Synthesis of New Chiral 2,2′-Bipyridyl-Type Ligands, Their Coordination to Molybdenum(0), Copper(II), and Palladium(II), and Application in Asymmetric Allylic Substitution, Allylic Oxidation, and Cyclopropanation

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Received October 3, 2000

A series of chiral bipyridine-type ligands **5**−**12** has been synthesized via a de novo construction of the pyridine nucleus. The chiral moieties of the ligands originate from the monoterpene realm, namely, pinocarvone (**13** → **6**, **7**, and **9**), myrtenal (**18** → **5**), nopinone (**21** → **8** and **10**), and menthone (**28** → **11** and **12**); the first three precursors can be obtained in one step from *β*- and α-pinene, respectively. Complexes of these ligands with molybdenum(0) (**38**−**40**) and copper(II) (**41**) have been characterized by single-crystal X-ray crystallography. While complex **38** exhibits polymorphism (monoclinic and tetragonal forms crystallize from the same batch), **41** is characterized by a tetrahedrally distorted geometry of the metal coordination. The Mo and Pd complexes exhibit modest asymmetric induction in allylic substitution (**43** → **44**), and the Cu(I) counterpart of **41**, derived from **10** (PINDY) and $Cu(OTf)_2$, shows promising enantioselectivity (49−75% ee) and reaction rate (≥30 min at room temperature) in allylic oxidation of cyclic olefins (**47** → **48**). The Cu(I) complex of **11** (MINDY) proved effective in cyclopropanation (**49** → **50**) with up to 72% ee.

Introduction

Transition metal complexes with sp^2-nitrogen(s) as the ligating atom(s) constitute an important class of chiral catalysts,[1] in which substituted oxazolines and bisoxazolines received the highest acclaim.[2] Aside from these successful chiral inducers, 2,2′-bipyridyl and 1,10-phenanthroline can be viewed as another potentially promising group since they can, a priori, be rendered chiral by appending additional substituents (**1**, **2** in Chart 1). However, despite their rich and well-documented coordination chemistry,[3] bipyridyl and phenanthroline derivatives received relatively little attention in asymmetric catalysis to date and became emerging only recently.[4−11] Among the sporadic entries into this realm are the bipyridyl derivatives **3**−**7**. While the monoterpene origin of ligands **5**−**7** can easily be recognized and their synthesis is relatively straightforward,[5−8] **3** and **4** are products of a "purely synthetic" effort: thus, for example, **4** was synthesized via a

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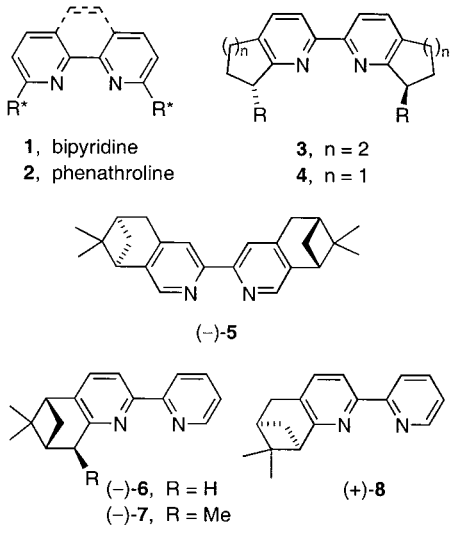
(9) Kwong, H.-L.; Lee, W.-S.; Ng, H.-F.; Chiu, W.-H.; Wong, W.-T. *J. Chem. Soc., Dalton Trans.* **1998**, 1043.

10.1021/om000850n CCC: $20.00
Publication on Web 01/20/2001

Chart 1



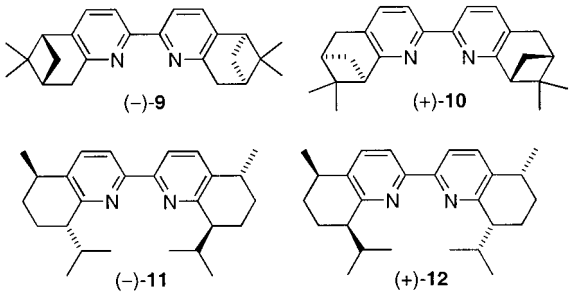
lengthy procedure, which itself required a rather elaborate synthesis of another chiral catalyst to be employed in one of the steps.[4]

Recently, the monoterpene-derived bipyridyls **5**−**7**[5−8] have been employed in Pd(0)-catalyzed allylic substitution[6,8] and the Ni/Cr-catalyzed Kishi coupling.[7] As part of a broader program aimed at development of new transition metal catalysts for asymmetric synthesis, we have now focused on bipyridyl-type complexes of transition metals.[12] Herein, we describe the preparation of chiral 2,2′-bipyridyls **5**−**12** (Charts 1 and 2), their complexation with Mo(0), Cu(II), and Pd(II), and selected examples of their application in asymmetric catalysis, namely, in allylic substitution (Mo and Pd), allylic oxidation (Cu), and cyclopropanation (Cu).

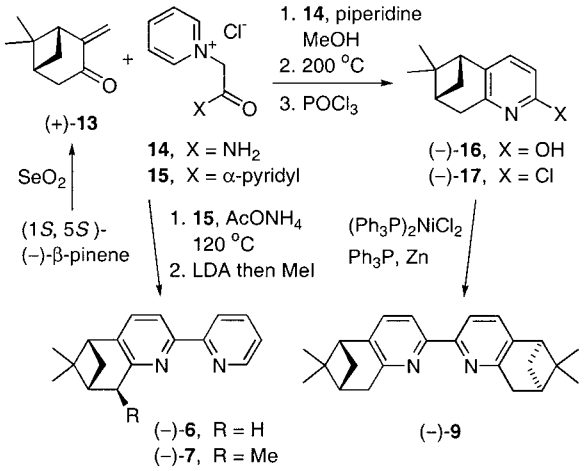
Results and Discussion

Synthesis of C_1 and C_2-Symmetrical 2,2′-Bipyridyl Ligands. The C_1-symmetrical bipyridyl derivative (−)-**6** was synthesized from (+)-pinocarvone (+)-**13** in analogy with the known procedure (Scheme 1):[8] (+)-**13**, obtained by allylic oxidation of (−)-*β*-pinene[13,14] (SeO_2, CCl_4, reflux, 24 h, 27%),[15] was condensed with Kröhnke salt **15** ($AcONH_4$, AcOH, 120 °C, 4 h) to afford (−)-**6** in 77% yield.[16] Deprotonation of (−)-**6** with LDA

Chart 2



Scheme 1



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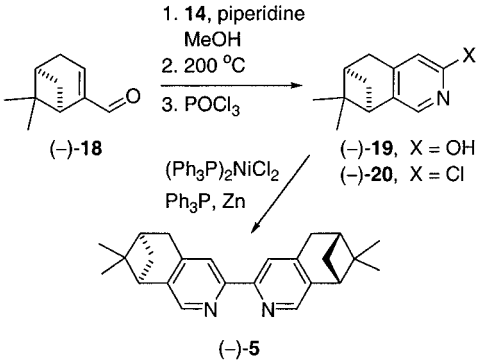
(13) (+)-Pinocarvone (+)-**13** thus obtained is generically related to (−)-*β*-pinene. Chelucci[8] employed (−)-*trans*-pinocarveol, genetically related (via allylic oxidation) to (+)-*β*-pinene, as starting material. Oxidation of (−)-*trans*-pinocarveol should, therefore, produce (−)-pinocarvone (−)-**13** in his case. Chelucci quoted his pinocarvone as dextrorotatory, which is apparently a mistake. Note that from his pinocarvone he eventually obtained (+)-**6**, whereas our product was levorotatory (vide infra), which further indicates an error in the sign of optical rotation of his pinocarvone; the rest of the generic tree in his paper is correct (including all the formulas and the absolute configuration of **6**).

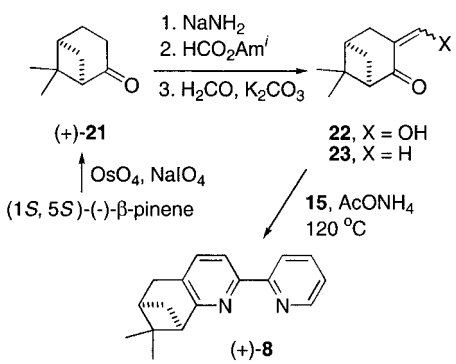
(14) (−)-*β*-Pinene was purchased from Aldrich, declared to have $[\alpha]_D$ −21 (neat); material of $[\alpha]_D$ −22 corresponds to 97% ee, according to the Aldrich catalogue. According to GC analysis on a Supelco *β*-DEX 120 column, this batch was of 95% ee. For determination of enantiopurity of monoterpene hydrocarbons by GC, see: Krüger, A.; Icheln, D.; Runge, T. *J. High Resolut. Chromatogr.* **1992**, *15*, 184.

(15) Hartshorn, M. P.; Wallis, A. F. A. *J. Chem. Soc.* **1964**, 5254.

Scheme 2



Scheme 3



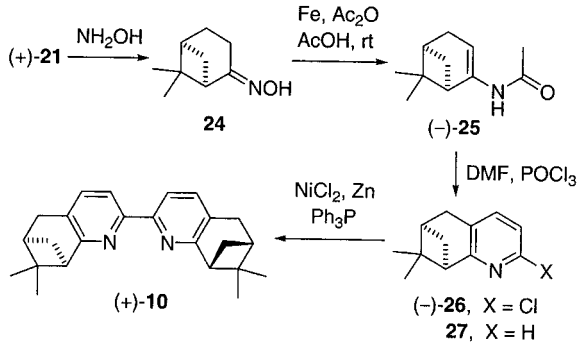
(THF, −40 °C, 2 h), followed by the reaction of the resulting organolithium with methyl iodide (−40 °C to room temperature, 12 h) produced (−)-**7** (80%).[17]

The C_2-symmetrical bipyridyl (−)-**9** was prepared form (+)-**13** via condensation with Kröhnke salt **14** (piperidine, MeOH, reflux, 24 h), followed by a ring closure with concomitant aromatization (200 °C, 2 h, $AcONH_4$, $HCONH_2$, AcOH), which afforded α-hydroxypyridine derivative (−)-**16** (39%), whose treatment with $POCl_3$−PCl_5 (neat, 100 °C, 5 h) led to α-chloropyridine derivative (−)-**17** (40%). Nickel(0)-mediated dimerization of the latter product [$NiCl_2$·$6H_2O$, Zn, Ph_3P, DMF, 65 °C, 20 h] then gave (−)-**9** (90%).[18]

The C_2-symmetrical bipyridine ligand (−)-**5** was prepared in an analogous way from (1*R*)-(−)-myrtenal (−)-**18** (Scheme 2), whose condensation with **14**, followed by cyclization, afforded (−)-**19** (15%). Treatment of the latter product with $POCl_3$ (DMF, 100 °C, 12 h) furnished the α-chloro derivative (−)-**20** (73% from crude **19**), whose Ni(0)-mediated dimerization [$NiCl_2$·$6H_2O$, Zn, Ph_3P, DMF, 65 °C, 20 h] gave rise to the desired ligand (−)-**5** (58%).

The C_1-symmetrical bipyridyl derivative (+)-**8**[6b] with positionally isomeric annulation of the terpene moiety was synthesized from (+)-nopinone (+)-**21** (Scheme 3), which in turn, was obtained by an oxidative cleavage of (−)-*β*-pinene (OsO_4, $NaIO_4$, Me_3NO, *t*-BuOH, H_2O, 80 °C, 2 h; 64%).[19,20] Enolization of (+)-**21** ($NaNH_2$, benzene, 60 °C, 15 h), followed by condensation with *iso*-amyl formate (0 °C → rt, 4 h), afforded crude **22**, which was converted into enone **23** via transaldolization (H_2CO, K_2CO_3, Et_2O, H_2O, rt, 40 min; overall 81%).[21] Condensation of the latter derivative with the Kröhnke salt **15** (120 °C, 12 h), followed by thermal cyclization, produced the required ligand (+)-**8** (51%).

Scheme 4



Synthesis of the C_2-symmetrical ligand (+)-**10** (Scheme 4) required a ready access to the α-chloropyridine derivative **26** as the key intermediate. We envisaged that the latter compound could be prepared via tandem Vilsmeier−Haack/aldol condensation reaction from **25**,[22] which in turn should be accessible from nopinone oxime **24**,[23] readily obtained from (+)-nopinone (+)-**21** (NH_2-OH·HCl, pyridine). The conversion of oximes into enamides has been known to occur in the presence of strong reducing agents, such as $(AcO)_2Cr$ or $(AcO)_3Ti$.[24] 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. Recently, iron metal has also been shown to convert ketoximes into enamides in good yields.[25] When applied to **24**, this method (Fe, Ac_2O, AcOH, 0 °C, 10 min), afforded **25** in 90% yield. Reaction of **25** under the Vilsmeier−Haack conditions (DMF, $POCl_3$, 0 °C, 2 h)[22] afforded the α-chloropyridine derivative **26** (70%). Stoichiometric, nickel(0)-mediated coupling of **26** ($NiCl_2$, Ph_3P, Zn, DMF, 60 °C, 18 h) furnished a mixture of the reduction product **27** (32%) and the desired dimer (+)-**10** (50%).[26] Although this coupling is, a priori, amenable to a catalytic process, reactions with substoichiometric amounts (e.g., 10 mol %) of Ni(0) turned out to lead predominantly to the reduction product **27**.

(16) Chelucci obtained *ent*-**6**, which had $[\alpha]_D$ +97.46 (*c* 2.6, $CHCl_3$).[8] In our case, **6** had $[\alpha]_D$ −86.5 (*c* 2.8, $CHCl_3$). The difference in the absolute value of the optical rotation is apparently associated with the enantiopurity of the starting materials, i.e., (−)-*β*-pinene and (−)-*trans*-pinocarveol, respectively (vide supra).

(17) For comparison with known data, see refs 7, 8.

(18) Dimer (−)-**9** has been reported before but without experimental details of its preparation.[7a]

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

(20) (+)-Nopinone (+)-**21** thus prepared from the commercially available (−)-*β*-pinene (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),[19] our nopinone corresponds to ∼86% ee.

(21) Gianini, M.; von Zelewsky, A. *Synthesis* **1996**, 702.

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

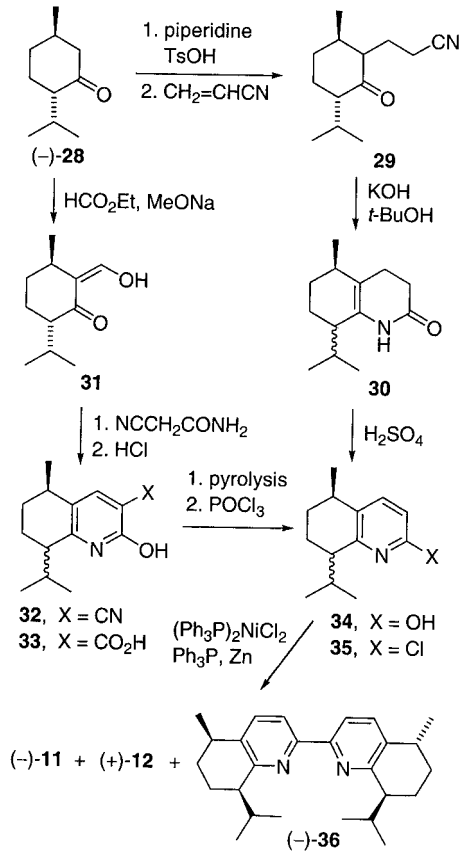
(23) (a) Hall, H. K. *J. Org. Chem.* **1963**, *28*, 3213. (b) Quon, H. H.; Chow, Y. L. *Tetrahedron* **1975**, *31*, 2349. (c) Yokoyama, Y.; Yunokihara, M. *Chem. Lett.* **1983**, 1245.

(24) (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.

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

(26) 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.

Scheme 5



The synthetic route to bipyridyl ligands **11** and **12** (Scheme 5) commenced by oxidation of (−)-menthol to (−)-menthone (−)-**28** [$Ca(ClO)_2$,[27,28] CH_2Cl_2, MeCN, AcOH, H_2O, 0 °C, 1 h, 98%] and its conversion into the corresponding enamine (piperidine, TsOH, Dean−Stark, 24 h; 42%).[29,30] Addition of acrylonitrile to the latter enamine (reflux for 3 h in EtOH), followed by hydrolysis (AcOH, AcONa, dioxane, H_2O, reflux, 2 h), afforded ketonitrile **29** as a mixture of diastereoisomers (94% on 20 mmol scale; 82% on 0.26 mol scale) that were not separated. Cyclization of **29** was effected by powdered KOH in *t*-BuOH (reflux, 1 h)[31] to produce **30** (75%) as a 1:1 epimeric mixture, which could be separated by chromatography. However, this separation was unnecessary since aromatization with both H_2SO_4[32] (rt, 12 h, 74%) and SO_2Cl_2 (100 °C, 30 min, 45%) also led to epimerization, giving the α-hydroxypyridine derivative **34** as a 1:1 mixture of epimers.

An alternative route to the latter product involved Claisen condensation of (−)-menthone (−)-**28** with HCO_2Et to furnish **31** (MeONa, toluene, rt, 48 h, 75%),[33] Knoevenagel condensation of which[34] with α-cyanoacetamide, followed by a spontaneous cyclization, furnished hydroxy nitrile **32** (EtOH, H_2O, reflux, 12 h, 54%)[35] as a 1:1 mixture of epimers that was hydrolyzed (concentrated HCl, reflux 6 h) to afford hydroxy acid **33** (81%). The latter two steps could also be carried out in one pot to give **33** in 62% yield (compare to the 44% overall yield in the stepwise process).[36] Subsequent pyrolytic decarboxylation of **33** (heating to the melting point, ≤1 h, 95%), followed by chlorination of the resulting α-hydroxypyridine derivative **34** (PCl_5, $POCl_3$, $PhNMe_2$, reflux, 12 h),[37] led to chloro derivative **35** (88%),[38,39] whose Ni(0)-catalyzed dimerization [$(Ph_3P)_2NiCl_2$ (2.5 mol %), Zn, Ph_3P, DMF, 80 °C, 7 h)[40] produced a mixture of (−)-**11** (16%), (+)-**12** (21%), and (−)-**36** (35%), easily separated by flash chromatography. The structure of the products was determined by single-crystal X-ray crystallography (see the Supporting Information). Interestingly, isomer **36** can be equilibrated (BuLi, THF, −78 °C, 1 h, followed by acidic quench) to produce a ∼1:1:1 mixture of the three diastereoisomers.

