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Synthesis of New Chiral 2,2′-Bipyridine Ligands and Their Application in Copper-Catalyzed Asymmetric Allylic Oxidation and Cyclopropanation

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A series of modular bipyridine-type ligands **1** and **3**−**9** has been synthesized via a de novo construction of the pyridine nucleus. The chiral moieties of these ligands originate from the isoprenoid chiral pool, namely, β-pinene (**10** → **1**), 3-carene (**14** → **3** and **5**), 2-carene (**28** → **4**), α-pinene (**43** → **6**-**8**), and dehydropregnenolone acetate (**48** → **9**), respectively. Copper(I) complexes, derived from these ligands and $(TfO)_2Cu$ (1 mol %) upon an in situ reduction with phenylhydrazine, exhibit good enantioselectivity (up to 82% ee) and unusually high reaction rate (typicaly 30 min at room temperature) in allylic oxidation of cyclic olefins (**52** → **53**). Copper-catalyzed cyclopropanation proceeded with ≤76% enantioselectivity and ∼3:1 to 99:1 *trans*/*cis*-diastereoselectivity (**54** → **55** + **56**). The level of the asymmetric induction is discussed in terms of the ligand architecture that controls the stereochemical environment of the coordinated metal.

Introduction

In asymmetric, transition metal catalyzed reactions, ligands with sp^2 nitrogen(s) as the coordinating atom(s) constitute an important class[1] that is currently dominated by substituted oxazolines and bisoxazolines.[2] It can be envisaged that the related 2,2′-bipyridyl and 1,10-phenanthrolines,[3] rendered chiral by annulation of chiral units,[4−7] would represent an interesting alternative that may offer new opportunities, such as electronic tuning of the ligating nitrogen via the substitution pattern at the pyridine ring,[3d,e] an option not readily available with oxazolines.[8]

As part of a broader program aimed at the development of new transition metal catalysts and organocatalysts for asymmetric synthesis, we have now focused on the synthesis of chiral bipyridines,[9] where chirality is introduced by the annulation of monoterpene moieties. Herein, we report on the preparation of the stereochemically modulated, C_2-symmetrical 2,2′-bipyridines **1** and **3**−**9** (Chart 1) and their application in copper-catalyzed asymmetric allylic oxidation and cyclopropanation.

Results and Discussion

Ligands (+)-**1** (PINDY) and (−)-**2** (MINDY) have previously been synthesized by us from (−)-β-pinene and (−)-menthol, respectively (vide infra).[9a,b,10,11] Crystallographic

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studies of the complexes of **1** with transition metals have revealed interesting structural characteristics. Thus, the $CuCl_2$ complex exhibits a strong tetrahedral distortion (with the Cl−Cu−Cl axis bent from the py−py plane by ca. 60°),[9a,b,12] whereas the $NiCl_2$ complex is regularly tetrahedral (i.e., the Cl−Ni−Cl axis is perpendicular to the py-py plane).[13,14] On the other hand, the $PtCl_2$ complex is known to assume an essentially square-planar geometry, causing a severe distortion of the ligand,[5f] which demonstrates the strong adherence of platinum(II) to its preferred geometry, contrasting with the flexibility of copper(II) and nickel(II).

CHART 1

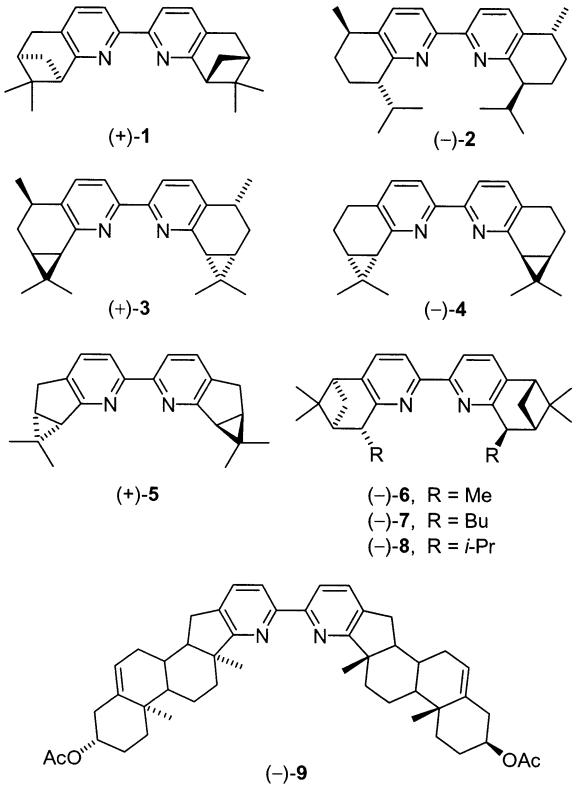
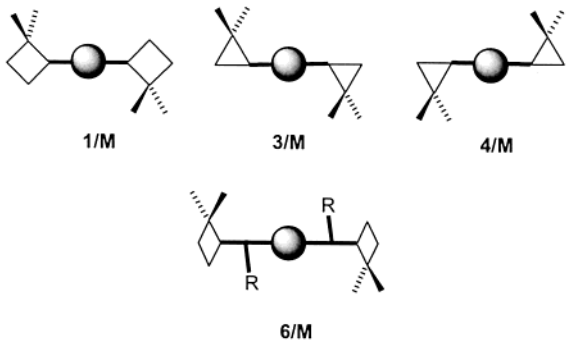


CHART 2. Side-On View of Metal Complexes of Ligands 1, 3, 4, and 6



Stereochemical Considerations and Ligand Design. Our preliminary results have demonstrated high reactivity of the Cu complex of **1** as catalyst in the allylic oxidation of cyclic olefins, with good enantioselectivity.[9a,b] Molecular modeling, carried out to shed light on the origin of this asymmetric induction, suggests that PINDY (**1**) may not be an ideal basis for the catalyst. The side-on view of its metal complex **1**/**M** (Chart 2) shows that, although the upper-left and lower-right front octants are

(6) For other chiral pyridine derivatives, see, for example: (a) Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2571. (b) Chelucci, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2667. (c) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 3183. (d) Chelucci, G.; Berta, D.; Saba, A. *Tetrahedron* **1997**, *53*, 3843. (e) Chelucci, G.; Saba, A.; Soccolini, F. *Tetrahedron* **2001**, *57*, 9989. (f) Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604. (g) Bremberg, U.; Rahm, F.; Moberg, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3437. (h) Wärnmark, K.; Stranne, R.; Cernerud, M.; Terrien, I.; Rahm, F.; Nordström, K.; Moberg, C. *Acta Chem. Scand.* **1998**, *52*, 961. For a recent overview of chiral pyridines, see: (i) Moberg, C.; Adolfsson, H.; Wärnmark, K. *Acta Chem. Scand.* **1996**, *50*, 195. (j) Canal, J. M.; Gómez, M.; Jiménez, F; Rocamora, M.; Muller, G.; Duñach, E.; Franco, D.; Jiménez, A.; Cano, F. H. *Organometallics* **2000**, *19*, 966. For recent examples of bipyridine ligands with planar chirality, see: (k) Wörsdorför, U.; Vögtle, F.; Nieger, M.; Waletzke, M.; Grimme, S.; Glorius, F.; Pfaltz, A. *Synthesis* **1999**, 597. (l) Rios, R.; Liang, J.; Mo, M. M.-C.; Fu, G. C. *Chem. Commun.* **2000**, 377. (m) Djukic, J.-P.; Michon, C.; Maisse-François, A.; Allagapen, R.; Pfeffer, M.; Dötz, K. H.; De Cian, A.; Fischer, J. *Chem. Eur. J.* **2000**, *6*, 1064. For recent examples of chiral terpyridines and their use in asymmetric cyclopropanation, see: (n) Kwong, H.-L.; Lee, W. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2299. (o) Kwong, H.-L.; Wong, W. L.; Lee, W.-S.; Cheng, L. S.; Wong, W.-T. *Tetrahedron: Asymmetry* **2001**, *12*, 2683.

(7) For catalytic application of phenanthroline complexes: (a) Gladiali, S.; Chelucci, G.; Soccolini, F.; Delogu, G.; Chiessa, G. *J. Organomet. Chem.* **1989**, *370*, 285. (b) Peña-Cabrera, E.; Norrby, P.-O.; Sjögren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299. Related nonchiral phenanthrolines: (c) Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16*, 3015. (d) Hansson, S.; Norrby, P.-O.; Sjögren, M. P. T.; Åkermark, B. *Organometallics* **1993**, *12*, 4940. (e) Sjögren, M. P. T.; Hansson, S.; Åkermark, B. *Organometallics* **1994**, *13*, 1963. (f) Frisell, H.; Åkermark, B. *Organometallics* **1995**, *14*, 561. (g) Sjögren, M. P. T.; Frisell, H.; Åkermark, B. *Organometallics* **1997**, *16*, 942. (h) Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18*, 2884. (i) Chelucci, G.; Iuliano, A.; Muroni, D.; Saba, A. *J. Mol. Catal.* **2003**, *191*, 29. (j) Chelucci, G.; Loriga, G.; Murineddu, G.; Pinna, G. A. *Synthesis* **2003**, 73.

(8) Aza-bis(oxazolines) have been reported to show noticeable changes in the electronics of the ligating sp^2 nitrogens and their ability to coordinate metals. For the first examples, see the following: (a) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045. For a different strategy of tuning the electronics of the oxazoline ring, see: (b) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206. Further modifications of the nitrogen electronics can be expected from bis(imidazolines). For the first reports on the use of imidazoline-type ligands in asymmetric synthesis, see the following: (c) Dupont, J.; Ebeling, G.; Delgado, M. R.; Consorti, C. S.; Burrow, R.; Farrar, D. H.; Lough, A. J. *Inorg. Chem. Commun.* **2001**, *4*, 471. (d) Casey, M.; Smyth, M. P. *Synlett* **2003**, 102.

(9) For our recent efforts in the area of chiral 2,2′-bipyridines, see: (a) Malkov, A. V.; Bella, M.; Langer, V.; Kočovský, P. *Org. Lett.* **2000**, *2*, 3047. (b) Malkov, A. V.; Baxendale, I. R.; Fawcett, J.; Russell, D. R.; Langer, V.; Mansfield, D. J.; Valko, M.; Kočovský, P. *Organometallics* **2001**, *20*, 673. (c) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047. For analogous (phosphinoaryl)pyridines, see: (d) Malkov, A. V.; Bella, M.; Stará, I. G.; Kočovský, P. *Tetrahedron Lett.* **2001**, *42*, 3045. For related, chiral monopyridines, see: (e) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal. A* **2003**, *196*, 179. For an overview, see: (f) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, in press.

(10) A different approach to ligands **1** and **6**−**8** was reported subsequently by von Zelewsky.[5e,f]

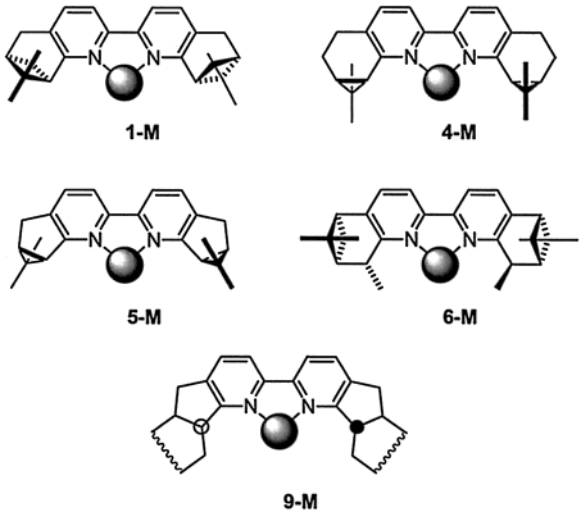
(11) For a conceptually different approach to 2,2′-bipyridines, based on the hetero-Diels−Alder reaction, see: (a) Bushby, N.; Moody, C. J.; Riddick, D. A.; Waldron, I. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2183. For a three-step double annulation, leading to analogous, axially chiral 2,2′-bipyridines, see: (b) Thumel, R. P.; Lefoulon, F. *J. Org. Chem.* **1985**, *50*, 666. (c) Nakajima, M.; Sasaku, Y.; Shiro, M. *Tetrahedron: Asymmetry* **1997**, *8*, 341. (d) Hashimoto, S.; Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (e) Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2000**, *48*, 306.

(12) An identical structure was reported subsequently by von Zelewsky.[5e] Similar distortion was reported by Kwong for a related bipyridine-type complex.[4g]

(13) Malkov, A. V.; Bella, M.; Langer, V.; Kočovský, P. Unpublished results.

(14) The closely related $CoCl_2$ complex of the isomeric ligand **47** (vide infra) exhibits tetrahedral geometry.[5g]

CHART 3. Face-On View of Metal Complexes of Ligands 1, 4−6, and 10

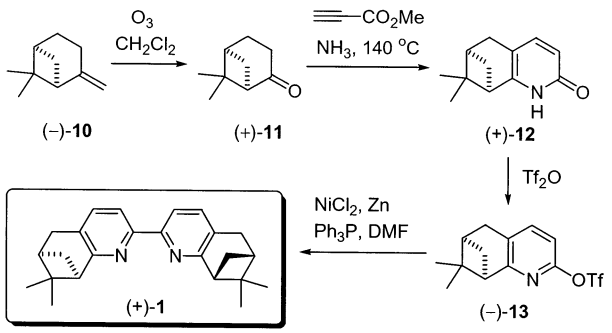


severely hindered by the CMe_2 groups, the remaining two octants experience nonnegligible shielding by the CH_2 groups of the cyclobutanes. The latter obstacle would be eliminated in the case of complex **3**/**M**, in which the CH_2 group in each of the two octants is removed and the remaining carbons are connected by a bond (forming part of a cyclopropane ring). This geometry, anticipated for complex **3**/**M**, can be attained with ligand (+)-**3** (Me-CANDY) and with the quasi-enantiomeric complexes **4**/**M**, derived from (−)-**4** (CANDY) and (+)-**5** (*nor*-CANDY), respectively. Note that **3**/**M** and **4**/**M**, being quasi-enantiomeric, should exhibit an opposite sense of asymmetric induction.[15] Further variation can be attained with **6**/**M**, where the chiral, terpene-based scaffold is moved away from the metal and the stereochemical influence is likely to be mainly exercised by the alkyl groups (R) of the parent ligand **6** (Me-*iso*-PINDY). This pattern would allow a modular approach and tailoring of the cavity that surrounds the metal, since the R groups will be introduced deliberately by alkylation of the basic framework (vide infra).

The face-on view of the ligand complexes (Chart 3) reveals further important features concerning the shape of the chiral cavity. Thus, comparison of complexes **1**-**M** and **4**-**M**, derived from **1** and **4**, respectively, reveals a dramatic difference in the cone angle of the cavity created by the two Me−C−Me axes of the pair of the CMe_2 groups in each complex: thus, in **1**-**M**, the cavity has a relatively wide "entrance door", whereas the "corridor" is rapidly narrowing, which brings the *endo*-Me groups closer to the metal. By contrast, the entrance door in **4**-**M** is more narrow, and the corridor retains this width, bringing the *exo*-Me groups closer to the metal but moving the *endo*-Me away (relative to the former complex). Further widening of the entrance can be anticipated for complex **5**-**M**, derived from ligand **5** (*nor*-CANDY), owing to the contraction of the cyclohexane scaffold to a five-membered ring. Note that ligands **3**−**5** (Chart 1), with the CMe_2 group being fixed, can be regarded as rigid analogues of **2**. Complex **6**-**M**, generated from ligand **6**, will

(15) This concept was successfully applied by us in the case of the related phosphino-pyridine ligands.[9d]

SCHEME 1[a]



[a] Tf = CF_3SO_2.

offer another modification of the geometry, rendering the entrance even more narrow than that in the previous complexes. The steroid ligand **9** can be expected to provide an essentially planar structure, from which the angular methyl groups will protrude above and below the bipyridine plane (**9**-**M**).

Ligands Synthesis. PINDY (+)-**1** was synthesized earlier by us[9a,b] and subsequently by von Zelewsky[5e,g] from (−)-*β*-pinene (−)-**10** via nopinone (+)-**11**. We have now developed a shorter procedure that involves four steps (Scheme 1) and appears more robust. (+)-Nopinone (+)-**11**,[16] obtained from (−)-*β*-pinene (−)-**10**[17] by ozonolysis on a 30-g scale [O_3, CH_2Cl_2/MeOH (1:1), −78 to −20 °C, 48 h; Zn/AcOH workup; 80%], was treated with an excess of methyl propiolate and ammonia in an autoclave to afford pyridone (+)-**12** (HC≡CCO_2Me, 7 M NH_3 in MeOH, 140 °C, 10 h, 15 bar; 61%), as a result of the Michael addition, followed by imine formation and ring closure.[18] The corresponding triflate (−)-**13**, prepared by a standard protocol [$(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, −45 °C to rt, 1.5 h; 99%], was then submitted to the nickel- and zinc-mediated dimerization ($NiCl_2$·$6H_2O$, Ph_3P, Zn, DMF, 60 °C, 17 h)[19] that afforded the required PINDY (+)-**1** (60%).

