlett* **1992**, 575. (b) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, 52, 3905.

(5) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, 370, 17.

(6) (a) Hayoz, P.; von Zelewsky, A. *Tetrahedron Lett.* **1992**, 33, 5165.

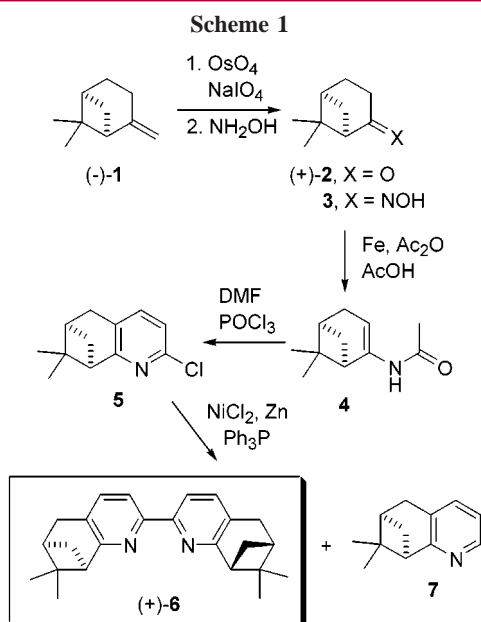
(b) Fletcher, N. C.; Keene, F. R.; Ziegler, M.; Stoeckli-Evans, H.; Viebrock, H.; von Zelewsky, A. *Helv. Chim. Acta* **1996**, 79, 1192. (c) Mamula, O.; von Zelewsky, A.; Bark, T.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1999**, 38, 2945. For an overview, see: (d) Knof, U.; von Zelewsky, A. *Angew. Chem., Int. Ed.* **1999**, 38, 303.

(7) (a) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, 60, 5386. (b) Chen, C. *Synlett* **1998**, 1311.

(8) Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1998**, 9, 531.

(9) Kwong, H.-L.; Lee, W.-S.; Ng, H.-F.; Chiu, W.-H.; Wong, W.-T. *J. Chem. Soc., Dalton Trans.* **1998**, 1043.

(10) Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. *Chem. Commun.* **2000**, 377.



presence of acetic anhydride<sup>17</sup> (Fe, Ac<sub>2</sub>O, toluene, AcOH, 0 °C, 10 min)<sup>18,19</sup> led to enamide **4** (90%), which afforded the chloropyridine derivative **5** (70%) under the conditions of Vilsmeier–Haack reaction (HCONMe<sub>2</sub>, POCl<sub>3</sub>, 0–5 °C, 1

(11) For other chiral pyridine derivatives, see, e.g.: (a) Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2571. (b) Chelucci, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2667. (c) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 3183. (d) Chelucci, G.; Berta, D.; Saba, A. *Tetrahedron* **1997**, *53*, 3843. (e) Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604. (f) Bremberg, U.; Rahm, F.; Moberg, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3437. (g) Wärnmark, K.; Stranne, R.; Cernerud, M.; Terrien, I.; Rahm, F.; Nordström, K.; Moberg, C. *Acta Chem. Scand.* **1998**, *52*, 961. For a recent overview of chiral pyridines, see: (h) Moberg, C.; Adolfsson, H.; Wärnmark, K. *Acta Chem. Scand.* **1996**, *50*, 195. (i) Canal, J. M.; Gómez, M.; Jiménez, F.; Rocamora, M.; Muller, G.; Duñach, E.; Franco, D.; Jiménez, A.; Cano, F. H. *Organometallics* **2000**, *19*, 966. For recent examples of bipyridine ligands with planar chirality, see ref 10 and: (j) Wörsdörfer, U.; Vögtle, F.; Nieger, M.; Waletzke, M.; Grimme, S.; Glorius, F.; Pfaltz, A. *Synthesis* **1999**, 597. (k) Djukic, J.-P.; Michon, C.; Maisse-François, A.; Allagapen, R.; Pfeffer, M.; Dötz, K. H.; De Cian, A.; Fischer, J. *Chem. Eur. J.* **2000**, *6*, 1064.