Since **10** and **11** proved to be the most promising ligands of this series (vide infra) and may, therefore, find wider application in asymmetric catalysis, we propose the acronym "PINDY" (*pin*ene-*d*erived bip*y*ridine) for the former and "MINDY" (*m*enthol- or *min*t-*d*erived bip*y*ridine) for the latter ligand.

Coordination of Bipyridyl Ligands to Molybdenum(0). Refluxing of $Mo(CO)_6$ and the corresponding ligand **5**−**8** in toluene for 2 h (Scheme 6), followed by cooling and adding hexane, led to the precipitation of the respective complexes **37** (orange-red), **38**, **39**,[41] and **40** (all dark red). By contrast, bipyridyls **9**−**12** failed to form a complex even after prolonged heating. Inspection of the crystal structures of ligands **11** and **12** revealed an *s-trans* conformation about the bond connecting the two nuclei, which is presumably dictated by the repul-

(27) (a) Nwaukwa, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, 35. (b) For a review on oxidations, see: Skarzewski, J.; Siedlecka, R. *Org. Prep. Proc. Int.* **1992**, *24*, 623.

(28) Jones oxidation of (−)-menthol, although high yielding (98%), was less suitable for large-scale preparation owing to the large quantities of Cr(III) produced. Moreover, the product in this case was a 10:1 mixture of (−)-menthone and isomenthone owing to partial epimerization at the α-position. The $Ca(ClO)_2$ method was more selective, affording a 15:1 mixture.

(29) (a) Könst, W. M. B.; Witteveen, J. G.; Boelens, H. *Tetrahedron* **1976**, *32*, 1415. (b) Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R.; Stuart, A. D. *Aust. J. Chem.* **1979**, *32*, 2079. (c) Hönel, M.; Vierhapper, F. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1933.

(30) This conversion is consistent with several previous preparations;[29] we were unable to match the quoted yield of 90% reported by Hieda even when repeating the procedure several times: Hieda, T.; Tazaki, M.; Morishita, Y.; Aoki, T.; Nagahama, S. *Phytochemistry* **1996**, *41*, 159.

(31) Hall, J. H.; Gisler, M. *J. Org. Chem.* **1976**, *41*, 3769.

(32) Meyers, A. I.; Garcia-Munoz, G. *J. Org. Chem.* **1964**, *29*, 1435.

(33) According to NMR, **31** contained ∼5% of its epimer.

(34) Sen-Gupta, H. K. *J. Chem. Soc.* **1915**, 1347.

(35) The relatively low yield of **32** reflects difficult isolation rather than poor reactivity.

(36) Although the epimers of **33** could be separated by crystallization of the α-methylbenzylamine salts, the subsequent decarboxylation led to epimerization.

(37) Zimmerman, S. C.; Zeng, Z.; Wu, W.; Reichert, D. E. *J. Am. Chem. Soc.* **1991**, *113*, 183.

(38) Chlorination is known to generally occur with concomitant equilibration of the chiral centers α-positioned to the 2-pyridinone ring: Monti, S. A.; Schmidt, R. S.; Shoulders, B. A.; Lochte, H. L. *J. Org. Chem.* **1972**, 37, 3834.

(39) Since the resulting epimers of 2-chloropyridine **35** proved to be too lipophilic, the latter mixture was converted into the corresponding *N*-oxides, whose separation by flash chromatography (1−2 g scale) proved viable. However, the subsequent reduction of one of the diastereoisomerically pure *N*-oxides (NaH_2PO_2, Pd/C) gave a mixture of **35** (35%, single diastereoisomer) and the corresponding dechlorinated product (47%), whose separation would add to the complexity of the sequence.

(40) This procedure represents a catalytic variant to the known stoichiometric reaction: (a) Tieco, M.; Testaferri, L.; Tingoli, M.; Chiranelli, D.; Montanucci, M. *Synthesis* **1984**, 736. (b) Torii, S.; Tanaka, H.; Morisaki, K. *Tetrahedron Lett.* **1985**, *26*, 1655. (c) Vanderesse, R.; Lourak, M.; Fort, Y.; Gaubere, P. *Tetrahedron Lett.* **1986**, *27*, 5483. (d) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, 80. (e) Ito, K.; Katsuki, T. *Tetrahedron* **1992**, *34*, 3653. (f) Chelucci, G.; Falorini, M.; Giacomelli, G. *Tetrahedron Lett.* **1993**, *48*, 2661.

(41) Complex **39** is thermally rather unstable so that lower temperature and shorter time (100 °C for 1 h) had to be used at the expense of conversion, which was not quantitative.

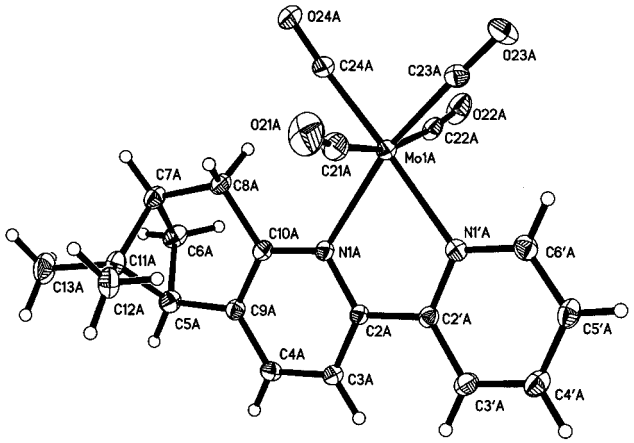
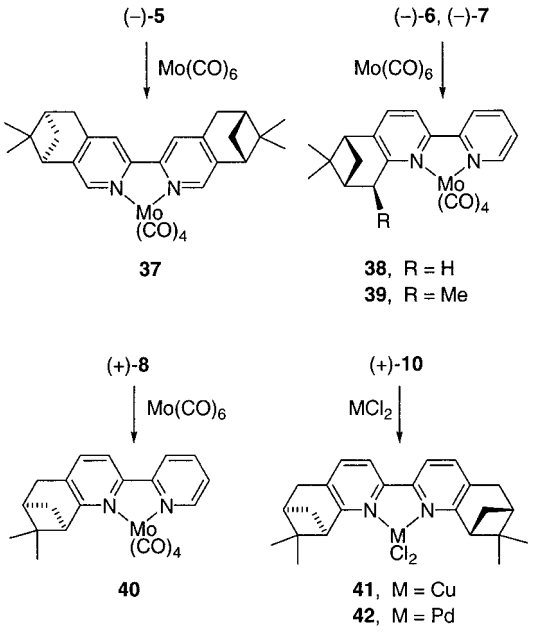


Figure 1. ORTEP diagram of the monoclinic **38** showing the atom-labeling scheme. Displacement parameters are shown at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

Scheme 6



sion of the bulky appendices (see the Supporting Information). The latter effect can also be anticipated to operate in the solution so that the failure to coordinate a bulky metal by these potentially bidentate ligands can be understood. Furthermore, even if the two nitrogen atoms in these ligands were available for chelation, the hexacoordinate molybdenum moiety is apparently too bulky to fit the cavity.

Complexes **38**−**40** were characterized by single-crystal X-ray crystallography.[42] Interestingly, complex **38** exhibited polymorphism: two different kinds of crystals (monoclinic and tetragonal) crystallized from the same batch and could be separated mechanically. In the monoclinic form of **38** (Figure 1), there are two molecules in the asymmetric unit. Molecules interact via hydrogen bonds as follows (Figure 2): C(8B) acts as a double donor: one hydrogen is donated to O(22B), i.e., to the same molecule, rotated by 2-fold axis, while

(42) For a recent crystallographic study on the related, nonchiral (phen)Mo(CO)$_2$(allyl)(CF$_3$CO$_2$) complexes, see: Eriksson, L.; Sjögren, M. P. T.; Åkermark, B. *Acta Crystallogr. (C)* **1996**, *52*, 77.

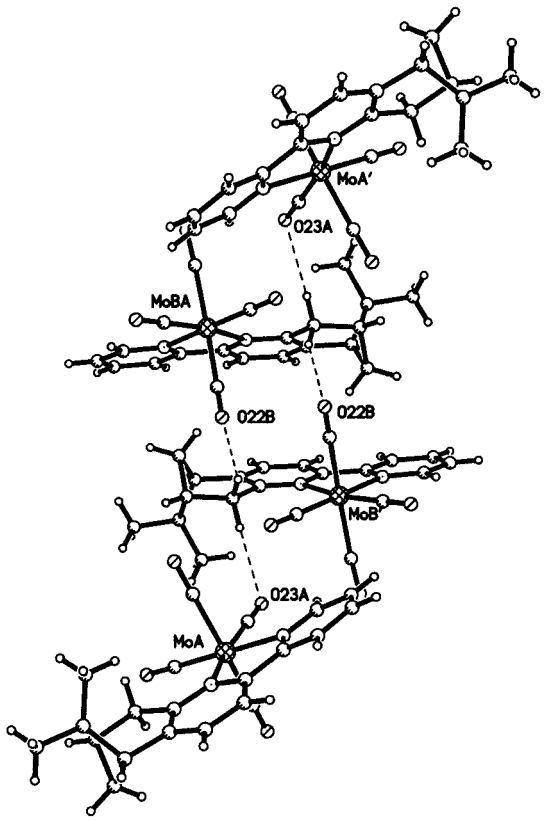


Figure 2. Packing of molecules in monoclinic **38**.

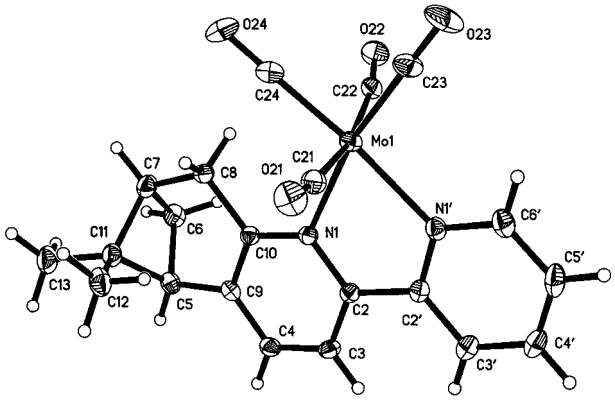


Figure 3. ORTEP diagram of the tetragonal **38** showing the atom-labeling scheme. Displacement parameters are shown at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

the other hydrogen is donated to O(23A), i.e., to the other molecule. This interaction is rather strong and is governing crystallization of this form. Hence, molecules A and B differ by a local charge distribution, which can explain the existence of two symmetrically independent entities in the solid state and the formation of tetramers. In the tetragonal form of **38** (Figure 3), the interaction of the molecules (one in the asymmetric unit) is entirely different and the molecules form infinite chains (Figure 4). These two kinds of conglomerations (linear chains and tetramers) should already exist in the solution, and their existence leads to polymorphism.

Crystals of **39** were monoclinic (Figure 5). Again there are two molecules in the asymmetric unit, but the 3D arrangement differs from that of the monoclinic complex **38**. Molecules B form an infinite two-dimensional net in the *a*,*c*-plane, while molecules A form just a one-

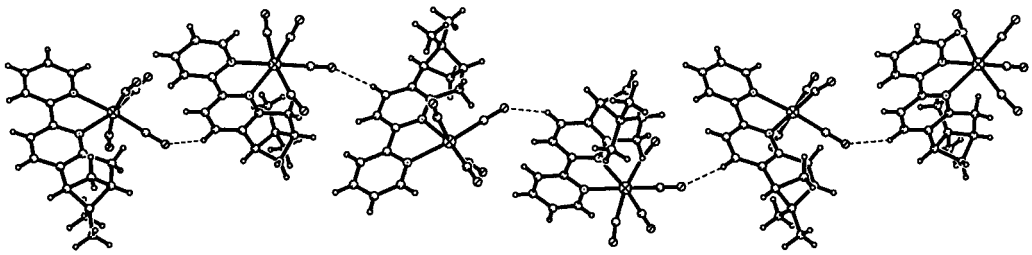


Figure 4. Packing of molecules in tetragonal **38**.

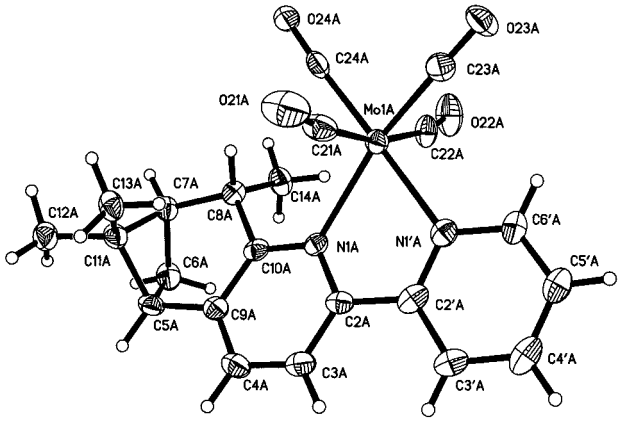


Figure 5. ORTEP diagram of **39** showing the atom-labeling scheme. Displacement parameters are shown at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

dimensional chain parallel to the *c*-axis (Figures 6 and 7). There is also a weak interaction between molecules A and B in the direction of the screw-axis *b*.

Crystalline **40** was monoclinic again (Figure 8) with two independent molecules in the asymmetric unit, forming an infinite two-dimensional net of molecules A and a linear chain of molecules B (Figures 9 and 10), similar to those of **39**, but without any interaction between these two types of molecules.

Coordination of PINDY (10) to Copper(II). Refluxing a mixture of (+)-**10** and $CuCl_2 \cdot H_2O$ in CH_2Cl_2–EtOH for 12 h led to a practically quantitative formation of complex **41** (75% after recrystallization).[43] Single-crystal X-ray analysis of the latter complex revealed an unusually distorted geometry at the metal (Figure 11), placing this complex closer to the family of Cu(I) compounds, which may have significant implications for its catalytic activity[44] (vide infra). There is one molecule in the asymmetric unit; hydrogen bonds give rise to an infinite one-dimensional chain of molecules (Figure 12), formed by a screw-axis parallel to the *c*-axis together with a translation in direction of the *b*-axis. The EPR spectrum of complex **41** (Figure 13) in the powder state is of axial symmetry with $g_{\parallel} = 2.305$ and $g_{\perp} = 2.049$. The EPR data are consistent with the C_{2v} tetrahedrally distorted rectangular geometry at the copper atom; the ground electronic state for this type of geometry is $d_{x^2-y^2}$ (A_1).[45,46]

Coordination of PINDY (10) to Palladium(II). Refluxing a mixture of (+)-**10** and $PdCl_2$ in MeCN for 30 min resulted in the precipitation of the expected complex (+)-**42**.[47] Although we failed to grow a monocrystal suitable for crystallographic analysis, the complex exhibited ^1H and ^{13}C NMR characteristics that would be expected for this class of compounds, namely, the differences in chemical shifts of the free ligand and the complex.

Asymmetric Allylic Substitution Catalyzed by Mo(0) Complexes. Since nonchiral Mo(0) complexes having α,α-bipyridine or phenanthroline as the ligand have been recognized as suitable catalysts for allylic substitution, we endeavored to evaluate the efficacy of our ligands **5**–**8** in the asymmetric version of this reaction.[48] To this end, we employed standard substrates, namely, cinnamyl acetate **43** and its phenyl analogue **45** and $NaCH(CO_2Me)_2$ as the nucleophile (Scheme 7). The catalysts were generated according to our recently developed protocol:[49] the deep red (LL*)-$Mo^0(CO)_4$ complex **37**–**40** (LL* = chiral bipyridine ligand) was first submitted to the oxidative addition of $SnCl_4$ in CH_2Cl_2 to precipitate the orange-yellow pre-catalyst $(LL)Mo^{II}(CO)_3(SnCl_3)Cl$, whose subsequent in situ reduction with excess NaH (employed to generate dimethyl sodiomalonate) produced the active Mo(0)

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

(44) 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 **41**). This type of distortion is believed to be responsible for high asymmetric induction observed for several classes of reactions. 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.

(45) With regard to the doublet d_{xz} (B_1) and d_{yz} (B_2) splitting, a nonaxial EPR spectrum should be expected for this type of symmetry. Inspection of the orbitals' symmetry in tetrahedral and pseudotetrahedral geometries suggests that the wave functions are mixed in the ground as well as in the other states. The ground state is given by the following equation: $\psi(A_1) = \alpha d_{x^2-y^2} + \delta d_{z^2} + \eta p_z + \delta_1 s$. To simplify the formulas for spin Hamiltonian parameters, admixtures from p and s orbitals ($\eta = \delta = \delta_1 = 0$) can be neglected. On neglecting the d_{z^2} admixture to the ground state, a plot of g (and A) versus the dihedral angle ϕ in symmetry C_{2v} is obtained, showing negligible change in g (and A) with the dihedral angle ϕ (for more details see: Hoffmann, S. K.; Goslar, J. *J. Solid State Chem.* **1982**, *44*, 343.). Thus, for a trigonal distortion ($0° < \phi < 90°$), the EPR data remain essentially unaffected and the nonaxiality of the EPR spectrum ($g_x - g_y$) is very small and practically negligible, which was, in fact, observed in case of the EPR spectrum of **41**.

(46) No improvement in resolution of the EPR spectrum was obtained for experiments employing a frozen solution of complex **41** in CH_2Cl_2.

(47) For bipy complexes of Pd(II), see, for example, ref 43.

(48) For the first reports on successful, highly enantioselective Mo(0)-catalyzed allylic substitution, see ref 12k and the following: (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (b) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141. (c) Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416. (d) Belda, O.; Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Hallberg, A.; Moberg, C. *J. Org. Chem.* **2000**, *65*, 5868. (e) Kočovský, P.; Malkov, A. V.; Vyskočil, Š.; Lloyd-Jones, G. C. *Pure Appl. Chem.* **1999**, *71*, 1425. For its W(0)-catalyzed counterpart, see: (f) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462.

(49) Baxendale, I. R.; Malkov, A. V.; Mansfield, D. J.; Kočovský, P., manuscript in preparation.