As a building block for the cyclopropane moiety in ligand (+)-**3**, we chose (+)-3-carene (+)-**14**[20] (Scheme 2). Allylic oxidation [O_2, CrO_3 (1 mol %), pyridine (5 mol %), rt, 24 h][21] gave enone (−)-**15** (20%), whose hydrogenation (H_2, 5% Pd/C, ether) produced the *cis*-derivative (+)-**16** (98%).[22] Attempted pyridine annulation, analogous to that described in Scheme 1, completely failed, apparently owing to the steric hindrance exercised by the methyl group in the *β*-position of ketone (+)-**16**. Therefore, a

(16) Nopinone is commercially available but rather expensive.

(17) (−)-*β*-Pinene (−)-**10** was of 95% ee according to chiral GC. For determination of enantiopurity of monoterpene hydrocarbons by GC, see: Krüger, A.; Icheln, D.; Runge, T. *J. High Resolut. Chromatogr.* **1992**, *15*, 184.

(18) For the method, see: Kozikowski, A. P.; Reddy, E. R.; Miller, C. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 195−197.

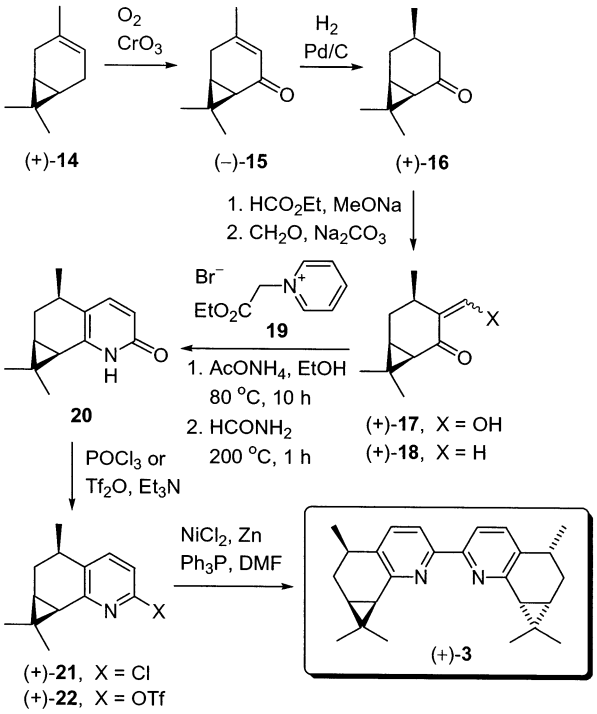
(19) For the method of an analogous dimerization of α-chloropyridines, see refs 5a, 9a,b, and the following: (a) Dehmlow, E. V.; Sleegers, A. *Liebigs Ann. Chem.* **1992**, *9*; 953. (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2881.

(20) (+)-3-Carene (+)-**14** was of 93% ee (by GC).

(21) (a) Rothenberg, G.; Yatziv, Y.; Sasson, Y. *Tetrahedron* **1998**, *54*, 593. (b) Vyglazov, O. G.; Manukov, E. N.; Fedorishcheva, M. N.; Ariko, N. G.; Chuiko, V. A.; Bazhina, G. N. *Chem. Nat. Compd. (Engl. Transl.)* **1991**, 27; *Khim. Prir. Soedin.* **1991**, 328.

(22) (a) Maas, D. D.; Blagg, M.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 853. For a less economical synthesis, see: (b) Cocker, W.; Shannon, P. V. R.; Staniland, P. A. *J. Chem. Soc. C* **1967**, 485.

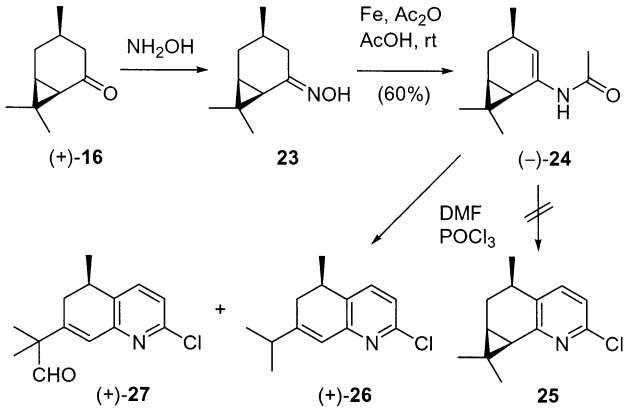
SCHEME 2



more elaborate protocol, relying on Kröhnke annulation,[23] was explored. To this end, *exo*-methylene ketone (+)-**18** was first prepared via Claisen condensation of (+)-**16** (HCO_2Et, MeONa, toluene, rt, 10 h; 76%), followed by transaldolization (37% CH_2O in H_2O, Na_2CO_3, ether, rt, 2 h; 90%). Reaction of (+)-**18** thus obtained with Kröhnke[23] salt **19**[24] ($AcONH_4$, piperidine, EtOH, 80 °C, 10 h; then $HCONH_2$, 200 °C, 1 h) afforded pyridone **20** (20%). Treatment of the latter derivative with $POCl_3$ (DMF, 60 °C, 6 h) produced the corresponding chloride (+)-**21** in modest yield (39%); by contrast, conversion into triflate (+)-**22** (Tf_2O, Et_3N, CH_2Cl_2, −45 °C, 30 min) occurred almost quantitatively (99%). Triflate (+)-**22** was then coupled using the Ni/Zn method[19] [$NiCl_2$, Zn, Ph_3P, Me_4NI, DMF, 60 °C, 24 h] to afford the required ligand (+)-**3** (54%), for which we propose the acronym "Me-CANDY" (as a methylated analogue of CANDY; see below).

An alternative approach to (+)-**3** was attempted in analogy to our original synthesis of PINDY (**1**)[9a,b] (Scheme 3). To this end, oxime (+)-**23**,[25] prepared from ketone (+)-**16**[22] (NH_2OH·HCl, pyridine, EtOH, reflux, 1 h; 95%), was reduced under the acetylation conditions[26] to afford acetimide (−)-**24** (Fe, Ac_2O, AcOH, toluene, 0 °C, 20 min;

SCHEME 3



52%). In the case of PINDY, the related acetimide was converted into the corresponding chloropyridine derivative via Vilsmeier−Haack reaction.[27] In this series, however, the pyridine ring closure required harsher conditions ($POCl_3$, DMF, rt, 1 h, then 80 °C, 4 h) and was accompanied by opening of the cyclopropane, giving a mixture of chloropyridines **26** (31%) and **27** (32%), separated by chromatography. No trace of the desired chloropyridine **25** was detected in the product mixture.

The synthesis of the quasi-enantiomeric ligand (−)-**4** (Scheme 4) commenced with the stereoselective epoxidation of the commercially available (+)-2-carene (+)-**28** (MCPBA, Et_2O, 0 °C, 24 h; 85%), followed by deprotonation of the resulting epoxide (+)-**29**[5c,28] with LDA[29] to afford allylic alcohol (+)-**30**[5c,30] (LDA, THF, −78 to 0 °C, 3 h, then rt, 6 h; 53%). Oxidation of the latter alcohol with a variety of oxidizing agents (MnO_2, PCC, PDC, Swern, etc.) led to mixtures of the desired exomethylene ketone (−)-**31**[5c,31] and its endocyclic regioisomer (+)-**32**[32] in various ratios but always with **32** being the major product. Finally, a catalytic modification of Dess−Martin oxidation [TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 5 h][33] afforded (−)-**31** as the major product (83%); under these conditions, the *endo*-isomer (+)-**32** was formed in less than 10% yield. The *exo*-methylene ketone (−)-**31** was treated with the pyridinium salt **19**[24] and ammonium acetate under the Kröhnke conditions[23] (**19**, $AcONH_4$, piperidine, *n*-BuOH, AcOH, reflux overnight) to produce pyridone (−)-**33** (39%). Triflation of pyridone (−)-**33** (Tf_2O, Et_3N,

(23) For the Kröhnke annulation, see: (a) Kröhnke, F.; Heffe, W. *Chem. Ber.* **1937**, *70*, 864. For an overview, see: (b) Kröhnke, F. *Synthesis* **1976**, 1. For a recent overview of its application in the synthesis of terpenoid bipyridines, see ref 5h,i.

(24) The Kröhnke salt **19** was obtained on reaction of ethyl bromoacetate with pyridine; see ref 23. See also: (a) Kröhnke, F. *Chem. Ber.* **1940**, *73*, 310. (b) Neilands, O. Ya.; Shebenina, E. V.; Pukitis, G. G. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1999**, *35*, 1443; *Khim. Geterotsikl. Soedin.* **1999**, 1647. (c) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3137. (d) Aldersley, M. F.; Dean, F. M.; Nayyir-Mazhir, R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1753. Apparently, the Kröhnke salts derived from α-haloketones give much higher yields of the annulated products than those derived from α-haloesters.

(25) Cocker, W.; Pratt, A. C.; Shannon, P. V. R. *J. Chem. Soc. C* **1968**, 484.

(26) For the method, see ref 9a,b and Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.

(27) For the method, see ref 9a,b and Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173.

(28) Crombie, L.; Crombie, W.; Mary, L.; Jamieson, S. V.; Palmer, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1243.

(29) A similar reaction with 3-carene epoxide has been reported to occur in 97% yield: Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.* **1990**, *55*, 1589.

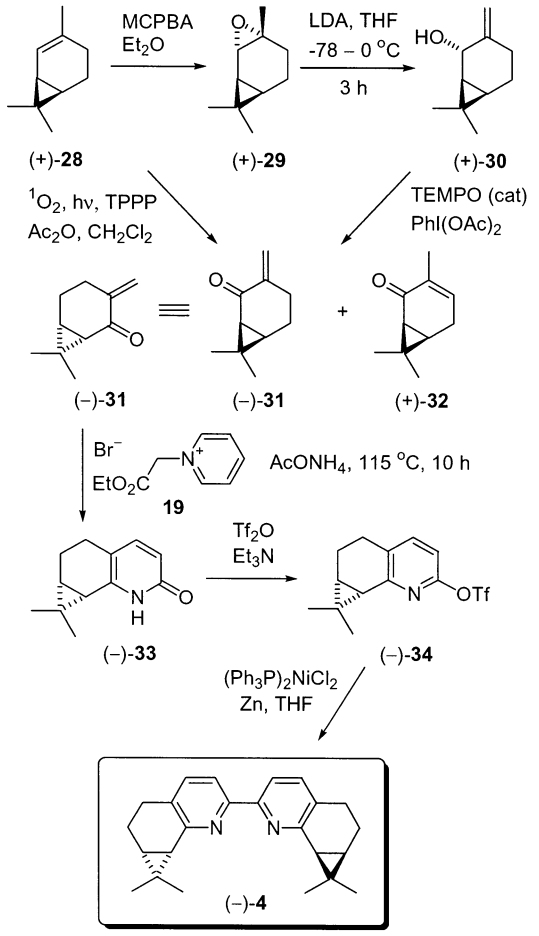
(30) (a) Arbuzov, B. A.; Isaeva, Z. G.; Vil'chinskaya, A. R.; Belyaeva, M. G. *Dokl. Chem. (Engl. Transl.)* **1971**, *199*, 690; *Dokl. Akad. Nauk SSSR Ser. Khim.* **1971**, *199*, 1304.

(31) Arbuzov, B. A.; Isaeva, Z. G.; Ratner, V. V. *J. Org. Chem. USSR (Engl. Transl.)* **1966**, *2*, 1391; *Zh. Org. Khim.* **1966**, *2*, 1401.

(32) See ref 22 and (a) Bellamy, A. J.; Crilly, W.; Farthing, J.; Kellie, G. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2417. (b) Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048. (c) Vyglazov, O. G.; Manukov, E. N.; Fedorishcheva, M. N.; Ariko, N. G.; Chuiko, V. A.; Bazhina, G. N. *Chem. Nat. Compd. (Engl. Transl.)* **1991**, *27*, 283; *Khim. Prir. Soedin.* **1990**, 328. (d) Lassak, E. V.; Southwell, I. A. *Aust. J. Chem.* **1974**, *27*, 2061.

(33) For the method, see: De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

SCHEME 4[a]



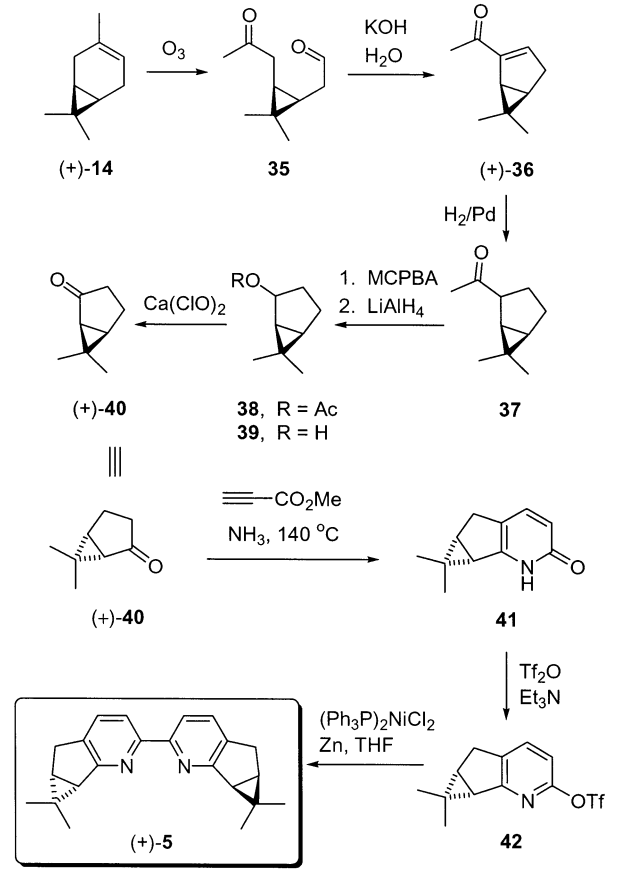
[a] TTTP = tetraphenylporphine.

CH_2Cl_2, −45 °C to rt, 30 min; 99%) afforded triflate (−)-**34**, which was dimerized under our standard conditions [$(Ph_3P)_2NiCl_2$, Zn, Me_4NI, THF, 50 °C, 72 h][19] to provide ligand (−)-**4** (40%), for which we propose the acronym "CANDY" (**ca**re**n**e-derived bipyri**d**ine).

As an alternative approach to enone (−)-**31**, direct photochemical ene reaction of (+)-2-carene (+)-**28** with singlet oxygen[34] was investigated. Under the standard conditions[34] (O_2, tetraphenylporphine, Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 14 h), a ∼1:3 mixture of (−)-**31** and (+)-**32** was obtained (75%),[5c] which may seem unattractive. However, this mixture needs not to be separated since only the *exo*-isomer (−)-**31** would undergo the Kröhnke annulation, leaving the easily separable, lipophilic enone (+)-**32** unreacted. Therefore, in view of the experimental simplicity of the ene reaction, this latter method can actually be regarded as a fairly competitive alternative.