(12) Chiral phenanthrolines: (a) Gladiali, S.; Chelucci, G.; Socolini, F.; Delogu, G.; Chiessa, G. *J. Organomet. Chem.* **1989**, *370*, 285. (b) 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. (c) Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16*, 3015. Related nonchiral phenanthrolines: (d) Hansson, S.; Norrby, P.-O.; Sjögren, M. P. T.; Åkermark, B. *Organometallics* **1993**, *12*, 4940. (e) Sjögren, M. P. T.; Hansson, S.; Åkermark, B. *Organometallics* **1994**, *13*, 1963. (f) Frisell, H.; Åkermark, B. *Organometallics* **1995**, *14*, 561. (g) Sjögren, M. P. T.; Frisell, H.; Åkermark, B. *Organometallics* **1997**, *16*, 942. (h) Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18*, 2884.

(13) PINene-Derived bipYridine.

(14) Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217.

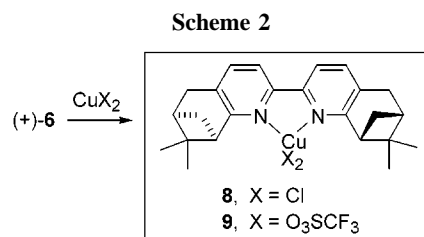
(15) (+)-Nopinone (+)-**2** thus prepared from the commercially available (–)-β-pinene (–)-**1** (Aldrich) exhibited [α]<sub>D</sub> +34.7 (c 4.0 MeOH). Since the highest optical rotation reported for enantiopure nopinone is [α]<sub>D</sub> +39.9 ± 0.3 (Grimshaw, N.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50) or [α]<sub>D</sub> +40.52 (c 4.0 MeOH),<sup>14</sup> our nopinone corresponds to 86% ee.

(16) Identical with the known compound: (a) Hall, H. K. *J. Org. Chem.* **1963**, *28*, 3213. (b) Quon, H. H.; Chow, Y. L. *Tetrahedron* **1975**, *31*, 2349. (c) Yokoyama, Y.; Yunokihara, M. *Chem. Lett.* **1983**, 1245.

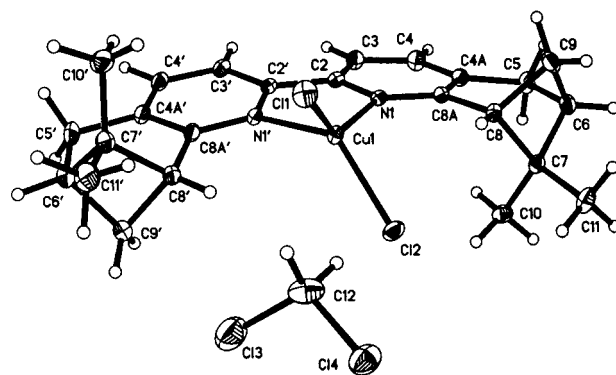
(17) For the method, see: Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.

h).<sup>20</sup> Stoichiometric, nickel(0)-mediated coupling of **5** (NiCl<sub>2</sub>, Ph<sub>3</sub>P, Zn, DMF, 60 °C, 18 h) furnished a mixture of the reduction product **7** (32%) and the desired dimer (+)-**6** (50%).<sup>21,22</sup>

Refluxing (+)-**6** (PINDY) with CuCl<sub>2</sub>·H<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>–EtOH for 12 h (Scheme 2) resulted in the quantitative



formation of **8** (75% after recrystallization).<sup>23</sup> Single-crystal X-ray analysis of the latter complex revealed an unusually distorted geometry at the metal center (Figure 1),<sup>24</sup> which may have interesting implications for its catalytic activity.<sup>25</sup>



**Figure 1.** ORTEP diagram of **8**·CH<sub>2</sub>Cl<sub>2</sub> showing the atom labeling scheme. Displacement parameters are shown at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

To explore the catalytic potential of copper complexes of PINDY (**6**), we elected to study asymmetric allylic oxidation—

(18) The conversion of oximes into enamides has also been known to occur in the presence of strong reducing agents, such as (AcO)<sub>2</sub>Cr or (AcO)<sub>3</sub>Ti.<sup>19</sup> However, in view of the cost of the former and the difficulties associated with the availability of the latter reagent, none of them was particularly suitable for large-scale operations.