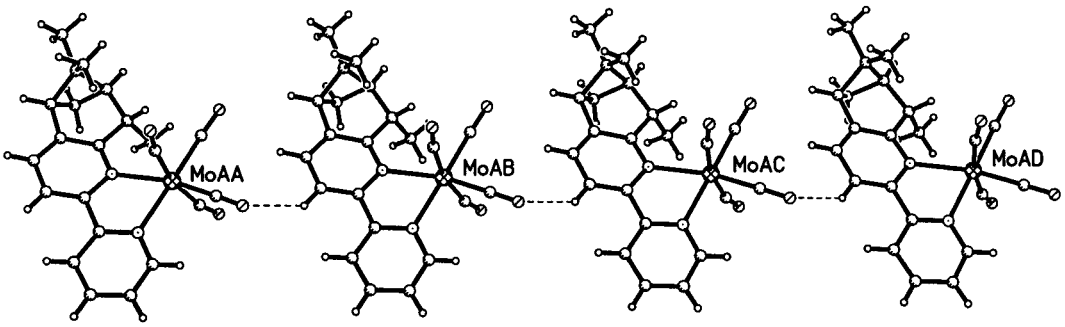


Figure 6. Packing of molecule A for **39**.

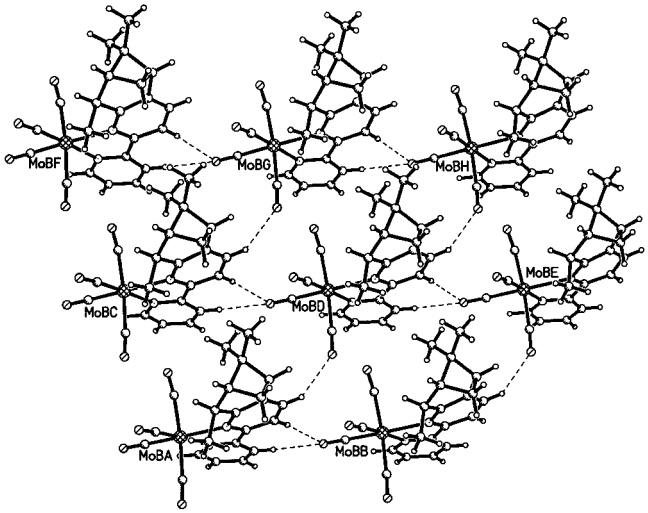


Figure 7. Packing of molecule B for **39**.

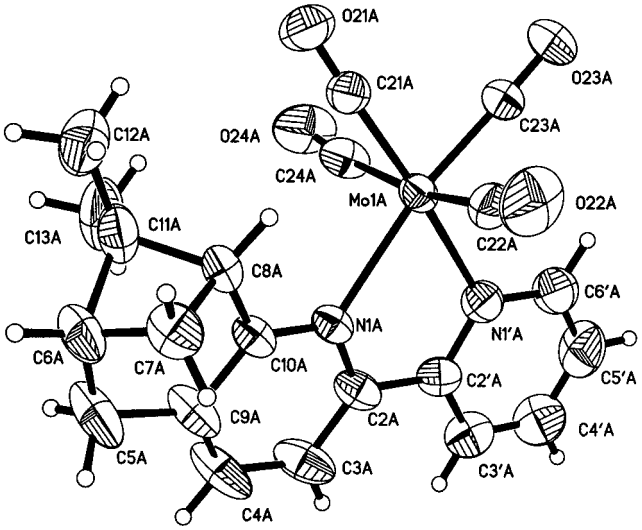


Figure 8. ORTEP diagram of the monoclinic **40** showing the atom-labeling scheme. Displacement parameters are shown at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

species.[49] The latter reduction was characterized by turning the color of the solution to blue or deep purple. The reactions were carried out at 80 °C in 1,4-dioxane, and the progress was monitored by TLC (30 min to 24 h).[50] With **37**, cinnamyl acetate **43** afforded (*R*)-(+)-**44** in 42% yield with good regioselectivity (78:22 in favor of the branched product **44**) but with low enantioselectivity (12% ee). With **45**, the reaction produced (*R*)-(+)-**46** (22% yield, 10% ee). Complex **38** catalyzed transformation of **43** into (*S*)-(−)-**44** in 52% yield (quantitative conversion) with good regioselectivity (86:14) but low enantioselectivity (22% ee). The more sterically encumbered methyl analogue **39**, on the other hand, proved to be inert to both **43** and **45**. Finally, complex **40** produced (*S*)-(−)-**44** in 33% yield (at ∼50% conversion) with good regioselectivity (87:13) but poor enantioselectivity (∼8% ee).[51]

Asymmetric Allylic Substitution Catalyzed by Pd(0) Complexes. The C_2-symmetrical complex **42** catalyzed the reaction of **45** to give (*S*)-(−)-**46** though in low yield (28%) and with only 20% ee. The Pd complex generated in situ from the C_1-symmetrical ligand (+)-**8** turned out to be a better catalyst, affording (*S*)-(−)-**46** in 60% yield and with 26% ee.[51] These results contrast with those obtained for the homologues of ligand **7** (e.g., R = *i*-Pr, Bn), which were reported to be high (79 and 89% ee, respectively).[8]

Asymmetric Allylic Oxidation Catalyzed by Cu(I) Complexes. Allylic oxidation is one of the testing grounds for new chiral ligands. A variety of complexes have been designed to facilitate this reaction, including those with the metal coordinated to sp^2-nitrogen, as in the oxazoline-type complexes.[52] However, the catalysts reported to date often require several days to allow completion of the reaction,[52a] and the enantioselectivity seldom exceeds ∼80% ee.[52] We felt that, owing to the unique geometry of **41**, Cu(II) complexes of PINDY (**10**) may offer an interesting entry in this area. Since this reaction requires weakly coordinating anionic ligands (rather than the strongly bound Cl^-), we first generated a Cu(II) complex from **10** and $Cu(OTf)_2$ that was in situ reduced with phenylhydrazine to the corresponding Cu(I) species. To probe the catalytic capability of the latter complex, we employed cyclohexene (**47b**) as the representative alkene and *tert*-butyl peroxybenzoate as the oxidant. Monitoring the reaction by TLC revealed a remarkably high catalytic activity of the **10**−CuOTf complex (employed at 1 mol % level): the oxidation was complete within ≤30 min at room temperature, giving

(50) Noteworthy is the color of the reaction mixture: a change from blue-purple to light red signals decomposition of the catalyst.

(51) The ee was determined by chiral HPLC on Chiralcel OD-H column for the reaction of **43** and by the ^{1}H NMR spectroscopy using $Eu(hfc)_3$ for the reactions of **45**.

(52) (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.

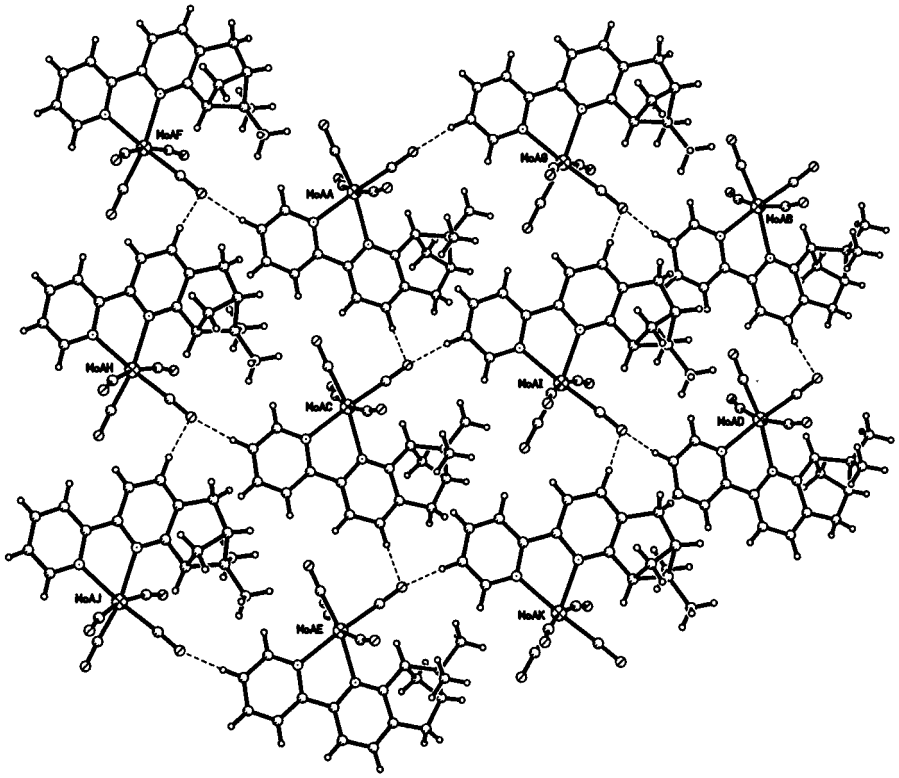


Figure 9. Packing of molecule A of **40**.

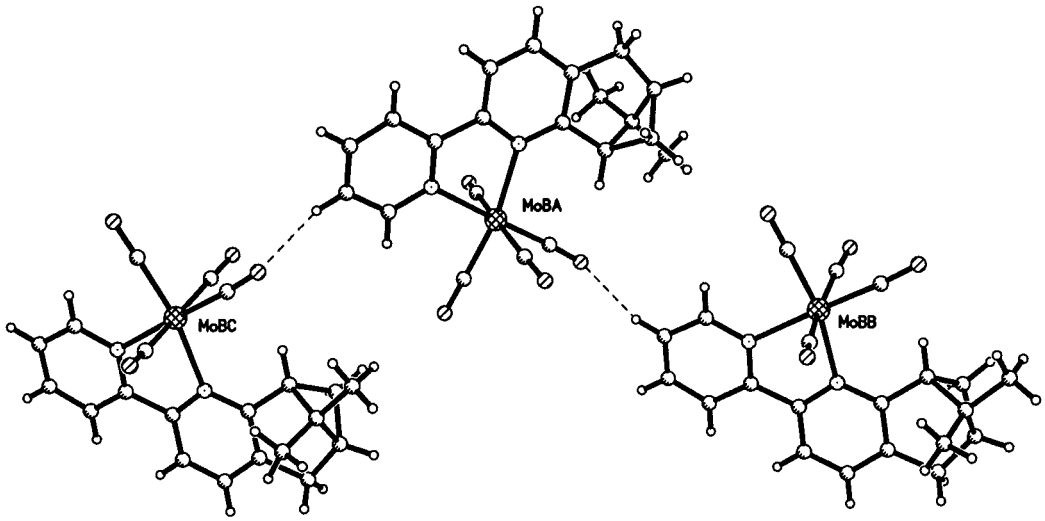


Figure 10. Packing of molecule B of **40**.

(*S*)-**48b** in 96% yield and of 49% ee (Table 1, entry 3). Practically identical results were obtained with the Cu(I) complex generated directly from **10** and $(CuOTf)_2 \cdot C_6H_6$ (entry 4). Lowering the reaction temperature to 0 and −20 °C, respectively, had a beneficial effect on enantioselectivity (55% and 60% ee, respectively; entries 5 and 6), though the reaction required longer periods. Similar results were obtained with cyclopentene **47a** (entries 1 and 2).[53,54] Cycloheptene (**47c**), on the other

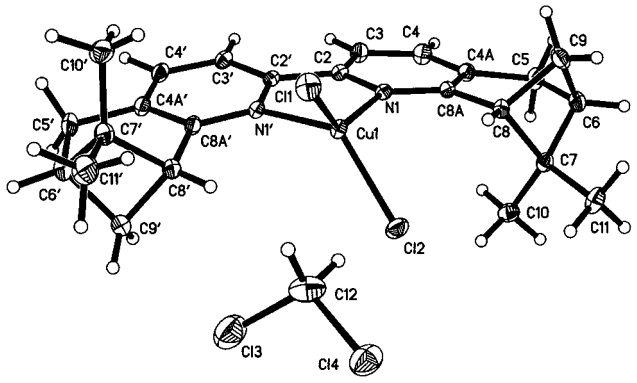


Figure 11. ORTEP diagram of **41** showing the atom-labeling scheme. Displacement parameters are shown at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

(53) Since the starting (+)-nopinone (+)-**21** was not enantiomerically pure (86% ee),[20] the observed enantioselectivities might, in principle, be higher. However, the synthesis of ligand (+)-**10** 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 (+)-**10** by chiral HPLC and by NMR spectroscopy [in the presence of $Eu(hfc)_3$], its ultimate precursor (−)-**26** was found to be of 95% ee by HPLC.

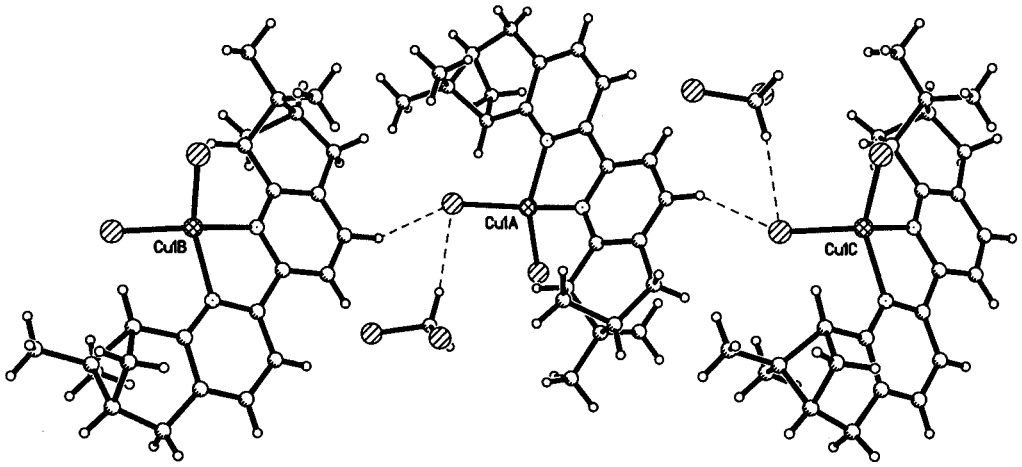


Figure 12. Packing of molecules in **41**.

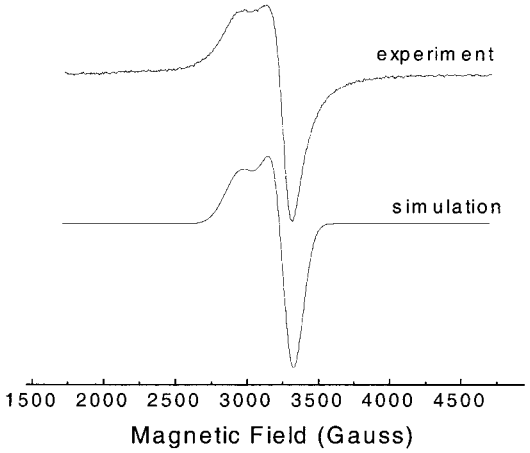
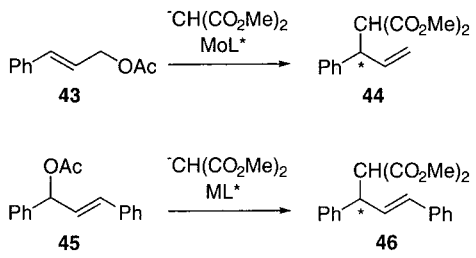


Figure 13. EPR spectrum (experimental and simulated) of complex **41** at room temperature.

hand, exhibited substantially better enantioselectivity (62% ee at room temperature and 75% ee at 0 °C; entries 9 and 10).[53,54] In all cases the reaction was significantly slower at 0 °C (5−10 h). These promising results suggest that optimization of the reaction conditions, of the counteranion,[55] and of the ligand may lead to a very efficient catalytic system.[56,57] By contrast, complexes of other ligands, generated in situ from $Cu(OTf)_2$ in a similar manner, turned out to be less stable to the oxidation to Cu(II) under the reaction condition (as evidenced by the color change from red to green) and gave less encouraging results. Thus, with **12**, (*S*)-**48b** was obtained in 70% yield and was of mere 11% ee (entry 8), and **11** induced the formation of (*R*)-**48b** (rt, 24 h, 74%) with 19% ee (entry 7). These findings clearly demonstrate the superiority of ligand **10** that can be attributed to the stabilization of Cu geometry halfway between square planar [favored by Cu(II)] and tetrahedral [favored by Cu(I)].

Asymmetric Cyclopropanation Catalyzed by Cu(I) Complexes. To further validate the PINDY-type

Scheme 7



ligands, we briefly studied cyclopropanation of styrene with esters of diazoacetic acid as the metallocarbene source (Scheme 9).[58,59] The reaction was carried out in CH_2Cl_2 in the presence of the catalyst (1 mol %) at room temperature via a slow addition of the diazoacetic ester over a period of 3 h (Table 2). The catalyst was generated in a manner similar to that for the allylic oxidation, i.e., via the in situ reduction with phenyl hydrazine of the complex of $Cu(TfO)_2$ and the ligand. This catalyst turned out to perform slightly better than the complex prepared from $(CuOTf)_2{\cdot}C_6H_6$. In contrast to allylic oxidation, PINDY (**10**) proved to be much less enantioselective (entries 1 and 2) than MINDY (**11**) (entries 3 and 4). Furthermore, while both ethyl and *tert*-butyl diazoacetates exhibited essentially identical enantioselectivities, the latter ester was considerably

(54) The absolute configuration of the product was determined by comparison of its optical rotation with the known values.[52]

(55) For the role of the counterion in Cu(I)- and Cu(II)-catalyzed reactions, see ref 44.

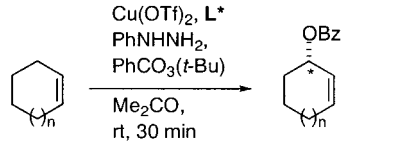
(56) Apparently, the reaction requires a trace of water since adding molecular sieves resulted in a dramatic deceleration (though the enantioselectivity remained essentially unaffected).

(57) Note that individual ligands[52] have different "optimal substrates"; in the case of PINDY it is **11c** that gives the highest enantioselectivity.

(58) For an overview of asymmetric, metal-catalyzed cyclopropanation, see, for example, ref 1 and the following: (a) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; J. Wiley: New York, 1998. For selected, recent examples, see the following. **Cu**: (b) Frischi, H.; Leuteneggar, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553, and references therein. (c) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (d) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373. (e) Müler, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (f) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (g) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430. (h) Schumacher, R.; Dammast, F.; Reissing, H. U. *Chem. Eur. J.* **1997**, *3*, 614. (i) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518. (j) Temme, O.; Taj, S.-A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 6007, and references therein. (k) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 649. **Co**: (l) Yamada, T.; Ikeno, T.; Sekino, H.; Sato, M. *Chem. Lett.* **1999**, 719. (m) Ikeno, T.; Sato, M.; Yamada, T. *Chem. Lett.* **1999**, 1345. (n) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647, and papers cited therein. **Ru**: ref 58n.