(+)-3-Carene (+)-**14** was also employed as the starting material in the synthesis of ligand (+)-**5** (Scheme 5). Ozonolysis of (+)-**14** (O_3, CH_2Cl_2, −45 °C, 24 h; Na_2SO_3/H_2O workup) afforded keto aldehyde **35**[35] (65%), which on controlled aldol-type cyclization afforded enone (+)-

SCHEME 5

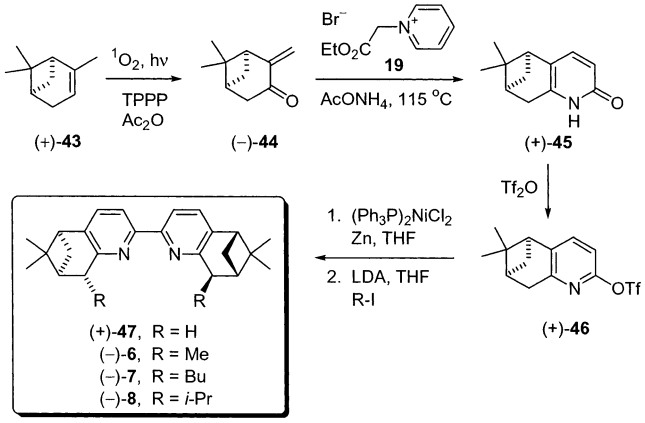


36 (NaOH, H_2O, rt, 30 min; 52%).[35−37] A nonstereoselective catalytic hydrogenation (+)-**36** → **37**[35,36] [H_2 (1 bar), 5% Pd−C, AcOEt/EtOH (1:1), rt, 3 h; 95%], followed by Baeyer−Villiger oxidation (MCPBA, CH_2Cl_2, rt, 24 h), furnished acetate **38**[35,36] (85%) as a diastereoisomeric mixture,[38] whose reduction with $LiAlH_4$ produced alcohol **39**[35,36] ($LiAlH_4$, Et_2O, rt, 30 min; 78%). Oxidation of the latter alcohol [$Ca(ClO)_2$, H_2O, CH_2Cl_2, MeCN, AcOH, H_2O, 0 °C, 2 h][39] provided ketone (+)-**40**[35,36] (82%), which was subjected to pyridine annulation[18] via the one-pot Michael addition to methyl propiolate, followed by imine formation and ring closure (HC≡CCO_2Me, 7 M NH_3 in MeOH, 140 °C, 10 h, in an autoclave), to produce pyridone **41** (20%).[40] Triflate (+)-**42**, obtained from pyridone **41** (Tf_2O, Et_3N, CH_2Cl_2, −45 °C to rt, 1 h; 94%), was then dimerized under our standard conditions [$(Ph_3P)_2NiCl_2$, Zn, THF, 50 °C, 72 h][19] to give bipyridine (+)-**5** (46%), for which we propose the acronym "*nor*-CANDY" (as an analogue of CANDY; see above).

The synthesis of the *iso*-PINDY series (**6**−**9**) commenced with the ene reaction of (+)-α-pinene (+)-**43** with

(34) Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135.
(35) (a) Boyle, P. H.; Cocker, W.; Gordon, R. L.; Shannon, P. V. R. *J. Chem. Soc. C* **1971**, 2127. (b) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.
(36) Lochynski, S.; Walkowicz, M. *Pol. J. Chem.* **1982**, *56*, 1333.
(37) It is crucial that the intramolecular aldol condensation is carried out with a ≤4% aqueous NaOH solution (see Experimental Section). Higher concentrations or using ethanol as the solvent leads to the deprotonation of the aldol product **36** in the allylic position, which triggers the opening of the cyclopropane ring to produce 1-acetyl-3,3-dimethyl-cyclohexa-1,4-diene. Therefore, the starting keto aldehyde **35** used in this reaction must be pure and alcohol-free.
(38) Since the new chiral center was to become an sp^2 carbon, there was no need to separate the diastereoisomers.
(39) Other oxidizing reagents are prone to open the cyclopropane ring.
(40) This procedure clearly needs to be optimized in order to improve the yield; for a much higher yield in a related system, see Scheme 1.

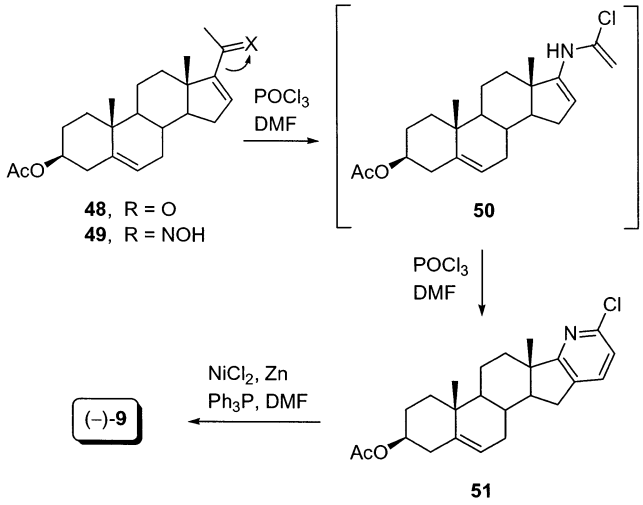
SCHEME 6



singlet oxygen[34] that afforded pinocarvone[4d] (−)-**44** (O_2, tetraphenylporphine, Ac_2O, DMAP, CH_2Cl_2, 20 °C, 18 h; 99%),[34,41] whose condensation with pyridinium salt **19**[24] and ammonium acetate under the Kröhnke conditions[23] led to pyridone (+)-**45** (**19**, $AcONH_4$, piperidine, EtOH, 80 °C, 10 h; then $HCONH_2$, 210 °C, 1 h; 43%).[42] Triflate **46**, obtained from pyridone (+)-**45** (Tf_2O, Et_3N, CH_2Cl_2, −45 to 0 °C, 2 h; 99%), was then dimerized via Ni-mediated coupling[19] to give (+)-**47** [$(Ph_3P)_2NiCl_2$, Zn, Me_4-NI, THF, 65 °C, overnight; 51%].[43] This sequence represents a substantial short-cut with respect to the procedure developed by von Zelewsky,[5f] which requires carrying out the Kröhnke annulation twice. In agreement with the von Zelewsky protocols,[5e−g] deprotonation of (+)-**47** in the benzylic positions with LDA, followed by the reaction with MeI, BuI, and *i*-PrI, respectively (LDA, THF, −40 °C, 2 h; then R-I, −40 °C to rt, overnight), afforded Me-*iso*-PINDY (−)-**6** (99%), Bu-*iso*-PINDY (−)-**7** (93%), and *i*-Pr-*iso*-PINDY (−)-**8** (56%), respectively (Scheme 6).[44]

Synthesis of the steroid dimer (−)-**9** (Scheme 7) commenced with the conversion of the commercially available dehydropregnenolone acetate **48** into oxime **49** (NH_2OH·HCl, EtOH, pyridine, rt, 24 h; 90%). Oxime **49** was then treated with $POCl_3$ in DMF (65 °C, 2 h) to undergo an initial Beckmann rearrangement (**49** → **50**), followed by Vilsmeier−Haack reaction of the intermediate with an excess of the reagent to produce the α-chloropyridine derivative **51**[45] (70%), whose dimerization under our standard conditions[19] ($NiCl_2$·$6H_2O$, Ph_3P, Zn, DMF, 65 °C, 24 h) afforded (−)-**9** (45%). A phenanthroline analogue of **9** with only one steroid unit annulated was reported recently by Chelucci.[7i]

SCHEME 7



Asymmetric Allylic Oxidation Catalyzed by Cu(I) Complexes. The chiral catalysts reported to date for allylic oxidation of olefins (Kharash−Sosnovsky reaction)[46] typically require several days to allow completion of the reaction,[46a] and the enantioselectivity usually does not exceed ∼80% ee.[46,47]

Owing to the unique, experimentally observed geometry, Cu complexes of ligands **1**−**9** have the promise of offering an interesting entry into the area of redox reactions, such as allylic oxidation. Following the previous reports[46] and our own preliminary work,[9a,b] we first generated Cu(II) complexes from $(TfO)_2Cu$ and the respective ligands **1**−**9**, which were in situ reduced with phenylhydrazine to the corresponding Cu(I) species. To probe the catalytic capability of the latter complexes, we employed five- to seven-membered cycloalkenes **52a**−**c** and *tert*-butyl peroxybenzoate as the oxidant (Scheme 8). The reaction of cyclohexene (**52b**), catalyzed by the Cu/**1** complex (1 mol %), proved to be complete within 30 min at room temperature, giving (*S*)-**53b** in 96% yield and 49% ee (Table 1, entry 3).[48] Practically identical results were obtained with the Cu(I) complex generated directly from **1** and $(Cu^IOTf)_2$·C_6H_6 (entry 4). Lowering the reaction temperature to 0 and −20 °C, respectively,

(41) The selenium dioxide mediated oxidation (SeO_2, CCl_4, reflux, 24 h) produced pinocarvone in a mere 27% yield: Hartshorn, M. P.; Wallis, A. F. A. *J. Chem. Soc.* **1964**, 5254.

(42) The use of *tert*-butyl ester analogue of **19** led to a marginally higher yield.

(43) Since the starting (+)-α-pinene was only of ∼90% ee, the dimerization can potentially lead to the formation of diastereoisomers. The crude product was purified by chromatography, and the ^1H NMR spectrum of the bipyridine (+)-**47** thus obtained showed no peaks corresponding to the minor *meso*-diastereoisomer.

(44) (a) Slightly lower yields have previously been reported for these alkylations.[5f] (b) The alkylations are remarkably stereoselective (the alkylating reagent approaches from the less hindered face). The minor epimers formed (usually no more than 2%, as detected by NMR) were removed during the chromatographic purification.

(45) (a) Ahmed, S.; Boruah, R. C. *Tetrahedron Lett.* **1996**, *37*, 8231. (b) Boruah, R. C.; Ahmed, S.; Sharma, U.; Sandhu, J. S. *Indian J. Chem. Sect. B* **1999**, *38*, 274.

(46) (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. (i) Andrus, M. B.; Asgari, D. *Tetrahedron* **2000**, *56*, 5775. (j) Lee, S.-Z.; Kwong, H.-L.; Chan, H.-L.; Choi, W.-W.; Ng, L.-Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1007. (k) Andrus, M. B.; Zhou, Z. *J. Am. Chem. Soc.* **2002**, *124*, 8806. (l) Chelucci, G.; Loriga, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron Lett.* **2002**, *43*, 3601. (m) Chelucci, G.; Iuliano, A.; Muroni, D. Saba, A. *J. Mol. Catal. A* **2003**, *191*, 29. For mechanistic issues in the nonasymmetric, Ru-catalyzed allylic oxidation, see: (m) Stultz, R. T.; Huynh, M. H. V.; Binstead, R. A.; Curry, M.; Meyer, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 5984. For reviews, see: (n) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567. (o) Andrus, M. B.; Lashley, J. *Tetrahedron* **2002**, *58*, 845.

(47) Up to 95% ee was recently reported by Andrus.[46k] However, the conversions in those cases were rather low, so that the reaction would better be described as substoichiometric rather than catalytic.

(48) The absolute configuration of the product was determined by comparison of its optical rotation with the known values.[46]

SCHEME 8

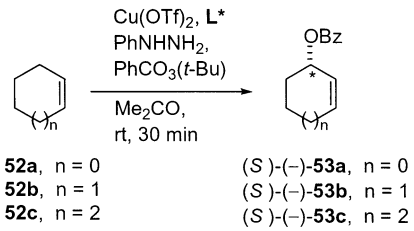


TABLE 1. Asymmetric Allylic Oxidation of Cycloalkenes 52a−c Catalyzed by Cu Complexes of Chiral Ligands 1−9 (Scheme 8)[a]

entry	ligand	olefin	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	(+)-**1**	**52a**	20	0.5	85	48 (*S*)[c]
2	(+)-**1**	**52a**	0	12	80	59 (*S*)[c]
3	(+)-**1**	**52b**	20	0.5	96	49 (*S*)[c]
4	(+)-**1**[d]	**52b**	20	2	95	49 (*S*)[c]
5	(+)-**1**	**52b**	0	5	88	55 (*S*)[c]
6	(+)-**1**	**52b**	−20	48	56	60 (*S*)[c]
7	(+)-**1**	**52c**	20	0.5	88	62 (*S*)[c]
8	(+)-**1**	**52c**	0	12	66	75 (*S*)[c]
9	(−)-**2**	**52b**	20	24	74	19 (*S*)[c,e]
10	(+)-**3**	**52b**	20	2	58	55 (*S*)[c]
11	(−)-**4**	**52a**	20	1	96	43 (*R*)[e]
12	(−)-**4**	**52b**	20	5	98	66 (*R*)[e]
13	(−)-**4**	**52b**	0	48	76	70 (*R*)[e]
14	(−)-**4**	**52b**	−20	96	33	77 (*R*)[e]
15	(−)-**4**	**52c**	20	12	60	72 (*R*)[e]
16	(−)-**4**	**52c**	0	48	57	75 (*R*)[e]
17	(−)-**4**	**52c**	−20	96	35	82 (*R*)[e]
18	(+)-**5**	**52b**	20	24	52	35 (*R*)[e]
19	(−)-**6**	**52b**	20	0.5	83	<5
20	(−)-**7**	**52b**	20	0.5	87	<5
21	(−)-**8**	**52b**	20	0.5	84	<5
22	(+)-**47**	**52b**	20	0.5	81	<5
23	(−)-**9**	**52b**	20	3	92	16 (*S*)[c]
24	(−)-**9**	**52c**	20	5	66	8 (*S*)[c]

[a] The reactions were carried out in Me_2CO in the presence of the catalysts (1 mol %), generated in situ by reduction of a mixture of $(TfO)_2Cu^{II}$ and the ligand with $PhNHNH_2$. [b] Determined by chiral HPLC; the absolute configuration was established by optical rotation with reference to the known compounds. [c] See ref 9a,b. [d] $(TfOCu^{I})_2 \cdot C_6H_6$ was used directly to generate the catalyst. [e] (*R*)-(+)-Enantiomer was formed owing to the opposite local chirality of the ligand.

resulted in enhancing the enantioselectivity (55% and 60% ee, respectively; entries 5 and 6). Similar results were obtained with cyclopentene **52a** (entries 1 and 2),[48] whereas cycloheptene (**52c**) exhibited notably higher enantioselectivity (62% ee at room temperature and 75% ee at 0 °C; entries 7 and 8).[48,49] Not surprisingly, the reactions carried out at 0 °C were slower (5−12 h) but still considerably faster than most of the reported cases of asymmetric allylic oxidation.

Very similar results were obtained by Chelucci with the phenathroline analogue of PINDY (**1**) while this full paper was in preparation: the absolute configuration of the resulting allylic benzoates **53** was the same, the reaction time was also very short (typically 30 min at room temperature), and the enantioselectivities were very close to ours.[46l] Other terpene-derived phenanthroline complexes proved inferior.[7i]

In contrast to PINDY (**1**), the menthol-derived ligand MINDY (**2**) exhibited very low reactivity and enantioselectivity (entry 9). An improvement was observed for Me-CANDY (**3**), which gave slightly better enantioselectivity with cyclohexene (entry 10) than **1** (entry 3). CANDY (**4**), compared with PINDY (**1**), exhibited improved enantioselectivity for cyclohexene and cycloheptene (compare entries 12−17 with 3−8), while slightly lower enantioselecivity was observed for cyclopentene (compare entries 11 and 1). Indeed, as predicted (Chart 2), removing the CH_2 groups (compare **1/M** with **4/M**) resulted in general improvement by ca. 15% ee. Furthermore, being quasi-enantiomeric to **3** (and **1**), CANDY (**4**) produced the opposite enantiomer (compare entries 11−17 with 10 and 1−8).[50] On the other hand, analogous cyclopropane ligand *nor*-CANDY (**5**) exhibited low reactivity and selectivity (entry 18), while the *iso*-PINDY-type ligands **6**−**8** and **47** proved highly reactive but gave racemic product (entries 19−22). Finally, the steroid ligand **9** (entries 23 and 24) also proved unsuccessful, leaving Me-CANDY (**3**) and CANDY (**4**) as the best ligands of this series.

Interestingly, complexes generated from Cu(II) by an in situ reduction with phenylhydrazine proved to be more robust and less prone to irreversible oxidation than those formed from Cu(I). Furthermore, the reaction apparently requires a trace of water since adding molecular sieves resulted in a dramatic deceleration (though the enantioselectivity remained essentially unaffected).[51]

Asymmetric Cyclopropanation Catalyzed by Cu(I) Complexes. To further explore the scope of the PINDY-type ligands, we have briefly studied cyclopropanation of styrene with esters of diazoacetic acid as the metallocarbene source (Scheme 9).[52,53] 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 the same way as in the case of allylic oxidation, i.e., from the in situ formed complex of $(TfO)_2Cu$ and the ligand by reduction with phenylhydrazine. This catalyst turned out to be superior to the complex prepared from $(CuOTf)_2 \cdot C_6H_6$ in terms of stability and efficiency.

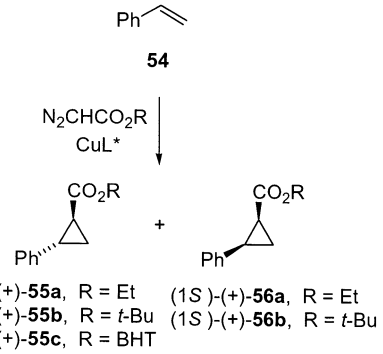
In contrast to allylic oxidation, PINDY (**1**) turned out to be much less enantioselective (entries 1 and 2) than MINDY (**2**) (entries 3 and 4).[9b] Furthermore, although

(49) At −20 °C, the reaction of cycloheptene proved to be extramely slow and the product was not analyzed because of low conversion.

