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

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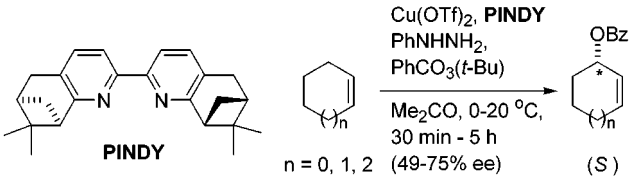
ABSTRACT



The title bipyridine ligand (+)-6(PINDY), prepared in five steps from (−)-β-pinene, forms a stable complex with $CuCl_2$ (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 → 11; rt, ∼30 min, 49−75% ee).

Transition metal complexes with sp^2-nitrogen as the ligating atom(s) constitute an important class of chiral catalysts[1] in which substituted oxazolines and bisoxazolines play the prime role.[2] By contrast, 2,2′-bipyridyl and 1,10-phenanthroline[3] received much less attention in asymmetric catalysis owing to the difficulties associated with their conversion into chiral molecules.[4−12] Herein, we report on an expedient synthesis of the bipyridine ligand **6** (PINDY),[13] derived from (−)-β-pinene, and its application in asymmetric allylic oxidation.

The C_2-symmetrical ligand (+)-**6** was synthesized via annulation of the pyridine ring to a building block originating from the chiral pool (Scheme 1): (−)-β-Pinene (−)-**1** was oxidized (OsO_4, $NaIO_4$, Me_3NO, *t*-BuOH, H_2O, 80 °C, 2 h) to produce (+)-nopinone (+)-**2** (64%),[14,15] which was converted into oxime **3** (NH_2OH·HCl, pyridine, ethanol).[16] Reduction of the latter oxime with powdered iron in the

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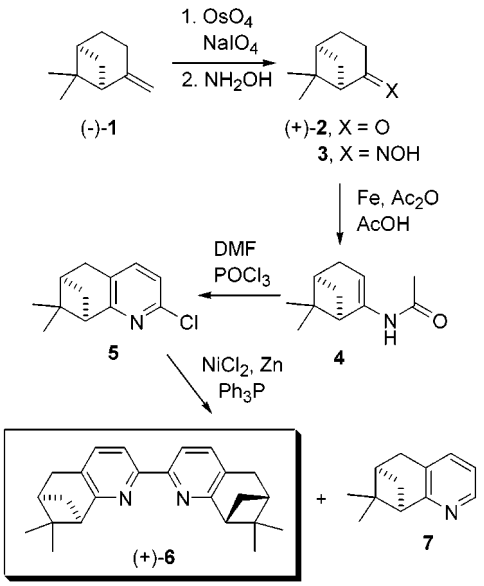
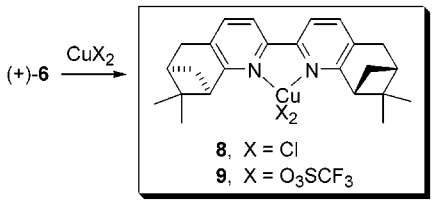
Scheme 1



presence of acetic anhydride[17] (Fe, Ac_2O, toluene, AcOH, 0 °C, 10 min)[18,19] led to enamide **4** (90%), which afforded the chloropyridine derivative **5** (70%) under the conditions of Vilsmeyer−Haack reaction ($HCONMe_2$, $POCl_3$, 0−5 °C, 1 h).[20] Stoichiometric, nickel(0)-mediated coupling of **5** ($NiCl_2$, Ph_3P, Zn, DMF, 60 °C, 18 h) furnished a mixture of the reduction product **7** (32%) and the desired dimer (+)-**6** (50%).[21,22]

Refluxing (+)-**6** (PINDY) with $CuCl_2 \cdot H_2O$ in CH_2Cl_2−EtOH for 12 h (Scheme 2) resulted in the quantitative formation of **8** (75% after recrystallization).[23] Single-crystal X-ray analysis of the latter complex revealed an unusually distorted geometry at the metal center (Figure 1),[24] which may have interesting implications for its catalytic activity.[25]