(59) For the recently developed bipyridine-type complexes that catalyze cyclopropanation, see, for example, refs 4a, 9, 10j,k and the following: (a) Ito, K.; Katsuki, T. *Tetrahedron Lett.* **1993**, *34*, 2661. (b) Ito, K.; Katsuki, T. *Synlett* **1993**, 638.

Scheme 8



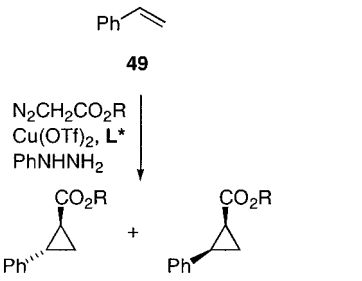
47a, n = 0 (*S*)-(−)-**48a**, n = 0
47b, n = 1 (*S*)-(−)-**48b**, n = 1
47c, n = 2 (*S*)-(−)-**48c**, n = 2

Table 1. Asymmetric Allylic Oxidation of Cycloalkenes 47a−c Catalyzed by Cu(I) Complexes with Chiral Ligands 10−12 (Scheme 8)[a]

entry	olefin	ligand	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	**47a**	**10**	20	0.5	85	48
2	**47a**	**10**	0	12	80	59
3	**47b**	**10**	20	0.5	96	49
4	**47b**	**10**[c]	20	2	95	49
5	**47b**	**10**	0	5	88	55
6	**47b**	**10**	−20	48	56	60
7	**47b**	**11**	20	24	74	19[d]
8	**47b**	**12**	20	24	70	11
9	**47c**	**10**	20	0.5	88	62
10	**47c**	**10**	0	12	66	75

[a] The reactions were carried out in Me_2CO in the presence of the catalysts (1 mol %), generated in situ by reduction of $Cu(OTf)_2$ with $PhNHNH_2$. [b] Determined by chiral HPLC. [c] $(CuOTf)_2 \cdot C_6H_6$ was used directly to generate the catalyst. [d] (*R*)-(+)-Enantiomer was formed owing to the opposite local chirality of the ligand.

Scheme 9



(1*S*)-(+)-**50a**, R = Et (1*S*)-(+)-**51a**, R = Et
(1*S*)-(+)-**50b**, R = *t*-Bu (1*S*)-(+)-**51b**, R = *t*-Bu

Table 2. Asymmetric Cyclopropanation of Styrene 49 with Alkyl Diazoacetates Catalyzed by Cu(I) Complexes of Chiral Ligands 10 and 11 (Scheme 9)[a]

entry	ligand	R	yield (%)	**50**: **51**	ee (**50**)[b,c]	ee (**51**)[b,c]
1	**10**	Et	≥95	65:35	10	15
2	**10**	t-Bu	61	83:17	16	16
3	**11**	Et	85	72:28	72	70
4	**11**	t-Bu	95	84:16	67	69

[a] The reaction was carried out in CH_2Cl_2 with a slow addition of diazoacetate (syringe pump) over 3 h at room temperature. The Cu(I) complex (1 mol %) was generated in situ from $Cu(OTf)_2$ and $PhNHNH_2$ in the presence of the ligand. [b] Determined by chiral HPLC. [c] The absolute configuration of the products was deduced from their optical rotation as (1*S*)-(+)-**50** and (1*S*)-(+)-**51** (ref 58).

more diastereoselective in favor of the *trans*-isomer of the product (compare entry 1 vs 2 and 3 vs 4) with each of the catalyst.

Conclusions

In conclusion, we have synthesized a series of bipyridine-type chiral ligands **5**−**12** via a de novo construction of the pyridine nucleus that had been annulated to a chiral synthon originating from the monoterpene realm. Complexes of these ligands with Mo(0), Pd(II), and Cu(II) have been prepared and several of them characterized by single-crystal X-ray crystallography (**38**−**41**); interestingly, **38** exhibited polymorphism. The C_2-symmetrical Cu(II) complex **41** is characterized by unique geometry of the metal coordination (Figure 11). The Mo and Pd complexes showed modest asymmetric induction in allylic substitution. The Cu(I) catalyst, derived from ligand (+)-**10** (PINDY), exhibited promising enantioselectivity (∼50−75% ee) and reaction rate (≤30 min at room temperature) in allylic oxidation (Scheme 8). Further encouraging results (≤72% ee) were obtained with the Cu(I) complex of ligand (−)-**11** (MINDY) for asymmetric cyclopropanation (Scheme 9). These experiments have demonstrated the effectiveness of this class of chiral bipyridine ligands. Their chiral cavity can, in principle, be further tuned by varying the sterics through employing different chiral building blocks. Furthermore, the de novo synthesis of the pyridine rings should allow controlling the electronics of the ligating nitrogen atoms through substitution in 4- and 4′-positions. The number of reactions known to be catalyzed by nonchiral bipyridine complexes suggests that these ligands can be expected to enjoy a broad scope in asymmetric catalysis.

Experimental Section

General Methods. Melting points were determined on a Kofler block and are uncorrected; molybdenum complexes **37**−**40** decomposed on heating at ca. 250 °C without melting. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated with an error of $<\pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^{1}H at 250 MHz and ^{13}C at 62.9 MHz with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0, ^{13}C) as internal standard. Various 2D techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film between KBr plates, for $CHCl_3$ solutions, or using the "Golden-Gate" technique. The mass spectra (EI and/or CI) were measured on a dual-sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. The X-band EPR spectrum in the powder state was recorded at room temperature on a Bruker SRC-200 D spectrometer coupled to an Aspect 2000 and equipped with a variable-temperature unit. Line positions were measured accurately using internal field markers generated by an NMR gaussmeter, while the microwave frequency was measured by a microwave frequency counter; a 100 kHz magnetic field modulation (peak-to-peak amplitude ≈3 G) was used.[60] The EPR spectrum was simulated on an IBM-compatible PC computer using a program developed in our laboratory.[61] The X-ray techniques are described for each individual experiment. The GC−MS analysis was performed with an RSL-150 column (25 m × 0.25 mm). All reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware twice evacuated and filled with nitrogen. Experiments involving copper complexes were carried out under an atmosphere of argon. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: diethyl ether from lithium aluminum hydride, tetrahydrofuran (THF) from sodium/benzophenone; dichloromethane from calcium

(60) For details, see: Valko, M.; Morris, H.; Mazur, M.; Telser, J.; McInnes, E.; Mabbs, F. *J. Phys. Chem. B* **1999**, *103*, 5591.
(61) Pelikan, P.; Liška, M.; Valko, M.; Mazur, M. *J. Magn. Reson.* **1996**, *A122*, 9.

hydride. Standard workup of an ethereal solution means washing 3× with 5% HCl (aqueous), water and 3× with 5% $KHCO_3$ (aqueous) and drying with $MgSO_4$. Petroleum ether refers to the fraction boiling in the range 40−60 °C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. (−)-*β*-Pinene was purchased from Aldrich and had $[\alpha]_D$ −21 (neat).[14] (−)-Menthol was purchased from Aldrich and had $[\alpha]_D$ −50 (*c* 10; EtOH). (−)-Myrtenal **18** was purchased from Aldrich and had $[\alpha]_D$ −15 (neat).

(6*R*,6′*R*,8*S*,8′*S*)-(−)-5,5′,6,6′,7,7′,8,8′-Octahydro-7,7,7′,7′-tetramethyl-3,3′-bis(6,8-methanoisoquinoline), (−)-5. Zinc powder (130 mg, 2.0 mmol) was added to a warm solution of $NiCl_2 \cdot 6H_2O$ (368 mg, 1.55 mmol) and PPh_3 (1.63 g, 6.2 mmol) in degassed DMF (5 mL). The mixture was heated at 60 °C for 2 h, during which period the color changed from blue to red. Then a solution of (−)-**20** (319 mg, 1.53 mmol) in DMF (2 mL) was added. The mixture was heated at 60 °C for a further 18 h and then poured into 10% aqueous NH_3 (50 mL). The resulting suspension was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was removed in a vacuum. The residue was purified by chromatography on silica gel with a mixture of hexane−ethyl acetate (9:1) as an eluent to give the title compound (−)-**5** (154 mg, 58%) as a white solid: $[\alpha]_D$ −80.2 (*c* 3.06, $CHCl_3$) (lit.[6b] $[\alpha]_D$ −104); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.55 (s, 6H, 7,7′-Me), 1.15 (d, *J* = 9.4 Hz, 2H, 9,9′-C*H*H), 1.31 (s, 6H, 7,7′-Me), 2.20 (m, 2H, 6,6′-CH), 2.60 (ddd, *J* = 9.4, 5.7, and 5.7 Hz, 2H, 9,9′-CH*H*), 2.76 (dd, *J* = 5.5 and 5.5 Hz, 2H, 8,8′−H), 2.95 (m, 4H, 5,5′-CH_2) 8.07 (s, 2H, 4,4′−H), 8.09 (s, 2H, 1,1′-H) in agreement with the literature.[6b]

(5*S*,7*R*)-(−)-5,6,7,8-Tetrahydro-6,6-dimethyl-2-(pyridin-2-yl)-5,7-methanoquinoline, (−)-6. It was prepared according to the literature[6a,8] by heating a mixture of (+)-pinocarvone **13** (1.50 g, 10.0 mmol), pyridinium salt **15** (3.26 g, 10.0 mmol), and ammonium acetate (10.0 g, 0.13 mol) in acetic acid (10 mL) at 120 °C for 4 h. Column chromatography on silica gel with a mixture of hexane−ethyl acetate (5:1) as an eluent afforded (−)-**6** (1.94 g, 77%) as a white solid: $[\alpha]_D$ −86.5 (*c* 2.85, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.69 (s, 3H, 6-Me), 1.32 (d, *J* = 9.4 Hz, 1H, 9-C*H*H), 1.42 (s, 3H, 6-Me), 2.40 (m, 1H, 7-CH), 2.69 (ddd, *J* = 9.7, 5.7, and 5.7 Hz, 1H, 9-CH*H*), 2.81 (dd, *J* = 5.7 and 5.7 Hz, 1H, 5-H), 3.20 (d, *J* = 2.9 Hz, 2H, 8-CH_2), 7.26 (m, 1H, 5′-H), 7.33 (d, *J* = 7.6 Hz, 1H, 3-H), 7.78 (ddd, *J* = 7.6, 7.6, and 1.8 Hz, 1H, 4′-H), 8.04 (d, *J* = 7.6 Hz, 1H, 4-H), 8.35 (d, *J* = 8.2 Hz, 1H, 3′-H), 8.66 (br d, *J* = 4.7 Hz, 1H, 6′-H) in agreement with the literature.[6a,8]

(5*S*,7*R*,8*R*)-(−)-5,6,7,8-Tetrahydro-6,6,8-trimethyl-2-(pyridin-2-yl)-5,7-methanoquinoline, (−)-7. It was prepared according to the literature[7,8] by deprotonation of (−)-**6** (550 mg, 2.20 mmol) with LDA and quenching the resulting carbanion with methyl iodide. Column chromatography on silica gel with a mixture of hexane−ethyl acetate (5:1) as an eluent afforded the title compound (−)-**7** (462 g, 80%) as a colorless oil: $[\alpha]_D$ −38.7 (*c* 1.80, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.68 (s, 3H, 6-Me), 1.34 (d, *J* = 9.9 Hz, 1H, 9-C*H*H), 1.43 (s, 3H, 6-Me), 1.46 (d, *J* = 7.1 Hz, 3H, 8-Me), 2.40 (ddd, *J* = 6.2, 6.2, and 2.5 Hz, 1H, 7-CH), 2.58 (ddd, *J* = 9.9, 5.5, and 5.5 Hz, 1H, 9-CH*H*), 2.80 (dd, *J* = 5.5 and 5.5 Hz, 1H, 5-H), 3.25 (qd, *J* = 7.1 and 2.3 Hz, 1H, 8-H), 7.26 (ddd, *J* = 7.6, 4.8, and 1.1 Hz, 1H, 5′−H), 7.31 (d, *J* = 7.8 Hz, 1H, 3-H), 7.77 (ddd, *J* = 7.6, 7.6, and 1.8 Hz, 1H, 4′−H), 8.07 (d, *J* = 7.8 Hz, 1H, 4-H), 8.45 (d, *J* = 8.0 Hz, 1H, 3′−H), 8.64 (br d, *J* = 4.8 Hz, 1H, 6′-H) in agreement with literature.[7,8]

(6*R*,8*R*)-(+)-5,6,7,8-Tetrahydro-7,7-dimethyl-2-(pyridin-2-yl)-6,8-methanoquinoline, (+)-8. The starting *α*,*β*-unsaturated ketone **23** was synthesized according to the von Zelewsky method[21] from (+)-nopinone (+)-**21**.[20] Heating a mixture of **23** (2.25 g, 15.0 mmol), pyridinium salt **15** (4.89 g, 15.0 mmol), and ammonium acetate (15.0 g, 0.20 mol) in acetic acid (15 mL) at 120 °C for 4 h [in analogy with the preparation of (−)-**6**], followed by workup and column chromatography on silica gel with a mixture of hexane−ethyl acetate (5:1) as an eluent, afforded (+)-**8** (1.91 g, 51%) as a white solid: mp 74−76 °C; $[\alpha]_D$ +26.1 (*c* 2.40, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.70 (s, 3H, 7-Me), 1.35 (d, *J* = 9.6 Hz, 1H, 9-C*H*H), 1.44 (s, 3H, 7-Me), 2.35 (m, 1H, 6-CH), 2.73 (ddd, *J* = 9.6, 5.7, and 5.7 Hz, 1H, 9-CH*H*), 2.98 (d, *J* = 2.8 Hz, 2H, 5-CH_2), 3.10 (dd, *J* = 5.7 and 5.5 Hz, 1H, 8-H), 7.24 (ddd, *J* = 7.6, 4.8, and 1.2 Hz, 1H, 5′-H), 7.52 (d, *J* = 7.8 Hz, 1H, 3-H), 7.76 (ddd, *J* = 7.8, 7.8, and 1.8 Hz, 1H, 4′-H), 8.14 (d, *J* = 7.8 Hz, 1H, 4-H), 8.35 (d, *J* = 8.0 Hz, 1H, 3′-H), 8.65 (br d, *J* = 4.8 Hz, 1H, 6′-H); ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 21.7 (Me), 26.4 (Me), 31.3 (CH_2), 31.7 (CH_2), 39.6 (C), 40.6 (CH), 50.9 (CH), 119.2 (CH), 121.4 (CH′), 123.4 (CH′), 131.0 (C), 136.3 (CH), 137.1 (CH′), 149.5 (CH′), 152.4 (C), 157.2 (C′), 166.3 (C); MS (ES) 273 (M + Na^+), 251 (M + H^+); HRMS (FAB) 251.15487 ($C_{17}H_{19}N_2$ requires 251.15482).

(5*S*,5′*S*,7*R*,7′*R*)-(−)-5,5′,6,6′,7,7′,8,8′-Octahydro-6,6,6′,6′-tetramethyl-2,2′-bis(5,7-methanoquinoline), (−)-9. Zinc powder (100 mg, 1.5 mmol) was added to a warm solution of $NiCl_2 \cdot 6H_2O$ (285 mg, 1.2 mmol) and PPh_3 (1.26 g, 4.8 mmol) in degassed DMF (5 mL). The mixture was heated at 60 °C for 2 h, during which period the color changed from blue to red. Then a solution of (−)-**17** (240 mg, 1.16 mmol) in DMF (2 mL) was added. The mixture was heated for a further 18 h at 60 °C and then poured into 10% aqueous NH_3 (50 mL). The resulting suspension was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was removed in a vacuum. The residue was purified by chromatography on silica gel with a hexane−ethyl acetate mixture (9:1) as an eluent to give (−)-**9** (180 mg, 90%) as a white microcrystalline solid: mp 170−172 °C; $[\alpha]_D$ −135.9 (*c* 2.10, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.66 (s, 6H, 6,6′-Me), 1.32 (d, *J* = 9.4 Hz, 2H, 9, 9′-C*H*H), 1.41 (s, 6H, 6,6′-Me), 2.39 (m, 2H, 7,7′-CH), 2.69 (ddd, *J* = 9.4, 5.5, and 5.5 Hz, 2H, 9,9′-CH*H*), 2.79 (dd, *J* = 5.7 and 5.5 Hz, 2H, 5,5′−H), 3.19 (m, 4H, 8,8′-CH_2) 7.29 (d, *J* = 7.8 Hz, 2H, 3-H), 7.99 (d, *J* = 7.8 Hz, 2H, 4-H); ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 21.7 (Me), 26.5 (Me), 32.4 (CH_2), 37.1 (CH_2), 40.0 (C), 40.7 (CH), 46.9 (CH), 118.1 (CH), 134.1 (CH), 141.9 (C), 154.7 (C), 156.7 (C); HRMS (FAB) 345.23308 ($C_{24}H_{29}N_2$ requires 345.23307).