(50) In principle, the quasi-enantiomeric ligands **3** and **4** should exhibit practically identical levels of enantioselectivities. The lower enantioselectivity observed for **3** (compare entries 10 and 12) apparently originates from its lower enantiopurity (93% ee).

(51) In the presence of molecular sieves, the oxidation of cyclohexene takes 26 h (74% yield) rather than 30 min, while the enantioselectivity (48% ee) remains unchanged (compare with Table 1, entry 3). At 0 °C, the addition of molecular sieves slows the reaction from 5 h to 7 days (51% yield), leaving the enantioselectivity (53% ee) intact again (compare with Table 1, entry 5). The actual nature of the effect of water is unknown. It can be tentatively attributed to a weak cordination to Cu, which may accelerate the departure of the product from Cu, allowing it to enter the next catalytic cycle. For similar observations of the water effect, see the following: (a) Mikami, K.; Kotera, O.; Motoyama, Y.; Sajaguchi, H. *Synlett* **1995**, 975. (b) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Chem. Commun.* **1997**, 281. (c) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (d) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936. (e) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (f) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (g) 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. (h) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. For an overview of the water effects in metal-catalyzed reactions, see: (i) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.

SCHEME 9[a]



[a] BHT = 2,6-di-*tert*-butyl-4-tolyl.

both ethyl and *tert*-butyl diazoacetates exhibited essentially identical enantioselectivities, the latter ester was considerably more diastereoselective in favor of the *trans*-isomer of the product (compare entry 1 vs 2 and 3 vs 4).[9b] As expected (Chart 2), CANDY (**4**) represented a considerable improvement (entry 5) compared with PINDY (**1**) but still did not reach the selectivity of MINDY (**2**; entries 3 and 4). The highest enantioselectivity was attained with the *iso*-PINDY series, namely, with the bis-methyl and bis-*n*-butyl derivatives **6** and **7** (entries 6 and 8); the bis-*iso*-propyl analogue **8** performed less satisfactorily (entry 9).[54] To increase the diastereoisomeric ratio, we employed ligand **6** in combination with a sterically demanding 2,6-di-*tert*-butyl-4-tolyl (BHT) diazoacetate.[55] As expected, only the *trans*-isomer was formed, but the reaction proved to be much slower, requiring 24 h for completion (as opposed to 1 h with ethyl diazoacetate), and the enantioselectivity dropped slightly (entry 7). Notably, ligand **7** failed to catalyze the reaction with both *tert*-butyl and BHT diazoacetate.

TABLE 2. Asymmetric Cyclopropanation of Styrene 54 with Alkyl Diazoacetates Catalyzed by Cu Complexes of Chiral Ligands 1−8 (Scheme 9)[a]

entry	ligand	R	yield (%)	**55**:**56**	ee (**55**)[b,c]	ee (**56**)[b,c]
1	(+)-**1**	Et	≥95	65:35	10 (1*S*)	15 (1*S*)
2	(+)-**1**	*t*-Bu	61	83:17	16 (1*S*)	16 (1*S*)
3	(−)-**2**	Et	85	72:28	72 (1*S*)	70 (1*S*)
4	(−)-**2**	*t*-Bu	95	84:16	67 (1*S*)	69 (1*S*)
5	(−)-**4**	*t*-Bu	96	86:14	59 (1*S*)	
6	(−)-**6**	Et	99	62:38	76 (1*S*)	74 (1*S*)
7	(−)-**6**	BHT	90	>99:1	70 (1*S*)[d]	
8	(−)-**7**	Et	99	67:33	74 (1*S*)	78 (1*S*)
9	(−)-**8**	Et	99	63:37	36 (1*S*)	40 (1*S*)

[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 $(TfO)_2Cu$ and $PhNHNH_2$ in the presence of the ligand. [b] Determined by chiral HPLC or GC. [c] The absolute configuration of the products was deduced from their optical rotation as (1*S*)-(+)-**55** and (1*S*)-(+)-**56** (ref 52). [d] Determined by chiral GC after the reduction with $LiAlH_4$ and conversion of the resulting alcohol into trifluoroacetate.

Comparison of our results with those recently reported by von Zelewsky for the cyclopropanation of styrene with ethyl diazoacetate[5e] shows the following. High enantioselectivity obtained with *n*-Bu-*iso*-PINDY (**7**; entry 8) is in agreement with his report for the ethyl analogue (Et-*iso*-PINDY). By contrast, analogous *n*-Pr-*iso*-PINDY has been reported by him to give unexpectedly low enantioselectivity, which does not seem to fit within the ethyl−propyl−butyl series. Furthermore, *i*-Pr-*iso*-PINDY (**8**) has been found by him to give racemic products, which also contrasts with our findings (entry 9); on the other hand, the *trans*/*cis* ratio was identical to ours in this instance.

Conclusions

A series of modular bipyridine-type ligands **1**−**9** has been synthesized via a de novo construction of the pyridine nucleus, which involved either Michael addition

(52) 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**: (c) Frischi, H.; Leuteneggar, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553 and references therein. (d) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (e) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373. (f) Müler, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (g) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (h) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430. (i) Schumacher, R.; Dammast, F.; Reissing, H. U. *Chem. Eur. J.* **1997**, *3*, 614. (j) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518. (k) 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. (l) Burguette, M. I.; Fraile, J. M.; García, J. I.; García-Verungo, E.; Herrerías, C. I.; Luis, S. V.; Mayoral, V. A. *J. Org. Chem.* **2001**, *66*, 8893. (m) Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, V. A.; Savatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616. (n) Che, C.-M.; Kwong, H.-L.; Che, W.-C.; Cheng, K.-F.; Lee, W.-S.; Yu, H.-S.; Yeung, C. T.; Cheung, K.-K. *Eur. J. Inorg. Chem.* **2002**, 1456. (o) Wong, W.-L.; Lee, W.-S.; Kwong, H.-L. *Tetrahedron: Asymmetry* **2002**, *13*, 1485. (p) Rasmussen, T.; Jensen, J. F.; Østergaard, N.; Tanner, D.; Ziegler, T.; Norrby, P.-O. *Chem. Eur. J.* **2002**, *8*, 177. **Co**: (q) Yamada, T.; Ikeno, T.; Sekino, H.; Sato, M. *Chem. Lett.* **1999**, 719. (r) Ikeno, T.; Sato, M.; Yamada, T. *Chem. Lett.* **1999**, 1345. (s) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647 and references therein. (t) Ikeno, T.; Iwakura, I.; Yabushita, S.; Yamada, T. *Org. Lett.* **2002**, *4*, 517. (u) Ikeno, T.; Iwakura, I.; Yamada, T. *J. Am. Chem. Soc.* **2002**, *124*, 15152. **Ru**: ref 52s and the following: (v) Che, C.-M.; Huang, J.-S.; Lee, F.-W.; Li, Y.; Lai, T.-S.; Kwong, H.-L.; Teng, P.-F.; Lee, W.-S.; Lo, W.-C.; Peng, S.-M.; Zhou, Z.-Y. *J. Am. Chem. Soc.* **2001**, *123*, 4119. (w) Cornejo, A.; Fraile, J. M.; García, J. I.; García-Verungo, E.; Gil, M. J.; Legarreta, G.; Luis, S. V.; Martínez-Merino, V.; Mayoral, V. A. *Org. Lett.* **2002**, *4*, 3927. **Rh**: (x) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919. (y) Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595. (z) Barberis, M.; Pérez-Prieto, J.; Stiriba, S.-E.; Lahuerta, P. *Org. Lett.* **2001**, *3*, 3317. (aa) Barberis, M.; Pérez-Prieto, J.; Herbst, K.; Lahuerta, P. *Organometallics* **2002**, *21*, 1667. (bb) Nagashima, T.; Davies, H. M. L. *Org. Lett.* **2002**, *4*, 1989. (cc) Chelucci, G.; Saba, A.; Soccolini, F.; Vignola, D. *J. Mol. Catal.* **2002**, *178*, 27. (dd) Doyle, M. P.; Forbes, C. D. *Chem. Rev.* **1998**, *98*, 911. **Fe**: (ee) Du. G.; Andrioletti, B.; Rose, E.; Woo, L. K. *Organometallics* **2002**, *21*, 4490. **Zn**/**Ti** (asymmetric Simmons−Smith addition): (ff) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168. (gg) Imai, N.; Nomura, T.; Yamamoto, S.; Ninomiya, Y.; Nokami, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2433.

(53) For the recently developed bipyridine-type complexes that catalyze cyclopropanation, see, for example, refs 4g and 6k,l and the following: (a) Ito, K.; Tabuchi, S.; Katsuki, T. *Synlett* **1992**, 575. (b) Ito, K.; Katsuki, T. *Tetrahedron Lett.* **1993**, *34*, 2661. (c) Ito, K.; Katsuki, T. *Synlett* **1993**, 638.

(54) The difference in the enantioselectivity observed for **6** and **8** (Me vs *i*-Pr groups) can be tentatively attributed to an increased steric hindrance in the latter ligand, so that the reaction may proceed with a different mechanism (either a monodentate Cu complex or a background reaction with free Cu may be involved). Note that $Mo(CO)_6$ readily forms complexes with analogous bipyridine ligands where one of the pyridine ring lacks the annulated terpene unit, whereas no complex formation was observed with **1**, owing to the increased steric hindrance.[9b]

(55) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906−1912.

of ketone enolate to methyl propiolate (Schemes 1 and 5), Kröhnke annulation (Schemes 2, 4, and 6), or Vilsmeier−Haack reaction (Scheme 7) as the crucial step, followed by Ni-mediated dimerization. The chiral moieties of these ligands originate from the isoprenoid chiral pool, namely, *β*-pinene (**10**), 3-carene (**14**), 2-carene (**28**), α-pinene (**43**), and dehydropregnenolone acetate (**48**), respectively. This strategy allowed to systematically modify the stereochemical architecture of the catalysts, namely the degree of the steric hindrance in the individual octants (Chart 2) and the shape of the corridor through which the reactants can approach (Chart 3).

Copper(I) complexes, generated in situ from these ligands and $(TfO)_2Cu$ (1 mol %) upon reduction with phenylhydrazine, have been investigated as catalysts for allylic oxidation of cyclic olefins (Scheme 8 and Table 1). Good enantioselectivities, previously reported for PINDY (**1**) in our preliminary communication,[9a] have been improved by up to ∼15% ee by using the new ligand CANDY (**4**), which is in agreement with the initial modeling (Chart 2). At 20 °C, the reaction is fast (∼30 min); lowering to 0 °C improves the enantioselectivity without compromising the conversion, although the reaction rate is reduced (12−48 h). By contrast, at −20 °C, the reaction was found to be substantially slower, while the enantioselectivity was further improved (Table 1). The highest level of asymmetric induction attained was 82% ee (Table 1, entry 17).

In the copper-catalyzed cyclopropanation, the *iso*-PINDY type ligands **6** and **7** proved to be superior to both **1** and **4**, indicating fundamental differences in the structural requirements of the respective transition states for the two reactions investigated. The highest enantioselectivity observed here was ≤76% ee (Scheme 9 and Table 2). The *trans*/*cis* selectivity was dramatically improved by employing 2,6-di-*tert*-butyl-4-tolyl (BHT) diazoacetate (instead of ethyl or *tert*-butyl esters), although at a slight expense of the enantioselectivity; only Me-*iso*-PINDY **6** could be used as ligand in the latter case since the butyl and *iso*-propyl analogues **7** and **8** failed to catalyze this reaction.

In conclusion, new copper catalysts have been designed and shown to be promising in two types of asymmetric catalytic reactions. Tailoring the stereochemical architecture proved particularly fruitful as it led to increased enantioselectivity. Further improvements in the ligand design can be envisaged, e.g., by modifying their electronics or by introducing auxiliary groups that would weakly chelate the metal and might accelerate the product departure from its coordination sphere.

Experimental Section

General Methods. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated with an error of less than ±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 400 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. 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 or for $CHCl_3$ solutions. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen (or argon where specified) in oven-dried glassware twice evacuated and filled with the 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 hydride. Standard workup of an ethereal solution means washing three times with 5% HCl (aqueous), water, and three times with 5% $KHCO_3$ (aqueous) and drying with $MgSO_4$. Petroleum ether refers to the fraction boiling in the range of 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.

Enantiopurity of Starting Materials and Intermediates. (−)-*β*-Pinene (−)-10 was purchased from Aldrich, declared to have $[\alpha]_D$ −21 (neat); material of $[\alpha]_D$ −22 corresponds to 97% ee, according to the Aldrich catalog. According to GC analysis on a Supelco *β*-DEX 120 column, this batch was of 95% ee.[17]

(+)-Nopinone (+)-11, prepared from the commercially available (−)-*β*-pinene (−)-**10** (Aldrich)[17] 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[56a] or $[\alpha]_D$ +40.52 (*c* 4.0, MeOH),[56a] this would suggest 86% ee for our sample. However, in view of the 95% ee of the starting (−)-*β*-pinene,[17] this sample of nopinone should also be of ∼95% ee.

(+)-3-Carene (+)-14 from Aldrich had a declared $[\alpha]_D$ +15 (neat); our batch had $[\alpha]_D$ +8 (neat). The highest reported value[57] is $[\alpha]_D$ +17.7. Chiral GC on a Supelco *β*-DEX 120 column showed 93% ee for our batch.

(+)-2-Carene (+)-28, purchased from Aldrich, had $[\alpha]_D$ +81 (*c* 6.0; EtOH), rather than $[\alpha]_D$ +90 ± 2 (*c*, 6.0; EtOH) declared on the bottle.

(+)-α-Pinene (+)-43 was purchased from Aldrich; according to GC analysis on a Supelco *β*-DEX 120 column, the ee was 90%.

(−)-Pinocarvone (−)-44 was obtained from (+)-α-pinene (+)-**43**. Chelucci[4d] synthesized pinocarvone from (−)-*trans*-pinocarveol, generically related (via allylic oxidation) to (+)-*β*-pinene, as starting material. Oxidation of (−)-*trans*-pinocarveol should, therefore, produce (−)-pinocarvone (−)-**44** in his case. Chelucci quoted his pinocarvone as dextrorotatory, which appears to be a mistake.

PINDY (+)-1. Zinc powder (224 mg, 3.42 mmol, 1 equiv) was activated by stirring with a few droplets of Me_3SiCl in a Schlenk tube under an argon atmosphere for 2 h. A dark blue colored solution of $NiCl_2 \cdot 6H_2O$ (821 mg, 3.45 mmol, 1.01 equiv) and Ph_3P (3.58 g, 13.69 mmol, 4 equiv) in degassed DMF (36 mL) was added via syringe. A change of color to dark red was observed within 5 min. The mixture was stirred under an argon atmosphere at 60 °C for 1 h, and then a solution of triflate **13** (1.1 g, 3.42 mmol, 1 equiv) in degassed DMF (6 mL) was added. The mixture was heated at the same temperature for 17 h, after which the disappearance of the starting material was detected by TLC. The mixture was cooled to room temperature, and 35% aqueous ammonia (50 mL) was added. The resulting suspension was stirred for 5 min, extracted with CH_2Cl_2 (4 × 60 mL), and the organic extract was dried over Na_2SO_4 and evaporated. The residue was dissolved in ethyl

(56) (a) Grimshaw, N.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50. (b) Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217.

(57) Jadhav, P. K.; Prasad, J. V. N. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 3203.

acetate (100 mL) and extracted with a 10% aqueous solution of HCl (5 × 50 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 50 mL), the pH was adjusted to 13 with concentrated aqueous NaOH, and the product was extracted into ethyl acetate (5 × 50 mL). The combined organic layers were washed with brine (1 × 60 mL), dried over Na_2SO_4, and evaporated in vacuo to give a yellowish solid. No reduction byproduct was detected. This solid was purified via flash chromatography on a silica gel column (15 × 2.5 cm) first with a petroleum ether/ether mixture (19:1) to separate Ph_3P, then with pure ethyl acetate to give PINDY (+)-**1** as a white solid (351 mg, 60%), identical with an authentic sample: $[\alpha]_D$ +34.3 (*c* 0.8, $CHCl_3$) {an authentic sample[9b] had $[\alpha]_D$ +35.8 (*c* 2.1, $CHCl_3$)}.