(19) For the Ti(III) and Cr(II) reduction, see: (a) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stuck, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1237. (b) Barton, D. H. R.; Bowles, T.; Husinec, S.; Forbes, J. E.; Llobera, A.; Porter, E. A.; Zard, S. Z. *Tetrahedron Lett.* **1988**, *29*, 3343.

(20) For the method, see: Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173.

(21) For the method of α-chloropyridine dimerization, see ref 6a and the following: (a) Dehmlow, E. V.; Slegers, A. *Liebigs Ann. Chem.* **1992**, *9*, 953. (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2881.

(22) Although this coupling is, a priori, amenable to a catalytic process, reactions with sub-stoichiometric amounts (e.g., 10 mol %) of Ni(0) turned out to lead predominantly to the reduction product **7**.

one of the reactions that have not yet been developed at a satisfactory level. The catalysts reported to date<sup>26</sup> often require several days to allow completion of the reaction<sup>26a</sup> and, as a rule, the enantioselectivity does not exceed ~80% ee.<sup>26</sup> To increase the reactivity of the Cu/PINDY catalyst, triflate analogue **9** was generated from (+)-**6** and Cu(OTf)<sub>2</sub>. Complex **9** was then reduced in situ with phenylhydrazine to the corresponding Cu(I) species. Oxidation of cyclohexene (**10b**) with *tert*-butyl peroxybenzoate, carried out in the presence of 1 mol % of the catalyst thus generated, proved to be complete within ≤30 min at room temperature, giving (*S*)-(-)-**11b** (96%, 49% ee). Improved enantioselectivity (55% ee) was observed at 0 °C, but the reaction required 5 h in this instance<sup>27</sup> (Scheme 3).<sup>28,29</sup> Similar results were

(23) For the preparation of Cu(II)–bipy complexes, see, e.g., ref 9 and the following: Bolm, C.; Ewald, M.; Zehnder, M.; Neuburger, M. A. *Chem. Ber.* **1992**, *125*, 453.

(24) Crystallographic data for **8**: C<sub>24</sub>H<sub>28</sub>Cl<sub>2</sub>CuN<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub>, *M* = 563.85. Crystals were obtained from solution of the complex in CH<sub>2</sub>Cl<sub>2</sub>, covered by hexane and left at –18 °C for 2 days. They are orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *a* = 10.3637(1) Å, *b* = 3.6592(2) Å, *c* = 17.9777(2) Å, *V* = 2544.92(5) Å<sup>3</sup>, *Z* = 4, *d*<sub>calc</sub> = 1.472 g cm<sup>–3</sup>, *μ* = 1.295 mm<sup>–1</sup>, 30160 reflections collected, 9036 unique (*R*<sub>int</sub> = 0.0198), with 8590 observed data having *I* > 2σ<sub>*i*</sub>, *R*<sub>*F*</sub> = 0.0332 for the observed data and *wR*(*F*<sup>2</sup>) = 0.0973 for all data, Flack factor = 0.003(7). The estimated error in C–C bond lengths is in the range of 0.002–0.003 Å.

(25) For a similar distortion, see ref 9. Several oxazoline-type Cu(II) complexes have also been reported to exhibit distortion at Cu (although not to the extent observed for **8**). For a recent summary, see: (a) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. (c) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635.

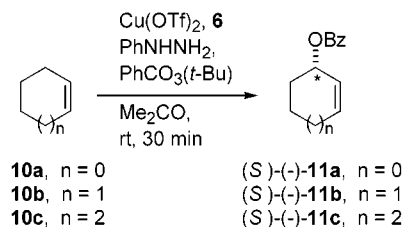
(26) (a) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831. (b) Andrus, M. A.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945. (c) Södergren, M. J.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 7577. (d) Hamachi, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4979. (e) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337. (f) Clark, J. S.; Tolhurst, K. F.; Taylor, M.; Swallow, S. J. *Chem. Soc., Perkin Trans. 1* **1998**, 1167. (g) Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961. (h) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941.