(6*R*,6′*R*,8*R*,8*R*′)-(+)-5,5′,6,6′,7,7′,8,8′-Octahydro-6,6′,7,7′-tetramethylbis(6,8-methanoquinoline), (+)-10. Zinc powder (0.990 g, 15.2 mmol) was added to a solution of $NiCl_2 \cdot 6H_2O$ (3.53 g, 14.6 mmol) and PPh_3 (15.3 g, 58.5 mmol) in degassed DMF (100 mL). The mixture was heated at 60 °C for 2 h, during which period the color changed from blue to red. Then a solution of (−)-**26** (3.00 g, 14.44 mmol) in DMF (10 mL) was added. The mixture was heated for a further 18 h and then poured into 10% aqueous NH_3 (50 mL). The resulting suspension was extracted with CH_2Cl_2 (4 × 200 mL), dried ($MgSO_4$), and evaporated to give a brown solid. This solid was dissolved in ethyl acetate (200 mL) and extracted with 6 M HCl (5 × 100 mL). The combined aqueous layers were extracted twice with ethyl acetate, adjusted to pH 13 with a concentrated aqueous NaOH solution, and extracted with ethyl acetate (5 × 200 mL). The combined organic layers were extracted with brine (1 × 100 mL), dried ($MgSO_4$), and evaporated in vacuo to give a viscose yellowish oil (2.20 g). This oil was heated under vacuum (0.3 Torr) at 200 °C for 1 h to distill off the reduction product **27** (0.80 g, 32%): ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.66 (s, 3 H), 1.38 (d, *J* = 9.6 Hz, 1 H), 1.41 (s, 3 H), 2.3−2.4 (m, 1 H), 2.71 (ddd, *J* = 9.6, 5.8, and 5.8 Hz, 2 H), 2.97 (m, 2 H), 7.18 (m, 1 H), 7.52 (m, 1 H), 8.32 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) *δ* 21.5 (Me), 26.4 (Me), 31.1 (CH_2), 31.6 (CH_2), 39.4 (C), 40.4(CH), 50.6 (CH), 121.6 (CH), 130.3 (C), 135.4 (CH), 145.6 (C), 166.5 (C); MS (ES) 274 (M + H^+). The resulting solid was purified via chromatography on silica gel, first with hexane, then with a hexanes−ethyl acetate mixture (9:1) to

give (+)-**10** (1.25 g, 50%). Alternatively, the crude product was crystallized from a methanol−water mixture to afford (+)-**10** as a white solid (0.73 g, 33%): mp 142−144 °C; $[\alpha]_D$ +35.8 (*c* 2.10, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.67 (s, 6 H), 1.34 (d, J = 9.6 Hz, 2 H), 1.42 (s, 6 H), 2.3−2.4 (m, 2 H), 2.73 (ddd, J = 9.6, 5.8, and 5.8 Hz, 2 H), 2.96 (d, J = 2.5 Hz, 4 H), 3.08 (dd, J = 5.8 and 5.8, Hz, 2 H) 7.48 (d, J = 7.9 Hz, 2 H), 8.07 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.6, 26. 5, 31.29, 3.63, 39.6, 40.6, 50.9, 119.2, 130.2, 136.3, 153.1, 166.1; IR ($CHCl_3$) ν_{max} 2960, 2880, 2840, 1590, 1565, 1470, 1440, 1420, 1390, 1365 cm^{-1}; HRMS (FAB) 345.23312 ($C_{24}H_{29}N_2$ requires 345.23307).

Coupling of (5*R*,8ξ)-2-Chloro-5-methyl-8-isopropyl-5,6,7,8-tetrahydroquinoline (35) to Produce 11, 12, and 36. Zinc powder (0.5 g; 7.65 mmol) was added to a solution of $Ni(PPh_3)_2Cl_2$ (1.06 g; 1.62 mmol; 2.5 mol %) and triphenylphosphine (1.06 g; 4.05 mmol) in DMF (60 mL) under argon, and the mixture was stirred at 60 °C for 1 h. A solution of 2-chloropyridine derivative **35** (14.50 g; 64.9 mmol) in DMF (40 mL) was then added, and the temperature was raised to 80 °C. Further zinc powder (5.87 g; 89. 76 mmol) was added over a period of 6 h, and the mixture was heated for an additional 1 h and then allowed to cool. The solution was extracted with dichloromethane (200 mL), and the organic phase was washed with water (2 × 150 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a light brown tar, which was purified by column chromatography (hexane−acetone−ether, 99:1:1) to give three main fractions. Fraction 1 (the least polar) consisted of **36**, contaminated with triphenylphosphine. Crystallization of this mixture from ether furnished pure **36** (4.22 g; 35%) as a crystalline solid. Fraction 2 contained **11** (1.98 g; 16%), and fraction 3 was identified as **12** (2.61 g; 21%). A combined mixed fraction (**11**, **12**, and **36**) was also obtained (1.94 g; 16%).

(5*R*,5′*R*,8*S*,8′*S*)-(−)-5,5′-dimethyl-8,8′-diisopropyl-5,5′,6,6′,7,7′,8,8′-octahydro-2,2′-biquinoline, (−)-11. 11 was obtained (along with **12** and **36**) on coupling of **35**: mp 104−106 °C (ethanol−ether, 2:1); $[\alpha]_D$ −216.58 (*c*, 2.92; CH_2Cl_2); ^{1}H NMR δ 8.13 (2 H, d, J = 8.3 Hz, 3-py), 7.59 (2 H, dd, J = 8.3, 0.6 Hz, 4-py), 3.03−2.77 (6 H, m, 2 × C*H*Me$_2$ + 2 × 8-H + 2 × 5-H), 2.00 (4 H, m, C*H*$_2$-*i*-Pr), 1.63 (2 H, m, CH_2), 1.40 (2 H, m, CH_2), 1.27 (6 H, d, J = 7 Hz, 2 × 5-Me), 1.07 (6 H, d, J = 7 Hz, 2 × Me$_a$ of *i*-Pr), 0.70 (6 H, d, J = 7 Hz, 2 × Me$_b$ of *i*-Pr); ^{13}C NMR δ 158.5 (2 × C), 153.5 (2 × C), 137.6 (2 × C), 135.2 (2 × CH), 117.7 (2 × CH), 46.8 (2 × CH), 32.9 (2 × CH), 31.3 (2 × CH_2), 30.3 (2 × CH), 21.7 (2 × CH_2), 21.5 (2 × CH_3), 20.8 (2 × CH_3), 17.2 (2 × CH_3); IR (neat) ν 2951, 2924, 2866, 1581, 1483, 1450, 1431, 1381, 1327, 1242, 1045, 833 cm^{-1}; MS (ES) 378.7 (M + 2H$^+$), 377.7 (M + H$^+$); MS (EI) *m*/*z* (%) 376 (42, M$^{\bullet+}$), 335 (25), 334 (100), 333 (28), 319 (10), 289 (10), 275 (11); HRMS (EI) 376.28784 ($C_{26}H_{36}N_2$ requires 376.28785). Anal. Calcd for $C_{26}H_{36}N_2$: C, 82.91; H, 9.65; N, 7.44. Found: C, 82.03; H, 9.94; N, 7.37. Crystallographic data for **11**: $C_{26}H_{36}N_2$, M = 376.58. Crystals were obtained from a 2:1 ethanol−ether mixture at room temperature; they are orthorhombic of space group $P2_12_12_1$, with a = 8.393(2), b = 10.119-(11), c = 26.630(4) Å, V = 2262(3) Å^3, Z = 4, d_{calc} = 1.106 g cm^{-3}, μ = 0.064 mm^{-1}. Data were collected at 190 K on a Bruker P4 diffractometer using Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and the ω scan mode. A total of 2706 reflections were measured, from which 2505 were unique (R_{int} = 0.032), with 1139 having $I > 2\sigma_I$. All reflections were used in the structure refinement based on F^2 by full-matrix least-squares techniques with hydrogen atoms calculated into theoretical positions, riding during refinement on the respective pivot atom (192 parameters). Final R_F = 0.097 for the observed data and $wR(F^2)$ = 0.316 for all data. The estimated error in C−C bond lengths is in the range 0.01−0.04 Å. The absolute configuration was established through the known configuration at the carbon carrying the methyl group (originating from menthone).

(5*R*,5′*R*,8*R*,8′*R*)-(+)-5,5′-Dimethyl-8,8′-diisopropyl-5,5′,6,6′,7,7′,8,8′-octahydro-2,2′-biquinoline, (+)-12. 12 was obtained (along with **11** and **36**) on coupling of **35**: mp 132−134 °C (ethanol−ether, 2:1); $[\alpha]_D$ +190.65 (*c* 2.51, CH_2Cl_2); ^{1}H NMR δ 8.18 (2 H, d, J = 8.3 Hz, 3-py), 7.49 (2 H, d, J = 8.3 Hz, 4-py), 3.10−2.90 (4 H, m, 2 × C*H*Me$_2$ + 2 × 5-H), 2.82 (2 H, m, 2 × 8-H), 1.90−1.65 (8 H, m, 4 × CH_2), 1.28 (6 H, d, J = 7 Hz, 2 × 5-Me), 1.12 (6 H, d, J = 7 Hz, 2 × Me$_a$ of *i*-Pr), 0.76 (6 H, d, J = 7 Hz, 2 × Me$_b$ of *i*-Pr); ^{13}C NMR δ 158.2 (2 × C), 153.7 (2 × C), 137.6 (2 × C), 136.8 (2 × CH), 117.7 (2 × CH), 46.4 (2 × CH), 32.4 (2 × CH), 29.8 (2 × CH), 28.7 (2 × CH_2), 23.0 (2 × CH_3), 20.9 (2 × CH_3), 18.5 (2 × CH_2), 17.3 (2 × CH_3); IR (neat) ν 2954, 2850, 1585, 1547, 1454, 1435, 1369, 1250, 1034, 995, 833 cm^{-1}; MS (ES) 399.7 (M + Na$^+$), 378.7 (M + 2H$^+$), 377.7 (M + H$^+$); MS (EI) *m*/*z* (%) 376 (18, M$^{\bullet+}$), 335 (25), 334 (100), 333 (23), 319 (9), 289 (8), 275 (9); HRMS (EI) 376.28788 ($C_{26}H_{36}N_2$ requires 376.28785). Anal. Calcd for $C_{26}H_{36}N_2$: C, 82.91; H, 9.65; N, 7.44. Found: C, 82.54; H, 9.84; N, 7.38. Crystallographic data for **12**: $C_{26}H_{36}N_2$, M = 376.58. Crystals were obtained from a 2:1 ethanol−ether mixture at room temperature; they are orthorhombic of space group $P2_12_12_1$, with a = 11.297(2), b = 11.682(2), c = 17.117(3) Å, V = 2259.0(7) Å^3, Z = 4, d_{calc} = 1.101 g cm^{-3}, μ = 0.064 mm^{-1}. Data were collected at 190 K on a Bruker P4 diffractometer using Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and the ω scan mode. A total of 2648 reflections were measured, from which 2483 were unique (R_{int} = 0.019), with 2049 having $I > 2\sigma_I$. All reflections were used in the structure refinement based on F^2 by full-matrix least-squares techniques with hydrogen atoms calculated into theoretical positions, riding during refinement on the respective pivot atom (259 parameters). Final R_F = 0.043 for the observed data and $wR(F^2)$ = 0.115 for all data. The esd error in C−C bond lengths is in the range 0.004−0.006 Å. The absolute configuration was established through the known configuration at the carbon carrying the methyl group (originating from menthone).

(5*S*,7*R*)-(−)-5,6,7,8-Tetrahydro-6,6-dimethyl-5,7-methanoquinolin-2-ol, (−)-16. A solution of (+)-pinocarvone **13** (3.42 g, 22.8 mmol), pyridinium salt **14** (3.92 g, 22.8 mmol), and piperidine (2.27 mL, 23 mmol) in methanol (50 mL) was heated at reflux for 3 h. After cooling, the solvent was removed in a vacuum. The brown oily residue was dissolved in formamide (20 mL), and glacial acetic acid (4 mL) was added. The mixture was heated at 200−210 °C for 1 h. To the cooled mixture was added dichloromethane (50 mL) and water (50 mL), the aqueous layer was basified with 1 M NaOH, the organic phase was separated, and the aqueous layer was extracted with dichloromethane (3 × 50 mL). Combined organic extracts were dried ($MgSO_4$), concentrated in a vacuum, and purified by chromatography on silica gel with a hexane−ethyl acetate−methanol mixture (15:8:2) as eluent to give a crude product as a yellow oil that slowly crystallized on standing. Pentane was added to the mixture, and the solid was separated by filtration and washed with pentane. The product (−)-**16** (1.7 g, 39%) was obtained as a yellowish sticky solid: $[\alpha]_D$ −73.0 (*c* 1.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (s, 3 H, 6-Me), 1.25 (d, J = 9.3 Hz, 1H, 9-C*H*H), 1.38 (s, 3H, 6-Me), 2.29 (m, 1H, 7-CH), 2.57 (dd, J = 5.9 and 5.5 Hz, 1H, 5-CH), 2.63 (ddd, J = 9.3, 5.5, and 5.5 Hz, 1 H, 9-CH*H*), 2.96 (m, 2H, 8-CH_2), 6.34 (d, J = 8.8 Hz, 1H, 3-CH), 7.15 (d, J = 8.8 Hz, 1H, 4-CH); MS (ES) 212 (M + Na$^+$), 190 (M + H$^+$); HRMS (FAB) 190.12316 ($C_{12}H_{16}NO$ requires 190.12319).

(5*S*,7*R*)-(-)-2-Chloro-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methanoquinoline, (−)-17. A mixture of phosphorus oxychloride (0.93 mL; 10 mmol), tetrahydroquinolinol **16** (500 mg; 2.65 mmol), and phosphorus pentachloride (260 mg; 1.25 mmol) was stirred at reflux for 12 h under nitrogen. The reaction mixture was cooled to 0 °C in an ice bath, quenched carefully with cold 1 M NaOH (5 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under

reduced pressure. Purification of the crude product by column chromatography on silica gel with a hexane−ethyl acetate mixture (20:1) as an eluent yielded (−)-**17** (220 mg; 40%) as a pale yellow oil: $[\alpha]_D$ −61.8 (*c* 1.50, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.64 (s, 3 H, 6-Me), 1.24 (d, J = 9.4 Hz, 1H, 9-C*H*H), 1.40 (s, 3H, 6-Me), 2.35 (m, 1H, 7-CH), 2.68 (ddd, J = 9.4, 5.7, and 5.7 Hz, 1 H, 9-CH*H*), 2.75 (dd, J = 5.9 and 5.7 Hz, 1H, 5-CH), 3.08 (m, 2H, 8-CH_2), 7.01 (d, J = 7.9 Hz, 1H, 3-CH), 7.17 (d, J = 7.9 Hz, 1H, 4-CH); ^{13}C NMR δ 21.6 (Me), 26.3 (Me), 32.2 (CH_2), 36.8 (CH_2), 39.7 (C), 40.3 (CH), 46.2 (CH), 120.9 (CH), 136.1 (CH), 141.1 (C), 148.2 (C), 158.2 (C); MS (ES) 232 (M + Na^+, ^{37}Cl), 230 (M + Na^+, ^{35}Cl), 210 (MH^+, ^{37}Cl), 208 (MH^+, ^{35}Cl).

(6*R*,8*S*)-(−)-5,6,7,8-Tetrahydro-7,7-dimethyl-6,8-methanoisoquinolin-3-ol, 19. A solution of (−)-myrtenal **18** (2.0 g, 13.3 mmol), pyridinium salt **14** (2.6 g, 15 mmol), and piperidine (1.48 mL, 15 mmol) in methanol (50 mL) was heated at reflux for 2 h. After cooling, the solvent was removed in a vacuum. The brown oily residue was dissolved in formamide (15 mL), and glacial acetic acid (3 mL) was added. The mixture was heated at 200−210 °C for 1 h. To the cooled mixture was added dichloromethane (50 mL) and water (50 mL), and the aqueous layer was basified with 1 M NaOH. The organic phase was separated, and the aqueous layer was extracted with dichloromethane (3 × 50 mL). Combined organic extracts were dried ($MgSO_4$), concentrated in a vacuum, and purified by chromatography on silica gel with a mixture of hexane−ethyl acetate−methanol (15:8:2) as an eluent to give crude **19** (377 mg, 15%) as a yellow oil, which was used in the next step without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.58 (s, 3 H, 7-Me), 1.08 (d, J = 9.2 Hz, 1H, 9-C*H*H), 1.25 (s, 3H, 7-Me), 2.08 (m, 1H, 6-CH), 2.50 (m, 2H, 8,9-CH), 2.80 (m, 2H, 5-CH_2), 6.32 (s, 1H, 4-CH), 6.83 (s, 1H, 1-CH); MS (ES) 401 (2M + Na^+), 212 (M + Na^+), 190 (M + H^+).

(6*R*,8*S*)-(−)-3-Chloro-5,6,7,8-tetrahydro-7,7-dimethyl-6,8-methanoisoquinoline, (−)-20. A mixture of phosphorus oxychloride (0.93 mL; 10 mmol) and tetrahydroquinolinol **19** (400 mg; 2.12 mmol) in dry DMF (3 mL) was stirred at reflux for 12 h under nitrogen. The reaction mixture was cooled to 0 °C in an ice bath, quenched carefully with cold 1 M NaOH (5 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification of the crude product by column chromatography on silica gel with a hexane−ethyl acetate mixture (20:1) as an eluent afforded (−)-**20** (319 mg; 73%) as a colorless oil: $[\alpha]_D$ −54.5 (*c* 3.19, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.59 (s, 3 H, 7-Me), 1.14 (d, J = 9.6 Hz, 1H, 9-C*H*H), 1.36 (s, 3H, 7-Me), 2.25 (m, 1H, 6-CH), 2.66 (ddd, J = 9.6, 5.7, and 5.7 Hz, 1 H, 9-CH*H*), 2.77 (dd, J = 5.5 and 5.5 Hz, 1H, 8-CH), 2.92 (m, 2H, 5-CH_2), 7.07 (s, 1H, 4-CH), 7.87 (s, 1H, 1-CH); MS (ES) 210 (MH^+, ^{37}Cl), 208 (MH^+, ^{35}Cl).

(4*S*,6*R*)-(−)-5,5-Dimethyl-4,6-methano-(*N*-methylacetamido)-cyclohexene, (−)-25. Iron powder (36.4 g, 652 mmol) was added to a solution of nopinone oxime **24** (10.0 g, 65.3 mmol) in toluene (20 mL), and the mixture was cooled to 0 °C. A solution of acetic anhydride (18.6 mL, 196 mmol) and acetic acid (11.3 mL, 196 mmol) was then added dropwise under mechanical stirring over a period of 10 min; the reaction was instantaneous. The residual iron powder was then filtered off and washed with ethyl acetate (4 × 100 mL). The combined organic solutions were washed with 2 M NaOH (2 × 100 mL), dried ($MgSO_4$), and evaporated to give (−)-**25** as a white solid (10.5 g, 90%) that was sufficiently pure for the next step: mp 66−68 °C; $[\alpha]_D$ −61.6 (*c* 2.18, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.11 (s, 3 H), 1.49 (s, 3 H), 1.52 (d, J = 8.7 Hz, 1 H), 2.22 (s, 3 H), 2.35−2.2 (m, 2 H), 2.55−2.45 (m, 1 H), 2.65−2.55 (m, 1 H), 6.11 (br s, 1 H), 7.20 (br s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.38, 24.76, 26.41, 29.76, 31.56, 38.80, 41.15, 47.56, 105.46, 141.04, 168.88; IR ($CHCl_3$) ν_{max} 3425, 3000, 2930, 2840, 1685, 1605, 1505, 1370 cm^{-1}; HRMS (FAB) 180.13892 ($C_{11}H_{18}NO$ requires 180.13884).