Me-CANDY (+)-3. Zinc powder (26 mg, 0.40 mmol, 1 equiv) was activated by stirring with a drop of Me_3SiCl in a Schlenk tube under an argon atmosphere for 2 h. A dark blue solution of $NiCl_2 \cdot 6H_2O$ (97 mg, 0.40 mmol, 1.0 equiv) and Ph_3P (420 mg, 1.60 mmol, 4 equiv) in degassed DMF (4.5 mL) was added via syringe. A change of color to dark red was observed within 5 min. The mixture was stirred under an argon atmosphere at 60 °C for 1 h, and then a solution of triflate **22** (83 mg, 0.25 mmol) in degassed DMF (1.5 mL) was added. The mixture was heated at the same temperature for 23 h, after which the disappearance of the starting material was detected by TLC. The mixture was cooled to room temperature, and a 35% aqueous ammonia (20 mL) was added. The resulting suspension was stirred for 5 min and extracted with CH_2Cl_2 (4 × 20 mL), and the organic extract was dried over Na_2SO_4 and evaporated. The residue was dissolved in ethyl acetate (50 mL) and extracted with a 10% aqueous solution of HCl (5 × 10 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 20 mL), the pH was adjusted to 13 with concentrated aqueous NaOH, and the product was extracted into ethyl acetate (5 × 20 mL). The combined organic layers were extracted with brine (1 × 30 mL), dried over Na_2SO_4, and evaporated in vacuo to give a yellowish solid. No reduction byproduct was detected. This solid was purified via flash chromatography on a silica gel column (15 × 1.5 cm) first with a petroleum ether/ether mixture (19:1) to separate Ph_3P, then with pure ethyl acetate to afford (+)-**3** as a white amorphous solid (25 mg, 54%): $[\alpha]_D$ +57.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 0.63 (s, 3 H), 1.12−1.16 (m, 1 H), 1.19 (s, 3 H), 1.21 (d, J = 6.8 Hz, 3 H), 1.28−1.36 (m, 1 H), 1.83 (d, J = 8.6 Hz, 1 H), 2.12−2.18 (m, 1 H), 2.82−2.91 (m, 1 H), 7.49 (d, J = 8.1 Hz, 1 H), 7.99 (d, J = 8.1 Hz, 1 H); ^{13}C NMR δ 16.76 (CH_3), 18.55 (CH_3), 23.43 (CH), 24.48 (C), 27.22 (CH), 28.42 (CH_3), 30.43 (CH_2), 32.95 (CH), 119.24 (CH), 133.03 (CH), 138.49 (C), 154.08 (C), 156.67 (C); HRMS (FAB) 372.2565 ($C_{26}H_{32}N_2$ requires 372.2566).

CANDY (−)-4. A 25-mL, round-bottomed, two-necked flask, containing a magnetic stirring bar, was charged with $(Ph_3P)_2NiCl_2$ (520 mg, 0.79 mmol), zinc dust (260 mg, 4.0 mmol), and Me_4NI (805 mg, 4.0 mmol). A rubber septum was placed over one neck of the flask, and the other neck was connected to a Schlenk line. The flask was evacuated and filled with nitrogen several times. Dry THF (10 mL) was added via syringe through the septum, and the mixture was stirred at room temperature. After the red-brown catalyst had formed (30 min), a nitrogen-purged solution of (−)-**34** (850 mg, 2.65 mmol) in THF (3.0 mL) was added via syringe. After stirring at 50 °C for 72 h, the mixture was poured into 2 M aqueous ammonia (15 mL). The precipitate was filtered off and washed with chloroform (50 mL). The aqueous layer was extracted with chloroform (2 × 30 mL), and the combined organic layers were washed with water and a saturated aqueous NaCl solution (50 mL), dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by chromatography on silica gel (100 g) using a hexane/ethyl acetate mixture (9:1), followed by ethyl acetate, to give (−)-**4** as a white crystalline solid (182 mg, 40%): mp 143−145 °C; $[\alpha]_D$ −21.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 0.75 (s, 3 H), 1.19 (s, 3 H), 1.26−1.32 (m, 1 H), 1.74−1.84 (m, 1 H), 1.95−2.04 (m, 1 H), 1.96 (d, J = 6.6 Hz, 1 H), 2.48 (dt, J = 16.1 and 6.8 Hz, 1 H), 2.73 (dt, J = 16.1 and 7.1 Hz, 1 H), 7.42 (d, J = 7.8 Hz, 1 H), 8.07 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 15.32 (CH_3), 17.84 (C), 17.85 (CH_2), 23.99 (CH_3), 27.23 (CH_2), 27.64 (CH), 28.15 (CH), 117.31 (CH), 130.24 (C), 135.35 (CH), 153.65 (C), 155.13 (C); MS (EI) *m*/*z* (%) 344.2 (100, $M^{+\bullet}$), 329.2 (56), 303.2 (32), 285.2 (11), 257.1 (7), 245.1 (4), 233.1 (3), 157.1 (5), 129.1 (4), 83.0 (16), 47.0 (3), 44.0 (3); HRMS (EI) 344.2251 ($C_{24}H_{28}N_2$ requires 344.2253).

***nor*-CANDY (+)-5.** A 5-mL, round-bottomed, two-necked flask containing a magnetic stirring bar was charged with $(PPh_3)_2NiCl_2$ (50 mg, 0.074 mmol), zinc dust (13 mg, 0.2 mmol), and Me_4NI (56 mg, 0.28 mmol). A rubber septum was placed over one neck of the flask, and the other neck was connected to a Schlenk line. The flask was evacuated and filled with nitrogen several times. Dry THF (3.0 mL) was added via syringe through the septum, and the mixture was stirred at room temperature. After the red-brown catalyst had formed (30 min), a nitrogen-purged solution of triflate **42** (56 mg, 0.18 mmol) in THF (0.3 mL) was added via syringe. After stirring at 50 °C for 72 h, the mixture was poured into 2 M aqueous ammonia (6 mL). Chloroform (10 mL) was added, and the precipitate was filtered off. The aqueous layer was extracted with chloroform (2 × 5 mL), and the combined organic layers were washed with water and a saturated aqueous NaCl solution, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by chromatography on silica gel (5 g) using a hexane/ethyl acetate mixture (9:1), followed ethyl acetate to give (+)-**5**, as a white crystalline solid (14 mg, 46%): mp 189−192 °C; $[\alpha]_D$ +2.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 0.71 (s, 3 H), 1.19 (s, 3 H), 1.72 (t, J = 6.7 Hz, 1 H), 2.45 (d, J = 5.0 Hz, 1 H), 2.83 (d, J = 17.6 Hz, 1 H), 2.26 (dd, J = 17.6 and 7.3 Hz, 1 H), 7.46 (d, J = 7.9 Hz, 1 H), 8.02 (d, J = 7.9 Hz, 1 H); ^{13}C NMR δ 12.79 (CH_3), 20.98 (C), 25.70 (CH_3), 27.15 (CH), 28.66 (CH_2), 36.78 (CH), 117.18 (CH), 129.15 (C), 131.11 (CH), 136.20 (C), 162.92 (C); HRMS (EI) 316.1940 ($C_{22}H_{24}N_2$ requires 316.1940).

Bis-Steroid (−)-9. Zinc powder (110 mg, 1.70 mmol) was activated by stirring with a few droplets of Me_3SiCl in a two-necked round-bottomed flask under argon atmosphere for 2 h. A dark blue colored solution of $NiCl_2 \cdot 6H_2O$ (408 mg, 1.71 mmol) and Ph_3P (1.78 g, 6.80 mmol) in degassed DMF (10 mL) was then added by syringe, and the mixture was stirred under argon atmosphere at 60 °C for 1 h. A solution of the chloropyridine **51** (678 mg, 1.70 mmol) in degassed DMF (10 mL) was added, and the mixture was heated at the same temperature for 24 h. The mixture was then cooled to room temperature, and a 10% aqueous ammonia solution (25 mL) was added. The resulting suspension was stirred for 5 min and extracted with CH_2Cl_2 (4 × 40 mL), and the combined organic layers were washed three times with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on a silica gel column (20 × 3 cm) with a petroleum ether/ethyl acetate mixture (98:2 to 9:1) to afford the unreacted starting material **51** (300 mg, 44%) as the less polar component and the more polar bis-steroid (−)-**9** as a white solid (279 mg, 45%, calculated on the recovered starting material): mp dec >230 °C without melting; $[\alpha]_D$ −13.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.77 (m, 1H), 0.94 (s, 3H, 18-H), 1.05 (s, 3H, 19-H), 1.20−1.05 (m, 2H), 1.90−1.50 (m, 3H), 1.97 (s, 3H, AcO), 2.07 (m, 1H), 2.31 (m, 2H), 2.46 (app bt, J = 13.5 Hz, 1H), 2.68 (dd, J = 15.0 and 6.3 Hz, 1H), 4.55 (m, 1H, 3α-H), 5.37 (m, 1H, 6-H), 7.48 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ 17.7 (CH_3), 19.7 (CH_3), 21.0 (CH_2), 21.8 (CH_3), 28.1 (CH_2), 30.7 (CH_2), 31.3 (CH), 31.8 (CH_2), 34.1 (CH_2), 37.3 (CH_2), 38.6 (CH_2), 45.8 (C), 51.1 (CH), 56.4 (CH), 74.2 (CH), 118.9 (CH), 122.5 (CH), 133.3 (CH), 136.1 (C), 140.6 (C), 155.3 (C), 170.9 (C), 172.8 (C); MS-FAB *m*/*z* (%) 729 ($M^{\bullet+}$ + H, 50), 669 (20), 608 (5), 495 (4), 355 (5), 251 (13), 207 (16), 147 (31), 74 (100); HRMS (FAB) 729.4631 (M + 1); $C_{48}H_{61}N_2O_4$ requires 729.4631).

(+)-Nopinone (+)-11. A solution of (−)-β-pinene (−)-**10** (40.0 g, 293.6 mmol) in a mixture of methanol (80 mL) and

dichloromethane (80 mL) was cooled to −78°C in a three-neck, round-bottomed flask. While the mixture was stirred at the same temperature, ozone was bubbled through the solution (1.3% w/w of O_3 in the air at 60 L/h) by means of a sinter-glass-ended tube for 20 h, until the blue color persisted. The reaction progress was monitored by TLC (petroleum ether/AcOEt, 95:5). Nitrogen was then bubbled through the reaction mixture for 30 min, which was then allowed to warm to 0 °C. Zinc powder (57.6 g, 880 mmol, 3 equiv) and acetic acid (84 mL, 1.468 mol, 5 equiv) were then added carefully, portionwise, at 0 °C over a 1 h period. (**CAUTION!** The reaction mixture tends to bubble off; effective stirring is required). The resulting suspension was filtered, and the solid material was washed with dichloromethane repeatedly. The organic layer was carefully washed with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (3 × 60 mL), the combined organic layers were washed with water (3 × 100 mL) and dried over Na_2SO_4, and the solvent was evaporated in vacuo to give the crude nopinone (32 g, 80%), which was of sufficient purity for the subsequent reactions. The latter product was further purified by vacuum distillation (bp 92−94 °C, 17 mmHg) to afford (+)-nopinone (+)-**11** (26 g, 65%) as a colorless liquid, identical with an authentic sample, obtained by the OsO_4/$NaIO_4$ method:[9b] ^{1}H NMR δ 0.79 (s, 3 H), 1.26 (s, 3 H), 1.51 (d, J = 10.2 Hz, 1 H), 1.87−1.99 (m, 2 H), 2.15−2.19 (m, 1 H), 2.24−2.31 (m, 1 H), 2.44−2.54 (m, 3 H).

Pyridone (+)-12. A solution of (+)-nopinone (+)-**11** (13.83 g, 0.1 mol) and methylpropiolate (17 mL, 0.191 mol, 1.9 equiv) in a 7 M solution of ammonia in methanol (500 mL) was heated and stirred in a 750 mL autoclave at 140 °C and 15 bar pressure for 10.5 h under an argon atmosphere. The autoclave was cooled to ambient temperature, and the disappearance of starting material was checked on TLC (petroleum ether/ether/acetone/methanol 50:30:17:3). The reaction mixture was transferred into a flask and the solvent was evaporated. The crude product was dissolved in dichloromethane, the most polar impurities were filtered off through a pad of Celite to afford a brown solution to which silica was added (20 g), and the solvent was evaporated in vacuo. The product was purified via flash chromatography on silica gel (8 × 15 cm column) with a mixture of petroleum ether, ether, acetone, and methanol (50:30:17:3) to give pure pyridone (+)-**12** (11.64 g, 61%) as a yellowish amorphous solid: mp 180−182 °C (petroleum ether/ether, 1:1); $[\alpha]_D$ +73.9 (c 0.37, CH_2Cl_2); IR ν 3383 w, several dimer peaks around 2800, 1651 vs, 1605 vs, 1562 s, 1461 s, 1414 m, 1386 w, 1370 m, 827 m cm^{-1}; ^{1}H NMR δ 0.69 (s, 3 H), 1.27 (d, J = 9.6 Hz, 1 H), 1.33 (s, 3 H), 2.19−2.23 (m, 1 H), 2.55−2.68 (m, 3 H), 2.76 (t, J = 5.6 Hz, 1 H), 6.32 (d, J = 9.0 Hz, 1 H), 7.21 (d, J = 9.0 Hz, 1 H), 13.42 (s, 1 H); ^{13}C NMR: 21.43 (CH_3), 26.15 (CH_3), 29.83 (CH_2), 31.09 (CH_2), 39.94 (C), 40.89 (CH), 45.51 (CH), 111.27 (C), 115.65 (CH), 143.00 (CH), 154.04 (C), 164.84 (C); MS (EI) m/z (%) 189 ($M^{+\bullet}$, 21), 174 (18), 146 (75), 145 (19), 128 (29), 78 (84), 63 (100), 61 (17), 45 (27), 44 (38), 43 (19); HRMS (EI) 189.1156 ($C_{12}H_{15}NO$ requires 189.1154).

Triflate (−)-13. Trifluoromethanesulfonic anhydride (5.33 mL, 31.70 mmol, 1.5 equiv) was added to a stirred solution of (+)-pyridone (+)-**12** (4.00 g, 21.14 mmol, 1 equiv) and anhydrous triethylamine (3.50 mL, 25.11 mmol, 1.2 equiv) in a freshly distilled dichloromethane (100 mL) under an argon atmosphere at −45°C. The reaction mixture was stirred at the same temperature for 15 min and then allowed to warm to ambient temperature over a period of 1.5 h. The progress of the reaction was monitored by TLC (petroleum ether/ether/acetone/methanol 50:30:17:3). After the reaction was complete (TLC), it was quenched by pouring onto ice, the organic layer was washed with 10% aqueous NaOH (3 × 50 mL), and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (1 × 50 mL) and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude material was purified via flash chromatography on silica gel (2.5 × 25 cm) with a mixture of petroleum ether and ether (95:5) to afford the desired triflate (−)-**13** (6.26 g, 92%) as an oil that solidified upon freezing as an amorphous solid: $[\alpha]_D$ −10.0 (c 1.9, CH_2Cl_2); ^{1}H NMR δ 0.58 (s, 3 H), 1.22 (d, J = 10.6 Hz, 1 H), 1.35 (s, 3 H), 2.26−2.31 (m, 1 H), 2.64−2.69 (m, 1 H), 2.84−2.94 (m, 3 H), 6.87 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H); ^{13}C NMR δ 21.48 (CH_3), 26.16 (CH_3), 30.85 (CH_2), 31.14 (CH_2), 39.45 (C), 40.22 (CH), 50.07 (CH), 112.34 (CH), 119.04 (d, J^1_{CF} = 320.6), 131.57 (C), 139.68 (CH), 153.21 (C), 167.10 (C); IR ν 1603 m, 1573 m, 1469 w, 1440 s, 1420 vs, 1387 w, 1371 w, 1229 vs, 1203 s, 1190 s, 1137 vs, 999 w, 614 s, 599 m, 584 w, 524 w cm^{-1}; MS (EI) m/z (%) 321 ($M^{+\bullet}$, 13), 279 (12), 278 (19), 277 (20), 188 (25), 160 (11), 147 (17), 146 (51), 145 (46), 128 (38), 91 (9), 87 (10), 85 (63), 83 (100), 78 (29), 63 (25), 48 (11), 47 (23), 41 (10); HRMS (EI) 321.0647 ($C_{13}H_{14}F_3NO_3S$ requires 321.0647).