Scheme 2



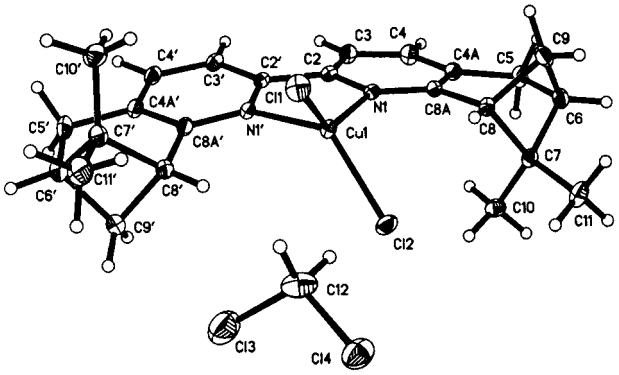


Figure 1. ORTEP diagram of **8**·CH_2Cl_2 showing the atom labeling scheme. Displacement parameters are shown at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

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

(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) Wörsdorför, 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.

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(13) **PIN**ene-**D**erived bip**Y**ridine.

(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 $[\alpha]_D$ +34.7 (*c* 4.0 MeOH). Since the highest optical rotation reported for enantiopure nopinone is $[\alpha]_D$ +39.9 ± 0.3 (Grimshaw, N.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50) or $[\alpha]_D$ +40.52 (*c* 4.0 MeOH),[14] 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.

(18) The conversion of oximes into enamides has also been known to occur in the presence of strong reducing agents, such as $(AcO)_2Cr$ or $(AcO)_3Ti$.[19] 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.; Stick, 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.

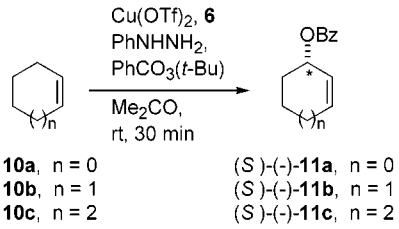
(20) For the method, see: Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173.

(21) For the method of α-chloropyridine dimerization, see ref 6a and the following: (a) Dehmlow, E. V.; Sleegers, 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[26] often require several days to allow completion of the reaction[26a] and, as a rule, the enantioselectivity does not exceed ~80% ee.[26] To increase the reactivity of the Cu/PINDY catalyst, triflate analogue **9** was generated from (+)-**6** and $Cu(OTf)_2$. 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[27] (Scheme 3).[28,29] Similar results were obtained with cyclopentene **10a** (48% ee at rt and 59% ee at 0 °C).[30] Cycloheptene, on the other hand, exhibited a substantially better enantioselectivity (62% ee at rt and 75% ee at 0 °C).[30] In all cases the reaction was significantly slower at 0 °C (5−10 h).

Scheme 3



In conclusion, novel, C_2-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 $CuCl_2$ (**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[31] and of the ligand may lead to a very efficient catalytic system.[32,33]

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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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(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**: $C_{24}H_{28}Cl_2CuN_2 \cdot CH_2Cl_2$, $M = 563.85$. Crystals were obtained from solution of the complex in CH_2Cl_2, covered by hexane and left at −18 °C for 2 days. They are orthorhombic, space group $P2_12_12_1$, $a = 10.3637(1)$ Å, $b = 3.6592(2)$ Å, $c = 17.9777(2)$ Å, $V = 2544.92(5)$ Å^3, $Z = 4$, $d_{calc} = 1.472$ g cm^{-3}, $\mu = 1.295$ mm^{-1}, 30160 reflections collected, 9036 unique ($R_{int} = 0.0198$), with 8590 observed data having $I > 2\sigma_I$, $R_F = 0.0332$ for the observed data and $wR(F^2) = 0.0973$ 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 extend 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 $(CuOTf)_2 \cdot C_6H_6$.

(28) Since the starting (+)-nopinone (+)-**2** was not enantiomerically pure (86% ee),[15] 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 $Eu(hfc)_3$], 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 $Cu(OTf)_2$ (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_2Cl_2 (15 mL), washed successively with a saturated aqueous $KHCO_3$ solution, brine, and water, and dried over $MgSO_4$. 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, $t_R = 12.6$ min (minor), $t_S = 13.8$ 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.[26]

(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[26] have different "optimal substrates"; in the case of PINDY it is **11c** that gives the highest enantioselectivity.