(6*R*,8*R*)-(−)-2-Chloro-5,6,7,8,-tetrahydro-7,7-dimethyl-[6,8-methanoquinoline], (−)-26. Phosphoryl chloride (59.9 g, 390 mmol) was added dropwise to a solution of **25** (10.0 g, 55.8 mmol) in DMF (12.9 mL, 167 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. Water (100 mL) was then carefully added (**CAUTION!** This reaction is strongly exothermic; the temperature must be kept below 5 °C). Aqueous 30% NaOH solution was then added to reach pH 13, and the mixture was extracted with ethyl acetate (4 × 200 mL). The combined organic layers were washed with brine (1 × 100 mL), dried ($MgSO_4$), and evaporated to give crude **26** as an oil (10.3 g) that was purified via chromatography on silica gel (200 g), first with hexane, then with a hexanes−ethyl acetate mixture (9:1) to afford pure (−)-**26** (8.08 g, 70%) as a white solid: mp 80−82 °C; $[\alpha]_D$ −18.6 (*c* 1.9, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.67 (s, 3 H), 1.27 (d, J = 9.8 Hz, 1 H), 1.41 (s, 3 H), 2.3−2.4 (m, 1 H), 2.71 (ddd, J = 6.0, 5.5, and 9.8 Hz, 1 H), 2.91 (d, J = 2.7 Hz, 1 H), 2.98 (dd, J = 6.0 and 5.5, Hz, 1 H), 7.10 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.58, 26.29, 30.94, 31.09, 39.46, 40.33, 50.40, 121.63, 129.20, 138.18, 147.29, 167.72; IR ($CHCl_3$) ν_{max} 2980, 2960, 2945, 1580, 1565, 1470, 1420, 1130 cm^{-1}; HRMS (FAB) 208.08921 ($C_{12}H_{15}ClN$ requires 208.08930).

(5*R*,8*S*)-2-Isopropyl-5-methyl-2-oxo-cyclohexyl-6-propionitrile, 29. Method A (Small-Scale Preparation). A solution of (−)-menthone (−)-**28** (15.4 g; 0.1 mol), pyrrolidine (14.2 g; 0.2 mol; 2 equiv), and *p*-toluenesulfonic acid (0.5 g; cat) in toluene (250 mL) was heated at reflux for 48 h using a Dean−Stark trap. After removal of the solvent, the residue was distilled under reduced pressure to yield the enamine intermediate (7.3−7.9 g; 35−38%; bp 70−72 °C at 0.46 mbar), as a pale yellow oil. The product consisted of a 7:1 mixture of diastereoisomers as shown by ^{1}H NMR: δ 4.41 (1 H, m, CH=Cpy minor), 5.52 (1 H, m, CH=Cpy major), in accordance with the literature.[29] A solution of the latter enamine (4.20 g; 20 mmol; 1 equiv) and acrylonitrile (4.24 g; 80 mmol; 4 equiv) in ethanol (20 mL) was heated at reflux for 24 h while stirring.[62] The ethanol was removed under reduced pressure, anhydrous sodium acetate (2.8 g; 34 mmol), acetic acid (3 mL; 48 mmol), water (5.7 mL), and 1,4-dioxane (25 mL) were added, and the solution was heated at reflux for 3 h. The cooled reaction mixture was extracted with dichloromethane (2 × 30 mL), and the organic phase was washed with 5% hydrochloric acid (2 × 25 mL), saturated aqueous sodium hydrogen carbonate (3 × 30 mL), and brine (30 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed to give a pale yellow oil, which was purified by flash chromatography (petroleum ether−ethyl acetate, 10:1) to produce fraction 1, which consisted of a mixture of three components and fraction 2 that proved to be a single diastereoisomer **29** (combined: 3.91 g, 94%): ^{1}H NMR (300 MHz) δ 2.41 (1 H, m), 2.35 (1 H, m), 2.12−1.95 (4 H, m), 1.91−1.80 (2 H, m), 1.54 (1 H, m), 1.56−1.40 (2 H, m), 1.29 (1 H, m), 1.02 (3 H, d, J = 7.6 Hz, Me), 0.84 (3 H, d, J = 7.7 Hz, Me_a of *i*-Pr), 0.79 (3 H, d, J = 7.9 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 212.3 (C), 119.7 (C), 56.7 (CH), 55.9 (CH), 40.1 (CH), 34.4 (CH_2), 29.2 (CH_2), 25.9 (CH), 22.2 (CH_2), 21.1 (CH_3), 20.2 (CH_3), 18.5 (CH_3), 15.0 (CH_2); MS (EI) *m*/*z* 207 (87, $M^{\bullet+}$), 192 (58), 165 (68), 150 (9), 140 (23), 136 (17), 122 (32), 111 (100), 97 (69), 83 (37), 81 (21), 69 (78), 55 (80); HRMS (EI) 207.16236 ($C_{13}H_{21}NO$ requires 207.16231).

Method B (Large-Scale Preparation). (−)-Menthone **28** (289.3 g; 1.88 mol), pyrrolidine (150.0 g; 2.11 mol; 1.12 equiv), and *p*-toluenesulfonic acid (5.0 g; 26.3 mmol; 0.014 equiv) in toluene (1 L) were placed in a flask equipped with a magnetic stirrer and a Dean−Stark trap (the trap containing 25 g of 4 Å molecular sieves was cooled to 0−5 °C) connected to a reflux

(62) Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993**, *49*, 8805.

condenser. After 12 h at reflux, a second equivalent of pyrrolidine (100.0 g; 1.4 mol; 0.74 equiv) was added, and the heating continued for a further 12 h. The solvent was removed, and the residue was distilled under reduced pressure to yield the corresponding enamine (164.1 g; 42%; bp 70−72 °C at 0.46 mbar) as a pale yellow oil. The spectroscopic data were identical to those obtained for the compound prepared according to procedure A. A stirred solution of the latter enamine (54.0 g; 0.26 mol; 1 equiv) and acrylonitrile (58.3 g; 1.1 mol; 4.2 equiv) in ethanol (135 mL) was heated at reflux for 3 h; after that period, TLC analysis (petroleum ether−ethyl acetate, 8:2) showed no enamine starting material. The ethanol was removed under reduced pressure, and anhydrous sodium acetate (36.4 g; 0.44 mol), acetic acid (39 mL; 0.64 mol), water (74.1 mL), and 1,4-dioxane (100 mL) were added. The mixture was heated at reflux for 4 h, then cooled and extracted with dichloromethane (3 × 100 mL). The combined extracts were washed with 10% hydrochloric acid (2 × 100 mL) and saturated aqueous sodium hydrogen carbonate (3 × 100 mL) and dried ($MgSO_4$). Removal of the solvent in a vacuum gave a pale yellow oil, which was purified by chromatographic filtration (petroleum ether−hexane−ethyl acetate, 5:5:1) to yield **29** (44.13 g; 82%), consisting of the same four components as for procedure A.

(5*R*,8*ξ*)-5-Methyl-8-isopropyl-5,6,7,8-tetrahydro-2-(1*H*)-quinolinone, 30.[31] A stirred solution of nitrile **29** (3.91 g; 18.9 mmol) and finely ground potassium hydroxide (10.0 g; 0.178 mol) in *tert*-butyl alcohol (50 mL) was heated at reflux for 45 min. The mixture was cooled and then poured into brine (100 mL), and the product was extracted with chloroform (3 × 75 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield crude **30** (3.48 g; 89%) as a pale yellow oil. Purification and separation of the two diastereoisomers were effected by flash chromatography on silica (85 g; petroleum ether−ethyl acetate−acetone, 7:2:1). **Epimer A** (fraction 1) (1.54 g; 39%): ^{1}H NMR δ 7.14 (1 H, br s, NH), 2.42−2.20 (2 H, m), 2.15−1.50 (7 H, m), 1.45−1.23 (1 H, m), 1.20−1.10 (1 H, m), 0.91 (3 H, d, J = 7 Hz, 5-Me), 0.89 (3 H, d, J = 7 Hz, Me_a of *i*-Pr), 0.71 (3 H, d, J = 7 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 171.3 (C), 130.9 (C), 117.3 (C), 40.9 (CH), 32.1 (CH), 30.8 (CH_2), 29.9 (CH_2), 28.7 (CH), 23.8 (CH_2), 21.4 (CH_3), 20.6 (CH_2), 20.4 (CH_3), 18.7 (CH_3); MS (EI) *m*/*z* 207 (24, $M^{\bullet+}$), 192 (100), 164 (16), 150 (16), 137 (9), 136 (8), 108 (6), 94 (7); HRMS (EI) 207.16236 ($C_{13}H_{21}NO$ requires 207.16231). **Epimer B** (fraction 2) (1.39 g; 36%): ^{1}H NMR δ 7.30 (1 H, br s, NH), 2.58 (1 H, m), 2.50−2.28 (2 H, m), 2.13−160 (4 H, m), 1.36−1.00 (3 H, m), 0.98 (3 H, d, J = 7 Hz, 5-Me), 0.93 (3 H, d, J = 7 Hz, Me_a of *i*-Pr), 0.90 (3 H, d, J = 7 Hz, Me_b of *i*-Pr), 0.80 (1 H, m); ^{13}C NMR δ 169.9 (C), 127.3 (C), 118.1 (C), 41.2 (CH), 34.0 (CH), 31.6 (CH_2), 31.0 (CH_2), 26.6 (CH), 25.0 (CH_2), 22.5 (CH_2), 20.2 (CH_3), 19.9 (CH_3), 19.8 (CH_3); MS (EI) *m*/*z* (%) 207 (27, $M^{\bullet+}$), 192 (100), 164 (19), 136 (6), 84 (7.6), 55 (7.2); HRMS (EI) 207.16240 ($C_{13}H_{21}NO$ requires 207.16231).

(5*R*,8*S*)-3-Oxo-*p*-menthane-2-carbaldehyde, 31.[63] To a vigorously stirred suspension of dry powdered sodium methoxide (89.1 g; 1.65 mol; 3 equiv) in dry toluene (500 mL) was added a solution of ethyl formate (122.3 g; 1.65 mol; 3 equiv) in toluene (250 mL) with external cooling to 0 °C. A solution of (−)-menthone **28** (85 g; 0.55 mol; a 15:1 mixture of **28** and its epimer) in a 1:3 toluene−THF mixture (350 mL) was added dropwise to the cooled solution over 1 h. The solution was allowed to warm to room temperature, and the stirring continued for 48 h. The solution was neutralized with ice cold 15% (w/v) sulfuric acid, the organic phase was separated, and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield **31** (75.1 g; 75%) as a pale red oil: ^{1}H NMR δ 14.80 (1 H, br s, =CHO*H*), 8.71 (1 H, s, =C*H*OH), 2.61 (1 H, m, CH), 2.42 (1 H, m, CH), 2.32 (1 H, m, CH), 1.61 (4 H, m, 2 × CH_2), 1.10 (3 H, d, J = 6.9 Hz, Me_a of *i*-Pr), 0.98 (3 H, d, J = 6.9 Hz, Me_b of *i*-Pr), 0.82 (3 H, d, J = 6.6 Hz, 1-Me); ^{13}C NMR δ 188.6 (CH), 186.7 (C), 115.0 (C), 46.6 (CH), 28.1 (CH_2), 27.6 (CH), 22.8 (CH_3), 20.0 (CH_3), 17.6 (CH_3), 17.2 (CH_2), in accordance with the literature.[63a]

(5*R*,8*ξ*)-3-Cyano-5-methyl-8-isopropyl-5,6,7,8-tetrahydro-2-quinolinone, 32.[34] The 1,3-dicarbonyl derivative **31** (18.2 g; 0.1 mol; 1 equiv) and piperidine (2.5 mL) were added to a solution of cyanoacetamide (8.4 g; 0.1 mol; 1 equiv) in ethanol−water (1:1; 50 mL). The resulting pale yellow solution was heated at 85 °C for 15 h, while the color changed to a dark red. The mixture was cooled, and the ethanol was removed under reduced pressure. The aqueous residue was extracted with chloroform (3 × 50 mL), the combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a thick red tar. A pale yellow-orange crystalline material was precipitated from the tar by the addition of diethyl ether followed by heating to reflux and cooling (0 °C) with vigorous stirring. Recrystallization (ether−ethanol, 10:1) gave **32** as a white crystalline solid (12.43 g; 54%), consisting of a 1:1 mixture of diastereoisomers, which were separated by preparative HPLC on a Dynamax 60 Å column (Si, 250 × 4.6 mm 8 μm i.d.) using a 97:3 hexane−isopropyl alcohol mixture, flow rate 60 mL min^{-1}, detection by UV at 320 nm. Analysis of the mixture was performed on a Dynamax 60 Å column (Si, 250 × 41.4 mm 8 μm i.d.) using a 95:5 hexane−isopropyl alcohol mixture, flow rate 1 mL min^{-1} at 2.19 kpsi, detection by UV at 320 nm. **Epimer A** was the less polar fraction (t_R = 16.28 min) obtained as a yellow crystalline solid: mp 238 °C (decomp) (lit. mp 227−228 °C; recrystallized from dilute acetic acid as an unspecified mixture of diastereoisomers[34]); ^{1}H NMR δ 12.85 (1 H, br s, OH), 7.72 (1 H, s, 4-py), 2.74 (1 H, m, 8-H), 2.54 (1 H, m, 5-H), 2.39 (1 H, m, $CHMe_2$), 1.85 (2 H, m, H_a of 6-CH_2 + H_a of 7-CH_2), 1.61 (1 H, m, H_b of 7-CH_2), 1.28 (1 H, m, H_b of 6-CH_2), 1.13 (3 H, d, J = 6.6 Hz, 5-Me), 1.02 (3 H, d, J = 6.9 Hz, Me_a of *i*-Pr), 0.71 (3 H, d, J = 6.9 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 162.1 (C), 154.0 (C), 147.8 (CH), 121.8 (C), 115.9 (C), 101.4 (C), 42.1 (CH), 31.5 (CH), 30.2 (CH), 29.3 (CH_2), 21.3 (CH_3), 20.6 (CH_3), 19.7 (CH_2), 17.3 (CH_3); IR (neat) ν 2954, 2927, 2866, 1982, 1651, 1601, 1554, 1454, 1412, 1119, 825 cm^{-1}; MS (ES) 483.7 (2M + Na^+), 461.7 (2M + H^+), 253.4 (M + Na^+), 231.4 (MH^+); MS (EI) *m*/*z* (%) 230 (2, $M^{\bullet+}$), 215 (3), 188 (11), 167 (44), 149 (100), 113 (12), 112 (8), 104 (6), 86 (17), 84 (11), 71 (20), 70 (14), 57 (25), 55-(11), 51 (4); HRMS (EI) 230.14196 ($C_{14}H_{18}N_2O$ requires 230.14191). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16 Found: C, 72.89; H, 7.71; N, 11.42. **Epimer B** was obtained as a pale yellow solid (t_R = 20.08 min): mp 128−130 °C (lit. mp 227−228 °C; recrystallized from dilute acetic acid as an unspecified mixture of diastereoisomers[34]); ^{1}H NMR δ 12.35 (1 H, br s, OH), 7.70 (1 H, s, 4-py), 2.62 (2 H, m, 8-H + 5-H), 2.37 (1 H, m, $CHMe_2$), 1.80−1.44 (6 H, m), 1.12 (3 H, d, J = 6.6 Hz, 5-Me), 1.02 (3 H, d, J = 6.9 Hz, Me_a of *i*-Pr), 0.73 (3 H, d, J = 6.9 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 161.9 (C), 153.4 (C), 148.9 (CH), 121.2 (C), 115.7 (C), 101.8 (C), 42.2 (CH), 30.7 (CH), 30.3 (CH), 27.6 (CH_2), 21.6 (CH_3), 20.7 (CH_3), 18.8 (CH_2), 17.8 (CH_3); IR (neat) ν 2951, 2866, 1655, 1601, 1554, 1442, 1415, 1377, 1327, 1165, 1119, 976, 903, 829 cm^{-1}; MS (ES) 483.7 (2M + Na^+), 461.7 (2M + H^+), 253.4 (M + Na^+), 231.4 (MH^+); MS (EI) *m*/*z* (%) 230 (2, $M^{\bullet+}$), 215 (3), 188 (10), 167 (43), 149 (100), 113 (12), 104 (5), 86 (17), 84 (28), 71 (14), 70 (13), 57 (21), 51 (8); HRMS (EI) 230.14199 ($C_{14}H_{18}N_2O$ requires 230.14191).