(+)-Caran-5-one (+)-16. A stirred solution of (−)-**15** (10.8 g, 72 mmol), obtained by oxidation of (+)-**14**,[21] was hydrogenated in ether (100 mL) at room temperature over 5% Pd/C, under atmospheric pressure of hydrogen. The reaction was monitored by TLC, and when no starting material was left (∼3 h), the mixture was filtered over Celite and the solvent was evaporated in vacuo to give pure ketone (+)-**16**[22,25,58] as an oil (10.9 g, 98%): $[\alpha]_D$ +243 (c 1.71, $CHCl_3$); ^{1}H NMR δ 0.97 (d, J = 5.6 Hz, 3 H), 1.15 (s, 3 H), 1.16 (s, 3 H), 1.41 (d, J = 7.6 Hz, 1 H), 1.57 (m, 1 H), 1.64 (br d, J = 16.7 Hz, 1 H), 1.96 (m, 1 H), 2.07 (m, 1 H), 2.25 (br d, J = 16.8 Hz, 1 H); ^{13}C NMR δ 16.99, 21.50, 27.95, 28.15, 29.51, 30.96, 34.51, 34.93, 48.72, 210.45; IR ν 2952, 2870, 1688, 1456, 1334, 902 cm^{-1}.

Keto Aldehyde (+)-17. (+)-Caran-5-one (+)-**16** (5.5 g, 36.2 mmol) was added dropwise to a suspension of sodium methoxide (3.9 g, 72.4 mmol) and ethyl formate (5.36 g, 72.4 mmol) in toluene (200 mL), and the mixture was stirred at room temperature for 10 h. A 2 M HCl solution (50 mL) was then added, and the resulting mixture was extracted into ethyl acetate (150 mL). The organic layer was washed with brine (50 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to afford (+)-**17** as a dense oil (5.0 g, 76%), pure enough for the next synthetic step: $[\alpha]_D$ +321 (c 8.33, $CHCl_3$); ^{1}H NMR δ 1.00 (s, 3 H), 1.06 (d, J = 6.8 Hz, 3 H), 1.17 (ddd, J = 8.8, 7.6, and 5.2 Hz, 1 H), 1.18 (s, 3 H), 1.39 (ddd, J = 8.0, 7.2, and 5.2 Hz, 1 H), 2.07 (ddd, J = 9.2, 8.8, and 4.6 Hz, 1 H), 2.2−2.3 (m, 1 H), 2.6−2.7 (m, 1 H), 7.58 (d, J = 10.0 Hz, 1 H), 14.85 (d, J = 10.0 Hz, 1 H); ^{13}C NMR δ 16.70, 17.87, 25.84, 27.05, 28.51, 29.52, 30.08, 31.31, 115.78, 168.53, 199.41; IR ν 3428, 2958, 2867, 1634, 1457, 1401, 1281, 1201 cm^{-1}; HRMS (EI) 180.1152 ($C_{11}H_{16}O_2$ requires 180.1150).

Enone (+)-18. A suspension of (+)-**17** (4.15 g, 27.7 mmol), sodium carbonate (15 g), and formaldehyde (37% solution in water, 15 mL) in ether (100 mL) was stirred at room temperature, until no starting material could be detected by TLC (∼2 h). Water (200 mL) was then added, and the product was taken up into ethyl acetate (100 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to afford an oil, that was purified via flash chromatography on silica gel (80 g) using petroleum ether, followed by a 9:1 mixture of petroleum ether and ethyl acetate to give pure (+)-**18** (4.09 g, 90%): $[\alpha]_D$ +217 (c 10.9, $CHCl_3$); ^{1}H NMR δ 1.00 (s, 3 H), 1.09 (d, J = 7.2 Hz, 3 H), 1.05−1.15 (m, 1 H), 1.15−1.25 (m, 1 H), 1.16 (s, 3 H), 1.21 (s, 3 H), 1.5−1.6 (m, 2 H), 2.15−2.25 (m, 1 H), 5.05 (s, 1 H), 5.81 (s, 1 H); ^{13}C NMR δ 16.54, 17.67, 27.97, 28.49, 28.67, 29.07, 34.48, 37.81, 116.46, 151.98, 210.27; IR ν 2957, 1681, 1619, 1457, 1253 cm^{-1}.

Kröhnke Salt 19. Ethyl α-bromoacetate (11.1 mL, 0.1 mol) was added dropwise to a solution of pyridine (8.1 mL, 0.1 mol) in ethyl acetate (20 mL), and the mixture was heated at 50 °C for 1 h and then cooled to room temperature. The yellow precipitate was isolated by suction and recrystallized from a

(58) The reported values for (+)-**16** of unspecified enantiopurity are $[\alpha]_D$ +249 and +254 (EtOH), respectively.[22,25]

methanol/toluene mixture to give **19**[24] as a pale yellow solid (20.7 g, 84%): mp 134−136 °C (methanol/toluene) (lit. 135−136 °C[24a] or 120−123 °C[24c]); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3 H), 4.32 (q, J = 7.1 Hz, 2 H), 5.70 (s, 2 H), 8.26 (dd, J = 7.7 and 6.7 Hz, 2H), 8.73 (t, J = 7.7 Hz, 1H), 9.06 (d, J = 6.5 Hz, 2H), in accordance with the literature. [24d]

Pyridone 20. Kröhnke salt **19** (615 mg, 2.5 mmol) and NH_4-OAc (2 g) were added to a solution of enone (+)-**18** (320 mg, 2.0 mmol) in dry ethanol (15 mL), followed by a dropwise addition of piperidine (0.25 mL, 2.5 mmol), which turned the solution bright yellow. The solution was refluxed for 2 h, and ethanol was then removed in vacuo. Formamide (2.0 mL) and glacial acetic acid (0.5 mL) were added to the residue, and the mixture was heated for 1 h at 200 °C. The mixture was cooled to room temperature, the reaction was quenched with aqueous 1 M NaOH (20 mL), and the product was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to give a brown oil, which was purified via flash chromatography on silica gel (40 g) with an ethyl acetate/methanol mixture (10:1) to give crude **20** as yellow solid (81 mg, 20%), which was used in the next step without further purification: ^{1}H NMR δ 0.78 (s, 3 H), 1.26 (d, J = 6.7 Hz, 3 H), 1.22 (s, 3 H), 1.23−1.37 (m, 2 H), 1.50 (d, J = 8.7 Hz, 1 H), 2.14 (ddd, J = 14.2, 9.4, 4.7 Hz, 1 H), 2.68 (m, 1 H), 6.36 (d, J = 9.2 Hz, 1 H), 7.36 (d, J = 9.3 Hz, 1 H).

Chloropyridine (+)-21. A solution of pyridone **20** (81 mg, 0.40 mmol) in DMF (3 mL) and $POCl_3$ (1 mL) was heated at 100 °C for 4 h and then cooled to 0 °C. The reaction was quenched with ice followed by aqueous 1 M $NaHCO_3$ (10 mL). The product was extracted with ether (3 × 20 mL), the combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$), and the solvent was evaporated in vacuo. The crude product was purified via flash chromatography on silica gel (20 g) with a hexane/ethyl acetate mixture (10:1) to give pure (+)-**21** as a light-yellow oil that solidified on standing (35 mg, 39%): $[\alpha]_D$ +56.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 0.69 (s, 3H), 1.23 (s, 3 H), 1.24 (d, J = 6.3 Hz, 3 H), 1.24−1.41 (m, 2 H), 1.54 (d, J = 7.2 Hz, 1 H), 2.21 (ddd, J = 14.2, 9.4, 4.8 Hz, 1 H), 2.85 (m, 1 H), 7.05 (d, J = 8.1 Hz, 1 H), 7.40 (d, J = 8.1 Hz, 1 H); ^{13}C NMR δ 16.5 (CH_3), 18.5 (CH_3), 23.4 (CH_3), 25.3 (C), 27.3 (CH), 28.2 (CH), 30.3 (CH_2), 32.5 (CH), 121.4 (CH), 135.1 (CH), 137.5 (C), 148.3 (C), 158.4 (C); HRMS (EI) 221.0963 ($C_{13}H_{16}NCl$ requires 221.0971).

Triflate (+)-22. Trifluoromethanesulfonic anhydride (0.2 mL, 1.2 mmol, neat) was added to a stirred solution of pyridone **20** (100 mg, 0.58 mmol) and Et_3N (0.13 mL, 0.87 mmol) in dichloromethane (10 mL) at −45 °C, and the stirring was continued at the same temperature for a further 30 min. The mixture was then allowed to warm to ambient temperature over a period of 1.5 h (the reaction was monitored by TLC). The reaction was then quenched by pouring onto ice, the product was taken up into dichloromethane and the organic layer with aqueous 1 M NaOH (3 × 10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (1 × 50 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil, which was purified via flash chromatography on silica gel (60 g) with petroleum ether, followed by a petroleum ether/ether mixture (19:1), which afforded the pure triflate (+)-**22**, as a yellow oil that partly solidified (180 mg, 99%): $[\alpha]_D$ +17.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.67 (s, 3 H), 1.25 (s, 3 H), 1.28 (d, J = 6.4 Hz, 3 H), 1.29 (m, 2 H), 1.82 (d, J = 8.6 Hz, 1 H), 2.23−2.29 (m, 1 H), 2.89−2.97 (m, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 16.30 (CH), 18.43 (CH_3), 23.65 (CH), 25.61 (C), 27.08 (CH), 28.19 (CH_3), 30.37 (CH_2), 32.80 (CH), 136.86 (CH), 139.93 (C), 154.01 (C), 157.79 (C).

Oxime 23. A solution of (+)-caran-5-one (+)-**16** (2.0 g, 1.31 mmol), hydroxylamine hydrochloride (913 mg, 13.1 mmol), and pyridine (0.5 mL) in ethanol (50 mL) was refluxed for 1 h. This solution was then cooled, 0.1 M HCl (10 mL) was added, and the mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to afford oxime **23** (*E*/*Z* mixture)[25] as an oil (2.09 g, 95%) that was used in the next step without any further purification.

Enamide (−)-24. A mixture of acetic anhydride (3.64 g, 35.7 mmol) and acetic acid (2.0 g, 35.7 mmol) was added dropwise to a suspension of iron powder (15 g) and oxime **23** (2.0 g, 11.9 mmol) in toluene (50 mL) at 0 °C under mechanical stirring. After 20 min, the mixture was filtered, water (30 mL) was added to the filtrate, and the product was taken up into ethyl acetate (3 × 50 mL). The combined organic layers were washed with a 2 M NaOH solution (2 × 50 mL) and brine (30 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to afford an amorphous solid, which was purified via flash chromatography on silica gel (60 g) using petroleum ether followed by a 1:1 mixture of petroleum ether and ethyl acetate to give pure enamide (−)-**24** (1.19 g, 52%) as a white wax: $[\alpha]_D$ −71 (*c* 6.4, $CHCl_3$); ^{1}H NMR δ 0.94 (d, J = 6.8 Hz, 3 H), 1.00 (s, 3 H), 1.12 (s, 3 H), 1.0−1.1 (m, 1 H), 1.65−1.7 (m, 2 H), 1.9−2.0 (m, 1 H), 2.05 (s, 3 H), 2.4−2.5 (m, 1 H), 6.04 (br s, 1 H), 6.36 (br, 1 H); ^{13}C NMR δ 15.72, 22.04, 22.93, 24.31, 24.41, 25.04, 27.92, 29.15, 29.48, 119.64, 132.19, 168.38; IR ν 3291, 1659, 1534, 1280 cm^{-1}; HRMS (FAB) 193.1469 ($C_{12}H_{19}NO$ requires 193.1467).

Vilsmeier−Haack Reaction of Enamide (−)-24. $POCl_3$ (1.19 g, 7.79 mmol) was added dropwise to a solution of (−)-**24** (200 mg, 1.01 mmol) in DMF (2 mL) at 0 °C. The resulting dark brown solution was stirred at room temperature for 1 h and then at 80 °C for 4 h. The solution was cooled with ice, and then water (2 mL) was cautiously added. The pH of the solution was made basic with a 40% aqueous NaOH solution, and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to afford a dense black oil, which was purified via flash chromatography on silica gel (30 g) using petroleum ether followed by a mixture of petroleum ether and ethyl acetate (9:1) to give (+)-**26** (70 mg, 31%), followed by (+)-**27** (80 mg, 32%) as yellow oils. (+)-**26:** $[\alpha]_D$ +60 (*c* 6.8, $CHCl_3$); ^{1}H NMR δ 1.02 (d, J = 6.8 Hz, 3 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.13 (d, J = 7.2 Hz, 3 H), 2.02 (dd, J = 16.8 and 8.0 Hz, 1 H), 2.34 (dq, J = 6.8 and 6.8 Hz, 1 H), 2.36 (ddd, J = 16.8, 6.4, and 0.8 Hz, 1 H), 6.28 (d, J = 0.8 Hz, 1 H), 7.00 (d, J = 8.0, Hz, 1 H), 7.28 (d, J = 8.0, Hz, 1 H); ^{13}C NMR δ 19.44, 20.34, 30.06, 31.59, 32.27, 52.45, 122.60, 125.41, 133.88, 136.38, 146.33, 149.08, 153.58; IR ν 2963, 1639, 1575, 1429, 1132, 1109 cm^{-1}; HRMS (FAB) 221.0972 ($C_{13}H_{16}ClN$ requires 221.0971). (+)-**27:** $[\alpha]_D$ +35 (*c* 15.3, $CHCl_3$); ^{1}H NMR δ 1.20 (d, J = 6.8 Hz, 3 H), 1.31 (s, 3 H), 1.32 (s, 3 H), 2.05 (dd, J = 16.8 and 8.0 Hz, 1 H), 2.37 (ddd, J = 16.8, 6.8, and 1.2 Hz, 1 H), 2.98 (ddd, J = 8.0, 6.8, and 0.8, Hz, 1 H), 6.60 (d, J = 1.2, Hz, 1 H), 7.10 (d, J = 7.9, Hz, 1 H), 7.39 (d, J = 7.9, Hz, 1 H), 9.41 (s, 1 H); ^{13}C NMR δ ($CDCl_3$; 100.6 MHz) 19.73, 20.91, 20.95, 31.56, 33.72, 35.35, 120.83, 121.34, 133.63, 136.04, 148.72, 154.34, 154.79; IR ν 2927, 2702, 2227, 1726, 1633, 1669, 1431, 1129, 902 cm^{-1}; HRMS (FAB) 249.0921 ($C_{14}H_{16}ClNO$ requires 249.0920).

Allylic Alcohol (+)-30. *n*-BuLi (29.6 mL, 2.0 M solution in hexane, 59.2 mmol) was added dropwise to a solution of diisopropylamine (6.0 g, 59.3 mmol) in THF (100 mL) at 0 °C. After 30 min, a solution of epoxide (+)-**29**[28] (3.0 g, 19.7 mmol) in THF (5 mL) was added dropwise via a syringe at the same temperature, and the mixture was warmed to room temperature and stirred for 6 h. A saturated solution of NH_4Cl (5 mL) was then cautiously added, followed by addition of water (50 mL). The mixture was extracted with ethyl acetate (3 × 100 mL), the combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to afford an oil, which was purified via flash chromatography on silica gel (100 g) using petroleum ether followed by a 9:1 mixture of petroleum ether/ethyl acetate to give pure (+)-**30**[30] as a colorless oil (1.60 g, 53%).

Enone (-)-31. 2,2′,6,6′-Tetramethylpiperidine-*N*-oxide (TEMPO; 72 mg, 0.46 mol, 0.07 equiv) and (bisacetoxyiodo)benzene (BAIB; 2.54 g, 7.89 mmol) were added to a solution of (+)-**30** (1.0 g, 6.58 mmol) in dichloromethane (50 mL) and the mixture was stirred at room temperature for 5 h.[33] Aqueous $Na_2S_2O_3$, (20 mL, saturated solution in water) and ethyl acetate (100 mL) were then added, and the product was extracted into ethyl acetate. The organic layer was washed with brine (30 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to afford an oil, which was purified via flash chromatography on silica gel (30 g) using petroleum ether followed by a 9:1 mixture of petroleum ether and ethyl acetate to afford pure (−)-**31**[5c,d,56b] as a pale yellow oil (820 mg, 83%).