(27) Practically identical results were obtained with the Cu(I) complex generated directly from (+)-**6** and the more expensive (CuOTf)<sub>2</sub>·C<sub>6</sub>H<sub>6</sub>.

(28) Since the starting (+)-nopinone (+)-**2** was not enantiomerically pure (86% ee),<sup>15</sup> the observed enantioselectivities might, in principle, be higher. However, the synthesis of ligand (+)-**6** included several crystallizations, which may have contributed to the increase of enantiomeric purity of the final product. Although we failed to detect the opposite enantiomer in (+)-**6** by chiral HPLC and by NMR spectroscopy [in the presence of Eu(hfc)<sub>3</sub>], its ultimate precursor **5** was found to be of 95% ee by HPLC.

(29) **Typical Procedure for Allylic Oxidation Catalyzed by Cu(I)/PINDY.** A green solution of (+)-**6** (21 mg, 0.06 mmol) and Cu(OTf)<sub>2</sub> (18 mg, 0.05 mmol) in acetone (4 mL) was stirred under a nitrogen atmosphere at 20 °C for 1 h. Phenylhydrazine (5.9 μL, 0.06 mmol) was then added, and the color of the solution changed to red. After 10 min, cyclohexene **10b** (0.52 mL, 5 mmol) was added, followed by the dropwise addition of *tert*-butyl peroxybenzoate (0.2 mL, 1.0 mmol). The progress of the reaction was monitored by TLC (hexane/ethyl acetate 9:1). Disappearance of the peroxyester indicated the completion of the reaction. The solvent was removed in a vacuum, and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL),

Scheme 3



obtained with cyclopentene **10a** (48% ee at rt and 59% ee at 0 °C).<sup>30</sup> Cycloheptene, on the other hand, exhibited a substantially better enantioselectivity (62% ee at rt and 75% ee at 0 °C).<sup>30</sup> In all cases the reaction was significantly slower at 0 °C (5–10 h).

In conclusion, novel, C<sub>2</sub>-symmetrical bipyridine ligand (+)-**6** (PINDY) has been prepared from (–)-β-pinene via a de novo construction of the pyridine ring followed by Ni(0)-mediated dimerization. This ligand has been found to form a stable complex with CuCl<sub>2</sub> (**8**) that exhibits an unusual geometry at Cu, as revealed by X-ray crystallography. Triflate **9** proved to catalyze asymmetric allylic oxidation (**10** → **11**) with high efficiency and good enantioselectivity. These promising results suggest that optimization of the counteranion<sup>31</sup> and of the ligand may lead to a very efficient catalytic system.<sup>32,33</sup>

**Acknowledgment.** We thank the University of Glasgow and the University of Rome “La Sapienza” for financial support.

**Supporting Information Available:** Experimental procedures for new compounds, analytical details for allylic oxidation, and crystallographic characterization of **8** and atomic coordinates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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washed successively with a saturated aqueous KHCO<sub>3</sub> solution, brine, and water, and dried over MgSO<sub>4</sub>. Evaporation followed by chromatography on silica gel (20 × 3 cm) with hexane/ethyl acetate (10:1) as eluent afforded pure cyclohexenyl benzoate (*S*)-**11b** (194 mg, 96%; ≥49% ee). Chiral HPLC analysis: Chiralpak AD, hexane–isopropyl alcohol (99.6:0.4), flow rate 1 mL/min, *t*<sub>R</sub> = 12.6 min (minor), *t*<sub>S</sub> = 13.8 min (major), UV detection at 220 nm.

(30) The absolute configuration of the product was determined by comparison of its optical rotation with the known values.<sup>26</sup>

(31) For the role of the counterion in Cu(I)- and Cu(II)-catalyzed reactions, see, e.g., ref 25.

(32) Apparently, the reaction requires a trace of water since adding molecular sieves resulted in a dramatic deceleration (though the enantioselectivity remained essentially unaffected).

(33) Note that individual ligands<sup>26</sup> have different “optimal substrates”; in the case of PINDY it is **11c** that gives the highest enantioselectivity.