(5*R*,8*ξ*)-5-Methyl-8-isopropyl-5,6,7,8-tetrahydro-2-quinolinone-3-carboxylic Acid, 33. Method A (Two-Pot). The 2-cyanopyridine derivative **32** (10.0 g; 43.5 mmol) was added to concentrated hydrochloric acid (65 mL), and the mixture

(63) (a) Sýkora, J.; Černý, V.; Herout, V.; Šorm, F. *Collect. Czech. Chem. Commun.* **1954**, *19*, 566. (b) Murphy, R.; Prager, R. H. *Aust. J. Chem.* **1976**, *29*, 617.

was heated at reflux for 6 h. During the reflux, the semisoluble nitrile dissolved and, after approximately 4 h, crystals of the acid **33** started to deposit from solution. On cooling of the mixture, more crystals were deposited, which were filtered (total 6.15 g; 57%). The acidic filtrate was poured onto crushed ice and diluted 3-fold with water, which precipitated more **33**. The mixture was filtered and the solid recrystallized from ethanol (2.64 g; 24%). Both collected batches of acid **33** (overall yield 8.79 g, 81%) consisted of a 1:1 mixture of diastereoisomers and showed the same spectroscopic and physical characteristics. **Diastereoisomer A:** ^{1}H NMR (300 MHz) δ 13.60 (1 H, br s, CO_2H), 12.66 (1 H, br s, OH), 8.39 (1 H, s, py-4H), 2.85 (1 H, m, 8-H), 2.78 (1 H, m, 5-H), 2.45 (1 H, m, 8-H), 2.05−1.60 (4 H, m), 1.20 (3 H, d, J = 7 Hz, 5-Me), 1.13 (3 H, d, J = 7 Hz, Me_a of *i*-Pr), 0.82 (3 H, d, J = 7 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 165.4 (C), 164.5 (C), 153.1 (C), 147.7 (CH), 125.2 (C), 114.7 (C), 42.3 (CH), 30.9 (CH), 30.3 (CH), 27.5 (CH_2), 21.4 (CH_3), 20.6 (CH_3), 18.5 (CH_2), 17.6 (CH_3); IR (neat) ν 3328, 2951, 2865, 1701, 1670, 1585, 1550, 1504, 1462, 1377, 1293, 1173, 806 cm^{-1}; MS (EI) *m*/*z* (%) 249 (28, $M^{\bullet+}$), 234 (14), 216 (17), 205 (100), 189 (21), 188 (20), 174 (10), 133 (8); HRMS (EI) 249.13646 ($C_8H_{12}O_2$ requires 249.13649). **Diastereoisomer B:** ^{1}H NMR (300 MHz) δ 13.89 (1 H, br s, CO_2H), 12.72 (1 H, br s, OH), 8.48 (1 H, s, py-4H), 2.83 (1 H, dt, J = 6, 5 Hz, 8-H), 2.73 (1 H, m, 5-H), 2.48 (1 H, m, 8-H), 2.05−1.90 (3 H, m), 1.74 (1 H, m), 1.28 (3 H, d, J = 7 Hz, 5-Me), 1.13 (3 H, d, J = 7 Hz, Me_a of *i*-Pr), 0.82 (3 H, d, J = 7 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 165.4 (C), 164.6 (C), 153.4 (C), 146.7 (CH), 125.4 (C), 114.5 (C), 42.4 (CH), 31.7 (CH), 30.5 (CH), 29.3 (CH_2), 21.3 (CH_3), 20.6 (CH_3), 19.6 (CH_2), 17.2 (CH_3); IR (neat) ν 3332, 2954, 2890, 2860, 1703, 1620, 1587, 1552, 1465, 1377, 1292, 1173, 914, 809 cm^{-1}; MS (EI) *m*/*z* (%) 249 (26, $M^{\bullet+}$), 234 (13), 216 (16), 205 (100), 189 (19), 174 (9), 144 (4), 133 (6), 117 (5), 84 (6); HRMS (EI) 249.13643 ($C_8H_{12}O_2$ requires 249.13649); mp 173−175 °C (lit. mp 182−184 °C as an unspecified mixture of diastereoisomers[34]). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.91; H, 7.62; N, 5.37.

Method B (One-Pot). As described for the preparation of **32**, a mixture of cyanoacetamide (144.1 g; 1.72 mol; 1.1 equiv), the β-dicarbonyl derivative **31** (283.9 g; 1.56 mol; 1 equiv), and piperidine (10 mL) in ethanol−water (1:1, 1 L) was heated at 85 °C for 15 h. The crude mixture after removal of the ethanol−water solvent mixture was heated at reflux for 6 h in concentrated hydrochloric acid (1 L), and the mixture was worked up as described above to yield **33** (254 g; 65%). A single recrystallization from ethyl acetate gave **33** (239 g; 62%), as a pale yellow solid of sufficient purity for subsequent reaction. The spectroscopic data were identical to those obtained for **33** prepared by method A.

(5*R*,8*ξ*)-5-Methyl-8-isopropyl-5,6,7,8-tetrahydroquinolin-2-ol, 34. Procedure A.[32] Hexahydroquinolinone derivative **30** (9.30 g; 45 mmol) was added to concentrated sulfuric acid (65 mL) at 0 °C, and the mixture was stirred at room temperature for 12 h; over this time the amide dissolved to give a blood red solution. The mixture was poured onto crushed ice and neutralized with cold 2 M NaOH. A white precipitate was deposited, which was extracted with chloroform (3 × 50 mL), the resulting solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by flash chromatography (petroleum ether−ethyl acetate, 11:9) gave **34** (6.81 g, 74%) as an off-white crystalline compound consisting of a 1:1 mixture of two diastereoisomers, which were separated by preparative HPLC on a Dynamax 60 Å column (Si, 8 μm, 250 × 41.4 mm i.d.) using a 95:5 hexane−isopropyl alcohol mixture, flow rate 60 mL min^{-1}, detection by UV at 320 nm. Analysis of the mixture was performed on a Dynamax 60 Å column (Si, 250 × 4.6 mm 8 μm i.d.) using a 95:5 hexane−isopropyl alcohol mixture, flow rate 1 mL min^{-1} at 2.30 kpsi, detection UV at 230 nm. **Epimer A** was the less polar fraction (t_R = 30.85 min), a pale yellow solid: mp 182−184 °C; ^{1}H NMR δ 11.70 (1 H, br s, OH), 7.26 (1 H, d, J = 9.4 Hz, 3-py), 6.31 (1 H, d, J = 9.4 Hz, 4-py), 2.58 (1 H, m, 8-H), 2.50 (1 H, m, 5-H), 2.22 (1 H, m, $CHMe_2$), 1.80 (2 H, m, H_a of 6-CH_2 + H_a of 7-CH_2), 1.53 (1 H, m, H_b of 7-CH_2), 1.23 (1 H, m, H_b of 6-CH_2), 1.09 (3 H, d, J = 6.9 Hz, 5-Me), 0.96 (3 H, d, J = 6.9 Hz, Me_a of *i*-Pr), 0.69 (3 H, d, J = 6.9 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 164.4 (C), 145.6 (C), 141.7 (CH), 120.5 (C), 117.1 (CH), 41.4 (CH), 30.8 (CH), 30.2 (CH), 29.4 (CH_2), 21.6 (CH_3), 20.7 (CH_3), 20.1 (CH_2), 17.5 (CH_3); IR (neat) ν 2954, 2870, 2225, 1643, 1601, 1566, 1489, 1554, 1211, 1165, 941, 868 cm^{-1}; MS (ES) 638.8 (3M + Na^+), 433.7 (2M + Na^+), 411.7 (2M + H^+), 228.4 (M + Na^+), 206.4 (MH^+); MS (EI) *m*/*z* (%) 206 (5, $M^{\bullet+}$), 205 (28), 190 (41), 163 (100), 149 (26), 148 (27), 134 (10), 84 (6), 57 (5); HRMS (EI) 205.14672 ($C_{13}H_{19}NO$ requires 205.14666). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.04; H, 9.35; N, 6.82 Found: C, 76.54; H, 9.47; N, 6.04. **Epimer B** (t_R = 35.94 min), a pale yellow oil: ^{1}H NMR δ 11.80 (1 H, br s, OH), 7.19 (1 H, d, J = 9.4 Hz, 3-py), 6.31 (1 H, d, J = 9.4 Hz, 4-py), 2.55 (2 H, m, 5-H + 8-H), 2.21 (1 H, m, $CHMe_2$), 1.74−1.48 (3 H, m), 1.27 (1 H, m), 1.10 (3 H, d, J = 6.6 Hz, 5-Me), 0.99 (3 H, d, J = 6.9 Hz, Me_a of *i*-Pr), 0.72 (3 H, d, J = 6.9 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 164.4 (C), 145.5 (C), 142.6 (CH), 120.1 (C), 117.4 (CH), 41.5 (CH), 30.4 (CH), 30.3 (CH), 28.0 (CH_2), 21.7 (CH_3), 20.7 (CH_3), 19.2 (CH_2), 17.7 (CH_3); IR (neat) ν 2958, 2924, 2870, 2235, 1643, 1597, 1562, 1458, 1277, 1169, 1119, 949, 830 cm^{-1}; MS (ES) 638.8 (3M + Na^+), 433.7 (2M + Na^+), 411.7 (2M + H^+), 228.4 (M + Na^+), 206.4 (MH^+); MS (EI) *m*/*z* (%) 206 (4, $M^{\bullet+}$), 205 (28), 190 (34), 164 (11), 163 (100), 162 (57), 148 (27), 146 (11), 134 (10), 128 (6), 85 (10), 83 (10), 51 (74); HRMS (EI) 205.14670 ($C_{13}H_{19}NO$ requires 205.14666). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.04; H, 9.35; N, 6.82. Found: C, 76.24; H, 9.39; N, 6.74.

Procedure B. A solution of sulfuryl chloride (2.16 g; 16 mmol) in chloroform (10 mL) was added dropwise to a stirred solution of pyridone **30** (2.0 g; 9.7 mmol) in chloroform (30 mL) at 50 °C. After 30 min, the solvent was evaporated under reduced pressure, and the residue was heated at 100 °C for 30 min. The mixture was cooled, diluted with water (20 mL), and neutralized with 2 M NaOH (2 M), and the product was extracted with dichloromethane (3 × 50 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield crude pyridinol **34**. Purification by flash chromatography (petroleum ether−ethyl acetate, 1:1) gave **34** (0.91 g; 45%) as a 1:1 mixture of diastereoisomers. The spectroscopic data were identical to those obtained for the compound obtained from procedure A.

(5*R*,8*ξ*)-2-Chloro-5-methyl-8-isopropyl-5,6,7,8-tetrahydroquinoline, 35.[37] A mixture of phosphorus oxychloride (37 mL; 0.39 mol; 2 equiv), *N*,*N*-dimethylaniline (23.6 g; 0.195 mol; 1 equiv), tetrahydroquinoline **34** (40.0 g; 0.195 mol; 1 equiv), and phosphorus pentachloride (20.3 g; 9.8 mmol; 0.5 equiv) was stirred at reflux for 12 h under nitrogen. The cooled reaction mixture was poured into cold (0 °C) 2 M sodium hydroxide (500 mL), and the product was extracted with dichloromethane (3 × 200 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification of the crude product by column chromatography (petroleum ether−dichloromethane, 5:4) yielded **35** (38.2 g; 88%) as a pale yellow oil consisting of a 1:1 mixture of diastereoisomers. Alternatively, distillation of the crude oil under reduced pressure yielded a pale yellow oil (41.3 g; 95%; 98−100 °C, 0.39 mbar), consisting of a 1:1 mixture of diastereoisomers. **Epimer A:** ^{1}H NMR δ 7.44 (1 H, d, J = 8.2 Hz, 3-py), 7.03 (1 H, d, J = 8.2 Hz, 4-py), 2.85−2.60 (3 H, m), 1.90 (1 H, m), 1.80−1.52 (3 H, m), 1.30 (1 H, m), 1.23 (3 H, d, J = 7 Hz, 5-Me), 0.95 (3 H, d, J = 7 Hz, Me_a of *i*-Pr), 0.59 (3 H, d, J = 7 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 160.9 (C), 147.9 (C), 137.3 (CH), 136.9 (C), 120.9 (CH), 46.2 (CH), 32.0 (CH), 29.9 (CH), 28.2 (CH_2), 22.7 (CH_3), 20.7 (CH_3), 17.8 (CH_2), 17.0 (CH_3); IR (neat) ν 2958, 2931, 2870, 1574, 1558, 1431, 1388, 1138, 822 cm^{-1}; MS (EI) *m*/*z* (%) 225 (2, $M^{\bullet+}$), 223 (6, $M^{\bullet+}$), 208 (18), 196 (4), 181 (100), 166 (12), 152 (42). **Epimer B:** ^{1}H NMR δ 7.33 (1 H, d, J = 7.6 Hz, 3-py), 7.01 (1 H, d, J = 7.6 Hz, 4-py),

2.88−2.67 (3 H, m), 1.90 (1 H, m), 1.76−1.50 (3 H, m), 1.30 (1 H, m), 1.21 (3 H, d, J = 7 Hz, 5-Me), 1.02 (3 H, d, J = 7 Hz, Me_a of *i*-Pr), 0.66 (3 H, d, J = 7 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 160.5 (C), 147.9 (C), 139.0 (CH), 137.0 (C), 121.0 (CH), 45.9 (CH), 32.4 (CH), 30.9 (CH_2), 30.5 (CH), 21.2 (CH_3), 21.1 (CH_2), 20.6 (CH_3), 16.7 (CH_3); IR (neat) ν 2954, 2920, 1575, 1555, 1454, 1365, 1173, 1111, 856 cm^{-1}; MS (EI) *m*/*z* (%) 225 (3, $M^{\bullet+}$), 223 (8, $M^{\bullet+}$), 208 (11), 181 (100), 166 (33).

(5*R*,5′*R*,8*R*,8′*S*)-(−)-5,5′-Dimethyl-8,8′-diisopropyl-5,5′,6,6′,7,7′,8,8′-octahydro-2,2′-biquinoline, (−)-36. 36 was obtained (along with **11** and **12**) on coupling of **35**: mp 129−133 °C (ethanol-ether 2:1); $[\alpha]_D$ −207.32 (*c*, 2.15 g; CH_2Cl_2); ^{1}H NMR δ 8.14 (1 H, d, J = 8.2 Hz, 3-py_a), 8.13 (1 H, d, J = 7.9 Hz, 3-py_b), 7.61 (1 H, d, J = 7.9 Hz, 4-py_b), 7.48 (1 H, d, J = 8.2 Hz, 4-py_a), 3.07−2.78 (6 H, m, 2 × C*H*Me_2 + 2 × 8-H + 2 × 5-H), 2.06−1.35 (8 H, m, 4 × CH_2), 1.30 (3 H, d, J = 7 Hz, 5′-Me), 1.26 (3 H, d, J = 7 Hz, 5-Me), 1.10 (3 H, d, J = 7 Hz, Me_a of *i*-Pr′), 1.06 (3 H, d, J = 7 Hz, Me_a of *i*-Pr), 0.73 (3 H, d, J = 7 Hz, Me_b of *i*-Pr′), 0.69 (3 H, d, J = 7 Hz, Me_b of *i*-Pr); ^{13}C NMR δ 158.5 (C), 158.2 (C), 153.8 (C), 153.5 (C), 137.6 (C), 137.5 (C), 136.8 (CH), 135.0 (CH), 117.7 (CH), 117.6 (CH), 46.8 (CH), 46.4 (CH), 32.8 (CH), 32.5 (CH), 31.4 (CH_2), 30.3 (CH), 29.9 (CH), 28.7 (CH_2), 22.9 (CH_3), 21.8 (CH_2), 21.4 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 18.5 (CH_2), 17.3 (CH_3), 17.1 (CH_3); IR (neat) ν 2954, 2920, 2866, 1585, 1547, 1454, 1435, 1377, 1365, 1246, 1169, 832 cm^{-1}; MS (ES) 399.7 (M + Na^+), 378.7 (M + 2H^+), 377.7 (M + H^+); MS (EI) *m*/*z* (%) 376 (33, $M^{\bullet+}$), 335 (25), 334 (100), 333 (25), 319 (10), 289 (7), 275 (8); HRMS (EI) 376.28773 ($C_{26}H_{36}N_2$ requires 376.28785). Anal. Calcd for $C_{26}H_{36}N_2$: C, 82.91; H, 9.65; N, 7.44. Found: C, 82.09; H, 9.83; N, 7.41. Crystallographic data for **36**: $C_{26}H_{36}N_2$, M = 376.58. Crystals were obtained from a 2:1 ethanol−ether mixture at room temperature; they are monoclinic of space group $P2_1$, with a = 7.625(2), b = 13.358(3), c = 11.640(3) Å, β = 105.89(2)°, V = 1140.3(5) Å^3, Z = 2, d_{calc} = 1.097 g cm^{-3}, μ = 0.063 mm^{-1}. Data were collected at 190 K on a Bruker P4 diffractometer using Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and the ω scan mode. A total of 2516 reflections were measured, from which 2268 were unique (R_{int} = 0.045), with 1796 having $I > 2\sigma_I$. All reflections were used in the structure refinement based on F^2 by full-matrix least-squares techniques with hydrogen atoms calculated into theoretical positions, riding during refinement on the respective pivot atom (259 parameters). Final R_F = 0.049 for the observed data and $wR(F^2)$ = 0.119 for all data. The estimated error in C−C bond lengths is in the range 0.005−0.007 Å. The absolute configuration was established through the known configuration at the carbon carrying the methyl group (originating from menthone).

(6*R*,6′*R*,8*S*,8′*S*)-[5,5′,6,6′,7,7′,8,8′-Octahydro-7,7,7′,7′-tetramethyl-3,3′-bis(6,8-methanoisoquinoline)]tetracarbonylmolybdenum(0), 37. A suspension of molybdenum hexacarbonyl (115 mg; 0.44 mmol) and (−)-**5** (150 mg; 0.44 mmol) in dry toluene (3 mL) was heated at reflux for 2 h. The red-colored solution was allowed to cool, a few drops of pentane were added, and the solid was filtered off, washed with pentane (10 mL), and dried in a vacuum to yield **37** (206 mg, 84%) as an orange microcrystalline complex. Additional purification was achieved by precipitation from a CH_2Cl_2 solution by addition of pentane: mp dec ≥250 °C without melting; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.55 (s, 6H, 7,7′-Me), 1.09 (d, J = 9.6 Hz, 2H, 9,9′-C*H*H), 1.30 (s, 6H, 7,7′-Me), 2.22 (m, 2H, 6,6′-CH), 2.62 (ddd, J = 9.8, 5.8, and 5.8 Hz, 2H, 9,9′-CH*H*), 2.78 (dd, J = 5.4 and 5.4 Hz, 2H, 8,8′-H), 2.94 (m, 4H, 5,5′-CH_2), 7.72 (s, 2H, 4,4′-H), 8.41 (s, 2H, 1,1′-H); IR (CH_2Cl_2) ν_{max} 2009m, 1901vs, 1875s, 1826s cm^{-1} (C≡O). Anal. Calcd for $C_{28}H_{28}N_2O_4Mo{\cdot}1.5CH_2Cl_2$: C, 52.12; H, 4.60; N, 4.12. Found: C, 52.48; H, 4.84; N, 4.31.