Pyridone (−)-33. Method A. A mixture of enone (−)-**31** (200 mg, 1.33 mmol), Kröhnke salt **19** (394 mg, 1.66 mmol), $AcONH_4$ (3.0 g), and piperidine (0.14 mL, 1.46 mmol) in *n*-butanol (5 mL) and acetic acid (1.4 mL)[23] was heated at reflux overnight. The mixture was cooled to room temperature, aqueous 1 M $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine (20 mL), and dried ($MgSO_4$), and the solvent was evaporated in a vacuum. The crude product was purified using flash chromatography on silica gel (20 g) with an ethyl acetate/methanol mixture (97:3) to give pyridone (−)-**33** as a yellowish oil (97 mg, 39%) that was used in the next step: $[\alpha]_D$ −41.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.83 (s, 3 H), 1.23 (s, 3 H), 1.37 (td, J = 7.0 and 3.9 Hz, 1 H), 1.48 (t, J = 7.0 Hz, 1 H), 1.74−1.81 (m, 1 H), 2.01−2.10 (m, 1 H), 2.25 (dt, J = 15.8 and 6.1 Hz), 2.50−2.58 (m, 1 H), 6.36 (d, J = 9.3 Hz, 1 H), 7.18 (d, J = 9.3 Hz, 1 H); MS (EI) *m*/*z* (%) 189.1 (100, $M^{\bullet+}$), 174.1 (81), 146.1 (46), 128.0 (23), 118.0 (7), 91.0 (7), 82.9 (33), 41.0 (11); HRMS (EI) 189.1152 ($C_{12}H_{15}NO$ requires 189.1154).

Method B. A mixture of the pyridinium salt **19** (850 mg, 3.4 mmol), anhydrous ammonium acetate (5.5 g, 71.4 mmol), piperidine (0.3 mL), acetic acid (1.4 mL), and enone **31** (500 mg, 2.7 mmol) in methanol (10 mL) was stirred in an autoclave at 150 °C for 10 h. After the mixture cooled to room temperature, water (50 mL) was added, and the mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to afford a dark oil. Purification via flash chromatography on silica gel (50 g) with ethyl acetate, followed by a mixture of ethyl acetate and methanol (9:1), gave the (crude) pyridone (−)-**33** (110 mg, 20%) as a pale yellow oil, which was employed in the next step without further purification.

Triflate (−)-34. Trifluoromethanesulfonic anhydride (0.90 mL, 5.35 mmol, neat) was added to a stirred solution of pyridone **33** (508 mg, 2.67 mmol) and Et_3N (0.56 mL, 4.0 mmol) in dichloromethane (100 mL) at −45° C, and the stirring was continued at the same temperature for a further 30 min. The mixture was then allowed to reach room temperature. The solution was washed with aqueous 1 M NaOH (2 × 100 mL), the aqueous phase was extracted with CH_2Cl_2 (100 mL), and the extract was added to the original organic phase. The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil, which was purified via flash chromatography on silica gel (150 g) with petroleum ether, followed by a petroleum ether/ethyl acetate mixture (9:1), which afforded pure triflate (−)-**34**, as a yellow oil (850 mg, 99%): $[\alpha]_D$ −78.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.71 (s, 3 H), 1.16 (s, 3 H), 1.28 (td, J = 8.0 and 4.0 Hz, 1 H), 1.70−1.78 (m, 1 H), 1.83 (d, J = 8.4 Hz, 1 H), 1.97−2.06 (m, 1 H), 2.47 (dt, J = 9.7 and 6.3 Hz, 1 H), 2.68−2.76 (m, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 7.49 (d, J = 8.1 Hz, 1 H); ^{13}C NMR δ 16.47 (CH_3), 19.19 (CH_2), 25.41 (CH_3), 26.76 (C), 28.13 (CH_2), 28.36 (CH), 29.17 (CH), 111.88 (CH), 133.41 (C), 140.40 (CH), 154.02 (C), 157.58 (C); MS (EI) *m*/*z* (%) 321.1 (67, $M^{\bullet+}$), 306.0 (49), 278.0 (9), 277.0 (7), 188.1 (88), 146.1 (35), 145.1 (27), 128.1 (24), 83.0 (100), 47.0 (18), 41.1 (11). HRMS (EI): 321.0613 ($C_{13}H_{14}O_3NF_3S$ requires 321.0610).

Keto Aldehyde 35. Method A. Ozone was introduced (1.3% of O_3 in the air at 60 L/h) via a sintered-glass diffuser through a vigorously stirred solution of (+)-3-carene (+)-**14** (60 g, 0.44 mol) in a mixture of methanol and dichloromethane (300 mL, 1:1) at −45 °C for 24 h (the disappearance of the product was monitored by TLC). A saturated, aqueous solution of sodium sulfite (500 mL) was then slowly added, taking care that the temperature of the bath did not reach 0 °C. The resulting mixture was extracted with dichloromethane (3 × 250 mL), the extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure, giving the crude keto aldehyde **35**[35,36] as a viscous oil (48 g, 65%), which was considered pure enough for the following step: ^{1}H NMR δ_H 1.12 (s, 3 H), 1.27 (s, 3 H), 1.37 (dd, J = 14.6 and 8.4 Hz, 1 H), 1.57 (dd, J = 8.4 and 5.6 Hz, 1 H), 1.78−2.05 (m, 2 H), 2.10 (s, 3 H), 2.42 (t, J = 7.2 Hz, 2 H), 9.50 (d, J = 5.6 Hz, 1 H).

Method B. A solution of potassium permanganate (27.6 g, 174.8 mmol) and sodium hydroxide (4.8 g, 120.0 mmol) in water (500 mL) was slowly added to a stirred solution of (+)-3-carene (+)-**14** (20 g, 147.0 mmol) in *tert*-butyl alcohol (300 mL) and water (120 mL) at 0 °C. After 10 min at 0 °C, the alcohol was removed at <40 °C under reduced pressure, the residue was saturated with solid sodium chloride, and the product was extracted with ethyl acetate (3 × 500 mL). After drying with $MgSO_4$, the solvent was removed in vacuo, giving the corresponding vicinal diol as an oil (7.5 g, 30%), which was used in the next step without further purification: ^{1}H NMR δ 0.65 (dt, J = 9.5 and 4.4 Hz, 1 H), 0.87 (t, J = 9.5 Hz, 2 H), 1.01 (s, 3 H), 1.21 (s, 3 H), 1.22−1.28 (m, 2 H), 1.60 (br s, 1 H), 1.67−1.73 (m, 1 H), 1.83 (br s, 1 H), 2.05−2.15 (m, 1 H), 3.19 (t, J = 8.3 Hz, 2 H).[59] A solution of the latter crude diol (5 g, 29.4 mmol) in CH_2Cl_2 (150 mL) was added to a vigorously stirred mixture of the silica-gel-supported $NaIO_4$ reagent (60 g, 41 mmol of $NaIO_4$)[35b] in CH_2Cl_2 (150 mL), placed in a round-bottomed flask. The reaction was monitored by TLC. When disappearance of the starting material was detected (ca. 30 min), the mixture was filtered through a sintered glass funnel, and the silica gel was washed with $CHCl_3$ (3 × 200 mL). Removal of solvents from the filtrate afforded the aldehyde **35** (4.4 g, 90%) as a colorless oil, which was identical with the product obtained by method A and sufficiently pure for the next step.

Enone (+)-36. Keto Aldehyde **35** (20.0 g, 0.11 mol, neat) was added to a 4% aqueous NaOH solution (300 mL), and the mixture was vigorously stirred at room temperature for 30 min.[37] The product was extracted with ether (3 × 150 mL), the extract was washed with water (3 × 100 mL) and dried, and the solvent was removed under reduced pressure to furnish the crude ketone (+)-**36**[35a] as an oil (9.0 g, 52%), which was used in the next step without further purification: ^{1}H NMR δ 0.77 (s, 3 H), 1.01 (s, 3 H), 1.20 (d, J = 9.6 Hz, 2 H), 1.31 (s, 3 H), 2.01 (s, 3 H), 2.23 (ddd, J = 8.8 Hz, J = 3.2 Hz, J = 3.2 Hz, 1 H), 2.60 (dt, J = 10 Hz, J = 6 Hz, 1H), 2.85 (s, 2 H), 2.93 (t, J = 6.0 Hz, 1 H), 7.24 (s, 2 H).

Ketone 37. A solution of the α,β-unsaturated ketone (+)-**36** (4.6 g, 30.6 mmol) in a 1:1 mixture of ethanol and ethyl acetate (100 mL) was stirred under a pressure of 1 bar of hydrogen, in the presence of 5% palladium on charcoal (1.25 g) for 3 h (TLC monitoring). The catalyst was then filtered off on a Celite pad, and the solvent was removed in vacuo to afford ketone **37**[60] (4.4 g, 95%), which was employed in the next step without further purification.

Acetate 38. *m*-CPBA (26 g, 80%w, 120 mmol) was added in portions to a stirred solution of ketone **37** (9.1 g, 60 mmol) in dichloromethane (300 mL) at 0 °C. The reaction mixture was then allowed to reach room temperature, and the stirring was continued for 24 h (TLC monitoring). A saturated, aqueous solution of sodium thiosulfate (200 mL) was added, and two

(59) Cocker, W.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1217.

(60) Compounds **37**−**40** have been reported, but without experimental details, in Walkowicz, M. *Rocz. Chem.* **1969**, *43*, 241.

layers were separated. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate (150 mL) and brine (100 mL) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give acetate **38**[60] as a colorless oil (8.6 g, 85%), which was used in the next step without further purification: ^{1}H NMR (major epimer) δ 1.01 (s, 3 H), 1.21 (s, 3 H), 1.38−1.53 (m, 2 H), 1.78 (ddd, J = 13.6, 9.7, and 2.5 Hz, 1 H), 1.87−1.97 (m, 2 H), 2.30 (dm, J = 2.5 Hz, 1 H), 5.43 (dt, J = 9.7 and 6.3 Hz, 1 H).

Alcohol 39. A solution of acetate **38** (1.80 g, 10.7 mmol) in ether (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (850 mg, 22.3 mmol) in ether (15 mL). After stirring for a further 30 min, the reaction was quenched by careful addition of a few crystals of $Na_2SO_4 \cdot 10H_2O$ followed by water (20 mL). The resulting mixture was extracted with ethyl acetate (3 × 30 mL), and the extract was washed with brine (50 mL) and dried over $MgSO_4$. Solvent removal under reduced pressure and purification of the residue by chromatography on silica gel (30 g) using a hexane/ethyl acetate mixture (9:1), furnished alcohol **39**[35,36] (690 mg, 78%) as a colorless oil: ^{1}H NMR (major epimer) δ 1.01 (s, 3 H), 1.21−1.27 (m, 1 H), 1.30 (s, 3 H), 1.36−1.46 (m, 1 H), 1.52−1.67 (m, 1 H), 1.80 (dd, J = 9.6 and 2.2 Hz, 1 H), 1.86−1.95 (m, 1 H), 2.21 (dm, J = 2.2, 1 H), 4.74 (m, 1 H); ^{13}C NMR (major epimer) δ 17.08 (CH_3), 24.38 (CH_2), 29.07 (CH_3), 32.05 (CH), 35.30 (CH_2), 36.29 (CH), 52.55 (C).

Ketone (+)-40. A solution of alcohol **39** (5.8 g, 46 mmol) in a mixture of dichloromethane, acetonitrile and acetic acid (56 mL, 23:6:16) was added dropwise to a stirred solution of calcium hypochlorite (10 g, 70 mmol) in water (45 mL) at 0 °C. The solution was stirred at 0 °C for 2 h, then water (15 mL) was added, and the organic components were extracted with dichloromethane. The organic phase was neutralized with aqueous 1 M sodium hydroxide solution and washed with saturated aqueous sodium hydrogen carbonate (3 × 15 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford crude ketone (+)-**40**[60,61] (4.6 g, 82%) as an oil, which was employed in the next step without further purification: ^{1}H NMR δ 1.13 (s, 3 H), 1.17 (s, 3 H), 1.51 (dd, J = 8.4 and 3.0 Hz, 1 H), 1.66 (d, J = 5.0 Hz, 1 H), 1.88−1.95 (m, 1 H), 2.01−2.09 (m, 1 H), 2.20−2.31 (m, 2 H); ^{13}C NMR δ 16.27 (CH_3), 19.99 (CH_2), 27.06 (CH_3), 31.22 (C), 35.96 (CH), 38.21 (CH_2), 41.67 (CH), 198.55 (C=O).

Pyridone 41. Methyl propiolate (1.7 mL, 10 mmol) and ketone **40** (620 mg, 5 mmol) were dissolved in a solution of 7 M ammonia in methanol (50 mL), and the resulting mixture was stirred in an autoclave at 140 °C for 10 h. After cooling, the solvent was evaporated under reduced pressure to give a red-brown solid, which was extracted with methanol/ethyl acetate 2:1 (3 × 50 mL). The solution was then evaporated in vacuo to afford an oil, which was purified via flash chromatography on silica gel (350 g) with ethyl acetate, followed by an ethyl acetate/methanol mixture (9:1) to give crude pyridone **41** (170 mg, 20%), accompanied by the ring-opened product (as deduced from NMR spectra) and by unknown impurities, as a yellowish solid: ^{1}H NMR δ 0.81 (s, 3 H), 1.22 (s, 3 H), 1.73 (t, J = 6.4 Hz, 1 H), 2.13 (dd, J = 6.4 and 2.0 Hz, 1 H), 2.55 (d, J = 16.6 Hz, 1 H), 2.83−2.88 (m, 1 H), 6.27 (d, J = 9.0 Hz, 1 H), 7.23 (d, J = 9.0 Hz, 1 H). This crude product was employed in the next step without any further purification.

Triflate (+)-42. Trifluoromethanesulfonic anhydride (0.1 mL, 0.7 mmol; neat) was added to a solution of crude **41** (40 mg, as obtained from the previous step) and Et_3N (0.1 mL, 0.67 mmol) in dichloromethane (5 mL) at −45 °C, and the resulting mixture was stirred at the same temperature for a further 30 min. The mixture was then allowed to reach room temperature and then was washed with an aqueous 1 M NaOH solution (2 × 5 mL), and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil, which was purified via flash chromatography on silica gel (30 g) with petroleum ether, followed by a petroleum ether/ethyl acetate mixture (9:1), affording pure triflate **42** (66 mg, 94%), as a yellow oil: $[\alpha]_D$ +45.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 0.69 (s, 3 H), 1.19 (s, 3 H), 1.81 (dt, J = 7.3 and 0.9 Hz, 1 H), 2.37 (dd, J = 6.1 and 1.7 Hz, 1 H), 2.82 (d, J = 17.6 Hz, 1 H), 3.09 (dd, J = 17.6 and 7.3 Hz, 1 H), 6.85 (d, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H); ^{13}C NMR δ 14.03 (CH_3), 23.05 (C), 26.86 (CH_3), 29.61 (CH_2), 29.64 (CH), 37.68 (CH), 112.24 (CH), 135.66 (CH), 138.96 (C), 155.09 (C), 164.96 (C); MS (EI) *m*/*z* (%) 307.0 (47, $M^{\bullet+}$), 292.0 (39), 266.0 (3), 254.0 (2), 228.1 (4), 174.1 (100), 159.1 (50), 131.1 (28), 130.1 (23), 83.0 (56), 77.1 (25), 41.1 (23); HRMS (EI) 307.0489 ($C_{12}H_{12}F_3NO_3$ requires 307.0490).

Pyridone (+)-45. Kröhnke salt **19** (1.79 g, 7.3 mmol) and NH_4OAc (5 g) were added to a solution of enone (−)-**44**[34] (1.01 g, 6.7 mmol) in dry ethanol (15 mL), followed by a dropwise addition of piperidine (0.1 mL, 10.1 mmol), which turned the solution bright yellow. The solution was refluxed for 2 h, and ethanol was then removed in vacuo. Formamide (3.5 mL) and glacial acetic acid (0.75 mL) were added to the residue, and the mixture was heated at 210 °C for 1 h to complete the cyclization of the Michael adduct. The mixture was cooled to room temperature, the reaction was quenched with aqueous 1 M NaOH (20 mL), and the product was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to give a brown oil, which was purified via flash chromatography on silica gel (40 g) with a mixture of petroleum ether, ether, acetone, and methanol (50:30:17:3) to give pure (+)-**45** as white crystals (542 mg, 43%): mp 141−143 °C (ethyl acetate/hexane); $[\alpha]_D$ +49.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.64 (s, 3 H), 1.20 (d, J = 9.4 Hz, 1 H), 1.30 (s, 3 H), 2.22 (m, 1 H), 2.50 (t, J = 5.7 Hz, 1 H), 2.57 (m, 1 H), 2.85 (m, 1 H), 6.26 (d, J = 8.9 Hz, 1 H), 7.07 (d, J = 8.9 Hz, 1 H), in accordance with the data for an authentic sample of the opposite enantiomer.[9b]

Triflate (+)-46. Trifluoromethanesulfonic anhydride (0.18 mL, 1.06 mmol) was added dropwise to a solution of solution of pyridone (+)-**45** (100 mg, 0.53 mmol) and triethylamine (0.6 mL, 0.78 mmol) in CH_2Cl_2 (10 mL) at −45 °C, and the resulting dark red mixture was stirred at this temperature left for 1 h, then warmed to 0 °C for 1 h, and finally taken to room temperature. The reaction was quenched with ice and aqueous 1 M $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), and dried ($MgSO_4$), and the solvent was evaporated in vacuo. The crude product was purified via flash chromatography on silica gel (20 g) with a petroleum ether/ethyl acetate mixture (9:1) to give pure (+)-**46** as a light-brown oil (162 mg, 99%), which was used directly in the following experiment: $[\alpha]_D$ +43.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.57 (s, 3 H), 1.17 (d, J = 9.6 Hz, 1 H), 1.34 (s, 3 H), 2.30 (m, 1 H), 2.64 (m, 1 H), 2.76 (t, J = 5.6 Hz, 1 H), 3.00 (d, J = 2.2 Hz, 2 H), 6.78 (d, J = 8.0 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), ^{13}C NMR δ 20.2 (CH_3), 24.8 (CH_3), 30.6 (CH_2), 35.1 (CH_2), 38.3 (C), 38.7 (CH), 44.8 (CH), 110.3 (CH), 136.1 (CH), 142.0 (C), 152.7 (C), 156.1 (C).

***iso*-PINDY (+)-47.** Zinc powder (0.74 g, 0.11 mol) was added under nitrogen to a suspension of $(Ph_3P)_2NiCl_2$ (1.49 g, 2.29 mmol) and Me_4NI (1.53 g, 7.63 mmol) in THF (50 mL), giving a green suspension; stirring at room temperature for 1 h gave a dark brown solution. A solution of triflate (+)-**46** (2.32 g, 7.63 mmol) in THF (2 mL) was added dropwise, and the mixture was stirred at 60 °C overnight. The mixture was cooled to room temperature, and aqueous 3 M HCl (30 mL) was added, followed by a 20% aqueous NH_3 solution (30 mL), giving a dark brown solution. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), leaving the aqueous layer light blue. The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$), and the solvent was evaporated in vacuo. The crude product was purified via flash chromatography on silica

(61) Nwaukwa, S. O.; Keehn, P. M., *Tetrahedron Lett.* **1982**, *23*, 35.

gel (20 g) with a petroleum ether/ethyl acetate mixture (10:1) to give the pure bipyridine (+)-**47** as white crystals (666 mg, 51%): mp 170−172 °C (ethyl acetate/hexane); $[\alpha]_D$ + 91.0 (*c*, 1.05, CH_2Cl_2); ^{1}H NMR δ 0.62 (s, 6 H), 1.32 (d, J = 9.4 Hz, 2 H), 1.41 (s, 6 H), 2.39 (m, 2 H), 2.70 (m, 2 H), 2.79 (t, J = 5.8 Hz, 2 H), 3.19 (s, 4 H), 7.31 (m, 2 H), 7.98 (d, J = 7.7 Hz, 2 H); ^{13}C NMR δ 21.7 (CH_3), 26.5 (CH_3), 32.9 (CH_2), 38.1 (CH_2), 39.9 (C), 43.6 (CH), 46.9 (CH), 118.4 (CH), 134.1 (CH), 141.9 (C), 154.8 (C), 156.7 (C) in accordance with the literature.[5e−g]

Alkylation of *iso*-PINDY (+)-47. *n*-Butyllithium (1.6 M, hexane, 5.4 mL, 8.70 mmol) was added dropwise to a solution of *iso*-PINDY (+)-**47** (1.0 g, 2.90 mmol) in THF (30 mL) at −35 °C, turning the color from pale yellow to deep blue.[62] The solution was stirred for 1 h at that temperature, then the neat alkyl halide (8.70 mmol) was added dropwise at −35 °C, and the mixture was then stirred at room temperature overnight. Aqueous 1 M NaOH was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), and dried ($MgSO_4$), and the solvent was evaporated under vacuum. The crude product was purified using flash chromatography on silica gel (40 g) with a petroleum ether/ethyl acetate mixture (10:1) to give pure **alkyl-*iso*-PINDY** as a white solid.

Me-*iso*-PINDY (−)-6 (99%): mp 58−60 °C (ethyl acetate/hexane); $[\alpha]_D$ −5.6 (*c*, 1.1, CH_2Cl_2); ^{1}H NMR δ 0.64 (s, 6 H), 1.33 (d, J = 9.4 Hz, 2 H), 1.42 (s, 6 H), 1.47 (d, J = 7.2 Hz, 6 H), 2.16 (m, 2 H), 2.57 (dt, J = 9.6 and 5.8 Hz, 2 H), 2.79 (t, J = 5.8 Hz, 2 H), 3.26 (dq, J = 7.2 and 2.4 Hz, 2 H), 7.30 (d, J = 7.6 and 2.3 Hz, 2 H), 7.98 (d, J = 7.7 and 2.4 Hz, 2 H);^{13}C NMR δ 18.6 (CH_3), 21.2 (CH_3), 26.7 (CH_3), 29.0 (CH_2), 39.3 (CH), 41.8 (C), 47.2 (CH), 47.5 (CH) in accordance with the data reported for the opposite enantiomer (except optical rotation, which has not been reported);[5e−g] MS (EI) *m*/*z* (%) 372 ($M^{\bullet+}$, 62%), 357 ($M^{\bullet+}$ − Me, 100%); HRMS (EI) 372.2565 ($C_{26}H_{32}N_2$ requires 372. 2566).

Bu-*iso*-PINDY (−)-7 (93%): mp 43−45 °C (ethyl acetate/hexane); $[\alpha]_D$ −30.4 (*c*, 1.05, CH_2Cl_2); ^{1}H NMR δ 0.62 (s, 6 H), 0.88 (t, J = 7.0 Hz, 6 H), 1.25 (d, J = 9.6 Hz, 2 H), 1.32 (s, 6 H), 1.40−1.49 (m, 10 H), 2.22−2.25 (m, 4 H), 2.28−2.33 (m, 2 H), 2.45 (dt, J = 9.7 and 5.8 Hz, 2 H), 2.66 (t, J = 5.8 Hz, 2 H), 2.97 (s, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 7.93 (d, J = 8.0 Hz, 2 H); ^{13}C NMR δ 14.6 (CH_3), 21.3 (CH_3), 23.5 (CH_2), 26.9 (CH_3), 28.9 (CH_2), 30.6 (CH_2), 32.7 (CH_2), 41.5 (C), 43.9 (CH), 44.7 (CH), 47.3 (CH), 117.7 (CH), 133.8 (CH), 141.6 (C), 154.6 (C), 160.1 (C) in accordance with the literature data reported for the opposite enantiomer (except optical rotation, which has not been reported);[5e−g] MS (EI) *m*/*z* 456 (M, 53%), 399 (M − Bu, 100%); HRMS (EI) 456.3508 ($C_{32}H_{44}N_2$ requires 456.3505).

***i*-Pr-*iso*-PINDY (−)-8** (56%): mp 50−53 °C (ethyl acetate/hexane); $[\alpha]_D$ −17.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 0.54 (s, 6 H), 0.81 (d, J = 6.8 Hz, 6 H), 1.17 (d, J = 6.8 Hz, 6 H), 1.35 (s, 6H), 1.35 (d, J = 9.6 Hz, 2 H), 2.29−2.32 (m, 2 H), 2.51 (dt, J = 9.7 and 5.8 Hz, 2 H), 2.68 (t, J = 5.8 Hz, 2 H), 2.76−2.84 (m, 2 H), 2.90−2.91 (m, 2 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.93 (d, J = 8.0 Hz, 2 H); ^{13}C NMR δ 20.6 (CH_3), 21.3 (CH_3), 22.7 (CH_3), 26.7 (CH_3), 29.7 (CH_2), 30.8 (CH_3), 41.9 (CH), 42.4 (C), 47.2 (CH), 49.6 (CH), 117.9 (CH), 133.9 (CH), 142.3 (C), 154.4 (C), 159.0 (C) in accordance with the literature data reported for the opposite enantiomer (except optical rotation, which has not been reported);[5e−g] MS (EI) *m*/*z* 428 ($M^{\bullet+}$, 13%), 385 ($M^{\bullet+}$ − *i*-Pr, 100%); HRMS (EI) 428.3191 ($C_{30}H_{40}N_2$ requires 428.31915).

20-Oximino-pregnane-5,16-dien-3β-ol Acetate (49). $NH_2OH\cdot HCl$ (3.80 g, 5.5 mmol) was added to a solution of dehydropregnenolone acetate **48** (1.50 g, 4.2 mmol) in a mixture of EtOH (10 mL), CH_2Cl_2 (5 mL) and pyridine (0.57 mL), and the mixture was set aside at room temperature for 24 h. Dichloromethane (100 mL) was then added, and the solution was extracted with brine (3 × 15 mL). The organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by flash chromatography on a silica gel column (15 × 3 cm) with petroleum ether, followed by a petroleum ether/ethyl acetate mixture (97:3) to afford pure oxime **49**[63] (1.40 g, 90%) as a white solid: ^{1}H NMR δ 0.86 (s, 3 H, 18-H), 1.02 (s, 3 H, 19-H), 1.50−1.10 (m, 4 H), 1.74−1.56 (m, 6 H), 2.00−1.87 (m, 4 H), 2.03 (s, 3 H, AcO), 2.05 (s, 3 H, 21-H), 2.41−2.21 (m, 4 H), 4.63 (m, 1 H, 3α-H), 5.41 (bd, J = 4.8 Hz, 1 H, 6-H), 6.08 (m, 1 H) in accordance with the literature.[63]

2′-Chloropyrido[17,16-b]androst-5-ene-3β-ol Acetate (51). A solution of oxime **49** (600 mg, 1.6 mmol) and $POCl_3$ (2.5 g, 16 mmol) in DMF (1.50 mL) was heated at 65 °C for 2 h while stirring. The solution was then cooled to 0 °C and quenched with ice (5 g) and aqueous saturated $NaHCO_3$ (4 mL). The mixture was extracted by CH_2Cl_2 (3 × 50 mL), the combined organic layers were washed with brine (3 × 10 mL) and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on a silica gel column (15 × 3 cm) with a petroleum ether/ethyl acetate mixture (98:2) to afford the **51** as a pale yellow solid (430 mg, 70%): mp 198−199 °C (lit.[45b] 200 °C); ^{1}H NMR δ 0.92 (s, 3H, 18-H), 1.03 (s, 3H, 19-H), 1.04−1.15 (m, 2H), 1.49−1.85 (m, 8H), 1.97 (s, 3H, AcO), 2.01 (m, 1H), 2.20−2.29 (m, 4H), 2.40 (dd, J = 14.7 and 12.3 Hz, 1H), 2.64 (dd, J = 15.0 and 6.4 Hz, 1H), 4.53 (m, 1H, 3α-H), 5.34 (bd, J = 5.2 Hz, 1H, 6-H), 6.96 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 17.5 (CH_3), 19.7 (CH_3), 20.9 (CH_2), 21.8 (CH_3), 28.1 (CH_2), 30.2 (CH_2), 31.1 (CH), 31.6 (CH_2), 33.7 (CH_2), 37.2 (CH_2), 37.3 (CH_2), 38.5 (CH_2), 46.1 (C), 50.8 (CH), 56.5 (CH), 74.1 (CH), 121.4 (CH), 122.2 (CH), 135.3 (CH), 135.4 (C), 140.6 (C), 149.4 (C), 170.8 (C), 174.3 (C) in accordance with the literature.[45b]

General Procedure for Asymmetric Allylic Oxidation Catalyzed by Cu(I) Complexes. Method A. The ligand (0.06 mmol) and $(TfO)_2Cu$ (18 mg, 0.05 mmol) were dissolved in acetone (4 mL), and the green solution 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 **52** (5 mmol) was added at the temperature indicated in Table 1, followed by a dropwise addition of *tert*-butyl peroxybenzoate (0.2 mL, 1.0 mmol). The progress of the reaction (at the temperature indicated in Table 1) was monitored by TLC (hexanes/ethyl acetate, 9:1). Disappearance of the peroxyester indicated the completion of the reaction. The solvent was evaporated 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 a silica gel column (15 × 2.5 cm) with a hexanes/ethyl acetate mixture (20:1) afforded pure allylic benzoate **53**. The yields and ee are given in Table 1. Enantiomeric purity of the products was determined by chiral HPLC as follows. **53a:** Chiralcel OD-H, hexane/isopropyl alcohol (99.8:0.2), flow rate 0.5 mL/min, t_S = 30.2 min (major), t_R = 38.3 min (minor), UV detection at 220 nm. **53b:** Chiralpak AD, hexane/isopropyl alcohol (99.6:0.4), flow rate 1 mL/min, t_R = 12.6 min (minor), t_S = 13.8 min (major), UV detection at 220 nm. **53c:** Chiralcel OJ, hexane/isopropyl alcohol (99.7:0.3), flow rate 0.5 mL/min, t_R = 23.7 min (minor), t_S = 25.7 min (major), UV detection at 220 nm.

Method B. The oxidation was performed analogously with the catalyst prepared from the ligand (0.06 mmol) and (OTf)-$Cu\cdot 0.5C_6H_6$ (12 mg, 0.05 mmol) without the use of phenylhydrazine.

General Procedure for Asymmetric Cyclopropanation Catalyzed by Cu(I) Complexes. A solution of the ligand (0.06 mmol) and $(TfO)_2Cu$ (18 mg, 0.05 mmol) in dichlo-

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romethane (5 mL) was stirred under the 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, 8.74 mmol). 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 chromatography on a silica gel column (15:2.5 cm) with hexanes/ethyl acetate (20:1). The enantiomeric purity of **55b** and **56b** was determined by chiral HPLC using Chiralcel OD-H (hexane/2-propanol 99.9:0.1, detection at λ 220 nm; **56b** flow rate 0.5 mL/min, t_R = 27.9 min, t_S = 30.4 min; **55b** flow rate 0.75 mL/min, t_S = 16.6 min, t_R = 19.3 min). The enantiomeric purity of **55a**, **55b**, and **56a** was determined by chiral GC on Supelco β-DEX 120 column (oven 100 °C for 2 min, than 1.5 °C/min to 200 °C, 10 min at that temperature; **55a** t_R = 33.51 min, t_S = 33.79 min; **56a** t_S = 31.41 min, t_R = 31.89 min; **55b** t_R = 35.90 min, t_S = 36.06 min).

Asymmetric Cyclopropanation with 2,6-di-*tert*-Butyl-4-tolyl Diazoacetate. This reaction, leading to **55c**, was carried in the same way as shown in the general procedure above but required 24 h for completion. To determine the enantiopurity of **55c**, the following procedure was employed, which involved reduction of the BHT ester group to the corresponding alcohol, followed by its conversion into the corresponding trifluoroacetate. A solution of ester **55c** (0.8 g, 2.22 mmol) in ether (10 mL) was added dropwise at room temperature to a suspension of $LiAlH_4$ (0.84 g, 22.2 mmol) in ether (10 mL). The mixture was stirred for 12 h and then quenched with $Na_2SO_4.10H_2O$ at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were washed with NH_4Cl (20 mL), dried ($MgSO_4$), and the solvent was removed in vacuo to give a brown oil. The crude product was passed through Celite using hexanes−ethyl acetate (10:1) and the filtrate was evaporated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (5 mL) and trifluoroacetic anhydride (0.53 mL, 3.78 mmol) was added at room temperature. The mixture was stirred for 90 min (until the TLC showed disappearance of the starting alcohol), water (10 mL) was then added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with NH_4Cl (20 mL) and dried with $MgSO_4$. An aliquot of that solution was analyzed by chiral GC on a Supelco β-DEX 120 column (oven 100 °C for 2 min, than 1.5 °C/min to 200 °C, 10 min at that temperature): t_R = 39.54 min, t_S = 39.86 min. ^{1}H NMR δ_H ($CDCl_3$, 400 MHz) 0.91−0.97 (m, 1H), 1.01−1.05 (m, 1H), 1.42−1.50 (m, 1H), 1.89 (dt, J = 5.1 and 8.8 Hz, 1H), 4.23−4.28 (m, 2H), 7.00 (dd, J = 1.4 and 7.6 Hz, 2H), 7.09−7.11 (m, 1H), 7.17−7.20 (dt, J = 1.6 and 7.7 Hz, 2H).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the new bipyridine ligands and key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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