(5*S*,7*R*)-[5,6,7,8-Tetrahydro-6,6-dimethyl-2-(pyridin-2-yl)-5,7-methanoquinoline]tetracarbonylmolybdenum-(0), 38. A suspension of molybdenum hexacarbonyl (1.06 g; 4.0 mmol) and (−)-**6** (1.0 g; 4.0 mmol) in dry toluene (15 mL) was heated at reflux for 2 h. The deep red colored solution was allowed to cool, a few drops of pentane were added, and the solid precipitated was filtered off, washed with pentane (10 mL), and dried in a vacuum to yield **38** (1.61 g, 88%) as a red-orange microcrystalline complex. It was recrystallized from CH_2Cl_2−pentane at −20 °C: mp dec ≥250 °C without melting; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.76 (s, 3H, 6-Me), 1.38 (d, J = 9.4 Hz, 1H, 9-C*H*H), 1.53 (s, 3H, 6-Me), 2.40 (m, 1H, 7-CH), 2.69 (ddd, J = 9.8, 5.6, and 5.6 Hz, 1H, 9-CH*H*), 2.98 (dd, J = 5.7 and 5.7 Hz, 1H, 5-H), 3.61 (d, J = 2.8 Hz, 2H, 8-CH_2), 7.40 (m, 1H, 5′-H), 7.53 (d, J = 8.0 Hz, 1H, 3-H), 7.92−8.00 (m, 2H, 4,4′-H), 8.12 (d, J = 8.0 Hz, 1H, 3′-H), 9.27 (br d, J = 4.8 Hz, 1H, 6′-H); IR (CH_2Cl_2) ν_{max} 2015s, 1905vs, 1875s, 1827s cm^{-1} (C≡O). Anal. Calcd for $C_{21}H_{18}N_2O_4Mo{\cdot}0.5CH_2Cl_2$: C, 51.57; H, 3.82; N, 5.59. Found: C, 51.10; H, 3.91; N, 5.32. The crystals exhibited polymorphism, and the individual forms (monoclinic and tetragonal) were separated mechanically. Crystallographic data for monoclinic **38**: $C_{21}H_{18}MoN_2O_4$, M = 458.31. Crystals were obtained from a toluene−pentane mixture at −20 °C. They are monoclinic, space group $C2$, a = 27.4627(1), b = 9.1280(1), c = 20.2505(1) Å, β = 129.106(1)°, V = 3939.17(5) Å^3, Z = 8, d_{calc} = 1.546 g cm^{-3}, μ = 0.695 mm^{-1}. Data were collected at 183 K on a Siemens SMART CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and ω scan mode at four different ϕ orientations covering thus the entire reciprocal sphere up to 0.65 Å resolution. A total of 30 108 reflections were measured, from which 13 422 were unique (R_{int} = 0.0280), with 11 779 observed data having $I > 2\sigma_I$. All reflections were used in the structure refinement based on F^2 by full-matrix least-squares technique with hydrogen atoms calculated into theoretical positions, riding during refinement on the respective pivot atom (545 parameters). Final R_F = 0.0331 for the observed data and $wR(F^2)$ = 0.0773 for all data. The estimated error in C−C bond lengths is in the range 0.003−0.005 Å. The absolute configuration determined with Flack factor = −0.037(19). Crystallographic data for tetragonal **38**: $C_{21}H_{18}MoN_2O_4$, M = 458.31. Crystals were obtained from a toluene−pentane mixture at −20 °C. They are tetragonal, space group $P4_12_12$, a = b = 10.6054(1), c = 34.7941(7) Å, V = 3913.45(9) Å^3, Z = 8, d_{calc} =1.556 g cm^{-3}, μ = 0.700 mm^{-1}. Data were collected at 183 K on a Siemens SMART CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and ω scan mode at four different ϕ orientations, covering thus the entire reciprocal sphere up to 0.75 Å resolution. A total of 45 876 reflections were measured, from which 4854 were unique (R_{int} = 0.0510), with 4553 observed data having $I > 2\sigma_I$. All reflections were used in the structure refinement based on F^2 by full-matrix least-squares technique with hydrogen atoms calculated into theoretical positions, riding during refinement on the respective pivot atom (273 parameters). Final R_F = 0.0278 for the observed data and $wR(F^2)$ = 0.0513 for all data. The estimated error in C−C bond lengths is in the range 0.003−0.004 Å. The absolute configuration determined with Flack factor = −0.03(3).

(5*S*,7*R*,8*R*)-[5,6,7,8-Tetrahydro-6,6,8-trimethyl-2-(pyridin-2-yl)-5,7-methanoquinoline]tetracarbonylmolybdenum(0), 39. A suspension of molybdenum hexacarbonyl (460 mg; 1.74 mmol) and (−)-**7** (460m g; 1.74 mmol) in dry toluene (15 mL) was heated at reflux for 1 h. The deep red colored solution was allowed to cool and was filtered and concentrated in a vacuum. Pentane was added dropwise to precipitate a solid that was filtered off, washed with pentane (10 mL), and dried in a vacuum to yield **39** (560 mg, 68%), as a red-orange microcrystalline complex. It was recrystallized from CH_2Cl_2−pentane at −20 °C: mp dec ≥250 °C without melting; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.64 (s, 3H, 6-Me), 1.34 (d, J = 10.5 Hz, 1H, 9-C*H*H), 1.40 (s, 3H, 6-Me), 1.55 (d, J = 6.9 Hz, 3H, 8-Me), 2.40 (ddd, J = 6.2, 6.2, and 3.2 Hz, 1H, 7-CH), 2.51 (m, 1H, 9-CH*H*), 2.81 (dd, J = 5.5 and 5.5 Hz, 1H, 5-H), 3.25 (qd, J = 6.9 and 3.2 Hz, 1H, 8-H), 7.25 (m, 1H, 5′−H), 7.37 (d, J = 8.0

Hz, 1H, 3-H), 7.71 (d, J = 8.0 Hz, 1H, 4-H), 7.80 (m, 1H, 4′-H), 7.88 (d, J = 8.0 Hz, 1H, 3′−H), 9.10 (br d, J = 5.5 Hz, 1H, 6′-H); IR (CH_2Cl_2) ν_{max} 2018s, 1905vs, 1879vs, 1829vs cm^{-1} (C≡O). Anal. Calcd for $C_{22}H_{20}N_2O_4Mo$: C, 55.94; H, 4.27; N, 5.93. Found: C, 55.58; H, 4.25; N, 5.68. Crystallographic data for **39**: $C_{22}H_{20}MoN_2O_4$, M = 472.34. Crystals were obtained from a toluene−pentane mixture at −20 °C. They are monoclinic, space group $P2_1$, a = 7.2940(1), b =31.7600(2), c = 9.7093(1) Å, β = 111.296(1)°, V = 2095.65(4) Å^3, Z = 4, d_{calc} = 1.497 g cm^{-3}, μ = 0.656 mm^{-1}. Data were collected at 183 K on a Siemens SMART CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and ω scan mode at four different ϕ orientations, covering thus the entire reciprocal sphere up to 0.83 Å resolution. A total of 15 192 reflections were measured, from which 6859 were unique (R_{int} = 0.0474), with 6287 observed data having $I > 2\sigma_I$. All reflections were used in the structure refinement based on F^2 by full-matrix least-squares technique with hydrogen atoms calculated into theoretical positions, riding during refinement on the respective pivot atom (569 parameters). Final R_F = 0.0414 for the observed data and $wR(F^2)$ = 0.0966 for all data. The estimated error in C−C bond lengths is in the range 0.007−0.010 Å. The absolute configuration determined with Flack factor = 0.00(3).

(6*R*,8*R*)-[5,6,7,8-Tetrahydro-7,7-dimethyl-2-(pyridin-2-yl)-6,8-methanoquinoline]tetracarbonylmolybdenum-(0), 40. A suspension of molybdenum hexacarbonyl (1.06 g; 4.0 mmol) and (+)-**8** (1.0 g; 4.0 mmol) in dry toluene (18 mL) was heated at reflux for 2 h. The deep red colored solution was allowed to cool, pentane (∼5 mL) was added, and the precipitated solid was filtered off, washed with pentane (10 mL), and dried in a vacuum to yield **40** (1.57 g, 85%), as a red-orange microcrystalline complex. It was recrystallized from CH_2Cl_2−pentane at −20 °C: mp dec ≥250 °C without melting; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.73 (s, 3H, 7-Me), 1.16 (d, J = 9.9 Hz, 1H, 9-C*H*H), 1.51 (s, 3H, 7-Me), 2.33 (m, 1H, 6-CH), 2.78 (ddd, J = 9.9, 6.0, and 6.0 Hz, 1H, 9-CH*H*), 2.98 (m, 2H, 5-CH_2), 4.04 (dd, J = 5.6 and 5.6 Hz, 1H, 8-H), 7.23 (m, 1H, 5′-H), 7.57 (d, J = 7.9 Hz, 1H, 3-H), 7.81 (m, 2H, 4,4′-H), 7.93 (d, J = 8.2 Hz, 1H, 3′-H), 9.08 (br d, J = 4.7 Hz, 1H, 6′-H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.7 (Me), 25.7 (Me), 31.0 (CH_2), 32.4 (CH_2), 40.0 (C), 40.3 (CH), 54.4 (CH), 120.1 (CH), 122.0 (CH′), 124.6 (CH′), 134.2 (C), 136.8 (CH), 137.7 (CH′), 151.6 (C), 153.1 (CH′), 156.8 (C′), 171.0 (C), 204.4 (CO), 205.4 (CO), 222.4 (CO), 224.5 (CO); IR (CH_2Cl_2) ν_{max} 2018s, 1909vs, 1875s, 1823s cm^{-1} (C≡O). Anal. Calcd for $C_{21}H_{18}N_2O_4Mo{\cdot}0.5CH_2Cl_2$: C, 51.57; H, 3.82; N, 5.59. Found: C, 51.05; H, 4.11; N, 5.29. Crystallographic data for **40**: $C_{21}H_{18}MoN_2O_4$, M = 458.31. Crystals were obtained from a toluene−hexane mixture at −24 °C overnight. They are monoclinic, space group $P2_1$, a = 9.2580(3), b =17.4034(5), c = 13.3858(4) Å, β = 107.758(1)°, V = 2053.97(11) Å^3, Z = 4, d_{calc} = 1.482 g cm^{-3}, μ = 0.666 mm^{-1}. Data were collected at 298 K on a Siemens SMART CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and ω scan mode at four different ϕ orientations covering thus the entire reciprocal sphere up to 0.76 Å resolution. A total of 24 251 reflections were measured, from which 9753 were unique (R_{int} = 0.0237), with 7555 observed data having $I > 2\sigma_I$. All reflections were used in the structure refinement based on F^2 by full-matrix least-squares technique with hydrogen atoms calculated into theoretical positions, riding during refinement on the respective pivot atom (545 parameters). Final R_F = 0.0349 for the observed data and $wR(F^2)$ = 0.0866 for all data. The estimated error in C−C bond lengths is in the range 0.005−0.010 Å. The absolute configuration determined with Flack factor = −0.02(3).

(6*R*,6*R*′,8*R*,8*R*′)-[5,5′,6,6′,7,7′,8,8′-Octahydro-6,6′,7,7′-tetramethylbis(6,8-methanoquinoline)]copper(II) Chloride Complex, 41. A solution of copper(II) chloride dihydrate (97 mg, 0.57 mmol) in EtOH (5 mL) was added to a solution of (+)-**10** (200 mg, 0.58 mmol) in CH_2Cl_2 (5 mL); the color of the solution instantaneously changed from green to deep red. The mixture was refluxed for 12 h to ensure completion of the complexation reaction. The solvent was evaporated, and the resulting red solid was recrystallized from a chloroform−hexane mixture to give the copper complex **41** (245 mg, 75%): mp dec >250 °C without melting. Anal**.** Calcd for $C_{24}H_{28}Cl_2N_2Cu{\cdot}CH_2Cl_2$: C, 53.25; H, 5.36; N, 4.97. Found: C, 52.91; H, 5.58; N, 4.71. Crystallographic data for **41**: $C_{25}H_{30}Cl_4CuN_2$, M = 563.85. Crystals were obtained from a 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), b =3.6592(2), c = 17.9777(2) Å, V = 2544.92(5) Å^3, Z = 4, d_{calc} = 1.472 g cm^{-3}, μ = 1.295 mm^{-1}. Data were collected at 183 K on a Siemens SMART CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and ω scan mode at four different ϕ orientations, covering thus the entire reciprocal sphere up to 0.65 Å resolution. A total of 30 160 reflections were measured, from which 9036 were unique (R_{int} = 0.0198), with 8590 observed data having $I > 2\sigma_I$. All reflections were used in the structure refinement based on F^2 by full-matrix least-squares technique with hydrogen atoms calculated into theoretical positions, riding during refinement on the respective pivot atom (328 parameters). Final R_F = 0.0332 for the observed data and $wR(F^2)$ = 0.0973 for all data. The estimated error in C−C bond lengths is in the range 0.002−0.003 Å. The absolute configuration determined with Flack factor = 0.003(7).

(6*R*,6*R*′,8*R*,8*R*′)-(+)-[5,5′,6,6′,7,7′,8,8′-Octahydro-6,6′,7,7′-tetramethylbis(6,8-methanoquinoline)]palladium(II) Chloride Complex, (+)-42. A solution of (+)-**10** (200 mg, 0.58 mmol) in CH_3CN (5 mL) was added to a suspension of palladium chloride (102 mg, 0.57 mmol) in CH_3CN (5 mL). The mixture was refluxed for 30 min to ensure completion of the complexation reaction; the originally dark brown solid gradually turned into a yellow precipitate. The solvent was then evaporated, and the resulting solid was crystallized from a chloroform−hexane mixture to give the yellow palladium complex (+)-**42** (226 mg, 76%): mp dec >250 °C without melting; $[\alpha]_D$ +95.3 (c 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (s, 6 H), 1.05 (d, J = 7.0 Hz, 2 H), 1.37 (s, 6 H), 2.20 (m, 2 H), 2.76 (m, 6 H), 3.97 (dd, J = 5.5 and 5.5, Hz, 2 H), 7.44 (d, J = 7.9 Hz, 2 H), 8.31 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.5, 24.0, 30.2, 30.6, 37.9, 38.0, 50.8, 119.8, 133.0, 137.9, 152.3, 170.8.

General Procedure for Asymmetric Allylic Substitution Catalyzed by Mo(0) Complexes. The catalyst was generated as follows:[64] Tin(IV) chloride (1.0 mmol) was added to a stirred suspension of tetracarbonyl **37**−**40** (1.0 mmol) in dry dichloromethane (5 mL) under a nitrogen atmosphere. The solution was stirred at room temperature for 30 min, and then hexane (2 mL) was added. The mixture was concentrated in a vacuum, and the precipitate formed was filtered off, washed successively with ether (10 mL) and pentane (10 mL), and dried under vacuum to yield (LL)$Mo^{II}(CO)_3(SnCl_3)Cl$ as an orange-yellow powder: IR (Nujol) ν(C≡O) 2010−2025(s), 1930−1935(s) cm^{-1}. The complexes thus obtained were used in subsequent reaction without further purification. Allylic substitution was carried out as follows: A flask was charged with sodium hydride (4.5 mmol) and 1,4-dioxane (6 mL), and to this stirred suspension was added dropwise a solution of dimethyl malonate (4 mmol) in the same solvent (2 mL). Then the catalyst (20 mol %) was added to the resulting solution, followed by a solution of the allylic substrate (2 mmol) in 1,4-dioxane (2 mL). The mixture was heated at 80 °C until the TLC analysis indicated disappearance of the starting material or until no further reaction was detected after 24 h. The mixture was then cooled, diluted with ether (20 mL), and

(64) (a) Baker, P. K.; Bury, A. *J. Organomet. Chem.* **1989**, *359*, 189. (b) Baker, P. K.; Quinlan, A. J. *Inorg. Chem.* **1989**, *28*, 179. (c) Baker, P. K.; Bury, A. *Polyhedron* **1989**, *8*, 7.

washed successively with 5% aqueous $NaHCO_3$ and water. The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15 × 2 cm) with a 9:1 hexanes−ethyl acetate mixture as an eluent. Enantiomeric purity of the products was determined by chiral HPLC using Chiralcel OD-H (**44**) or Chiralpak AD (**46**) columns with the eluent hexane−2-propanol (99.5:0.5 and 90:10, respectively), UV detection at 220 nm. The yields and ee are given in the Results and Discussion section.

General Procedure for Asymmetric Allylic Oxidation Catalyzed by Cu(I) Complexes. A green solution of the ligand (0.06 mmol, i.e., 21 mg of **10** or 23 mg of **11** or **12**) 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, olefin **47** (5 mmol) was added, followed by a 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 an aqueous $KHCO_3$ solution, brine, and water, and dried over $MgSO_4$. Concentration and chromatography on silica gel afforded pure allylic benzoate (*S*)-**48**. The yields and ee are given in the Results and Discussion section. Enantiomeric purity of the products was determined by chiral HPLC using Chiralcel OD-H (**48a**), Chiralpak AD (**48b**), or Chiralcel OJ (**48c**) columns.

General Procedure for Asymmetric Cyclopropanation Catalyzed by Cu(I) Complexes. A solution of the ligand (0.06 mmol, i.e., 21 mg of **10** or 23 mg of **11** or **12**) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) in dichloromethane (5 mL) was stirred under a nitrogen atmosphere at 20 °C for 1 h. The solution was filtered through glass-wool under nitrogen, and to the filtrate were successively added phenylhydrazine (5.9 μL, 0.06 mmol) and styrene (1 mL). A solution of diazoacetate (3−5 mmol) in dichloromethane (3 mL) was then added dropwise over a period of 3 h using a syringe pump. The mixture was stirred for an additional 1 h and concentrated in a vacuum. The ratio of *trans*- and *cis*-isomers was determined by capillary GC. Separation of the isomers was performed by column chromatography on silica gel with hexane−ethyl acetate (20:1) as an eluent. Enantiomeric purity of the products was determined by chiral HPLC using Chiralcel OD-H (**50a**, **50b**, **51b**) or Chiralpak AD (**51a**) columns.

Note Added in Proof: After the publication of our preliminary report (Malkov, A. V.; Bella, M.; Langer, V.; Kočovský, P. *Org. Lett.* **2000**, *2*, 3047) and while this paper was in press, von Zelewsky reported on ligands **6**, **7** (with R = H, Me, Et, *i*-Pr), **9** (analogously mono- and bis-functionalized with R = H, Me, Et, Pr, *i*-Pr, Bn, and Me_3Si), and **10** (Lötscher, D.; Rupprecht, S.; Stoeckli-Evans, H.; von Zelewsky, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4341). This paper also contained crystallographic characterization of the $CuCl_2$ complex **41** that appears to be identical to our data (both published here and in our preliminary communication) and of two other $CuCl_2$ complexes, namely, with **9** and its bis-dimethyl analogue. Reported asymmetric induction in the cyclopropanation of styrene is consistent with our findings, i.e., low selectivity for **41** and high ee values for the Cu(I) complex of **9** and its bis-alkylated analogues that can be regarded as close congeners to our MINDY ligand **11**.

Acknowledgment. We thank the EPSRC for Grants No. GR/H92067 and GR/K07140 and EPSRC and Aventis CropScience UK Ltd for a CASE award to I.R.B.

Supporting Information Available: Additional experimental procedures and details of the crystallographic analysis with atomic coordinates, selected bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, and fully labeled ORTEP diagrams for **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM000850N