JOC*Article*

New Lewis-Basic *N*-Oxides as Chiral Organocatalysts in Asymmetric Allylation of Aldehydes

Andrei V. Malkov,*[,†] Mark Bell,[†] Monica Orsini,[†,‡] Daniele Pernazza,[†,§] Antonio Massa,[†,∥] Pavel Herrmann,[†,⊥] Premji Meghani,[#] and Pavel Kočovský*[,†]

Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, U.K., and AstraZeneca R&D, Loughborough, Leics. LE11 5RH, U.K.

amalkov@chem.gla.ac.uk; p.kocovsky@chem.gla.ac.uk

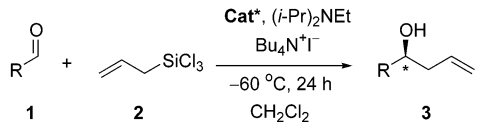
Received July 24, 2003

Allylation of aromatic and heteroaromatic aldehydes **1a**−**k** with allyltrichlorosilane **2** can be catalyzed by the new heterobidentate, terpene-derived bipyridine *N*-monoxides **4**, **6a,b**, and **8**−**11** (≤10 mol %) to afford (*S*)-(−)-**3** with high enantioselectivities (≤99% ee). The stereochemical outcome has been found to be controlled by the axial chirality of the catalyst, which in turn is determined by the central chirality of the annulated terpene units. Solvent effects on the conversion and the level of asymmetric induction have been elucidated, and MeCN has been identified as the optimal solvent for these catalysts.

Introduction

The Lewis-basic catalysis in the asymmetric Sakurai−Hosomi−Denmark allylation[1,2] of aldehydes **1** with allyltrichlorosilanes, such as **2** (Scheme 1), has now been firmly established.[2−5] Particularly good enantioselectivities (≤90% ee) and conversions have been attained with 2,2′-bipyridine-type *N*,*N*-dioxides as catalysts.[3,4,6,7]

SCHEME 1[a]



[a] For R, see Table 1.

In a preliminary communication, we have recently reported on the synthesis of new terpene-derived bipyridine monoxides **4** (PINDOX) and **6a** (Me_2PINDOX, Chart 1), which exhibited enhanced enantioselectivity in the latter reaction.[7] Herein, we present an orchestration of this theme, extended by the synthesis and application of the *iso*-PINDOX series **8**−**11**.

Results and Discussion

Catalyst Design and Synthesis. The synthesis of PINDY, the core bipyridine precursor to PINDOX (+)-**4**, was described by us earlier in detail (Scheme 2; R = H).[7−10] Thus, (+)-nopinone (+)-**13**,[8] prepared on a 20 g scale from (−)-*β*-pinene (−)-**12** either by $NaIO_4/OsO_4$

[†] University of Glasgow.
[‡] Current address: Department of Chemistry, University of Rome "La Sapienza", P. A. Moro 5, 00185 Rome, Italy.
[§] Current address: Department of Chemistry, University of Cardiff, P.O. Box 912, Cardiff CF10 3TB, U.K.
[∥] On leave from Department of Chemistry, University of Salerno, Via S. Allende, 84081 Baronissi (Salerno), Italy.
[⊥] Current address: Department of Organic Chemistry, Charles University, Albertov 2030, 12840 Prague 2, Czech Republic.
[#] AstraZeneca.
* Corresponding author.

(1) (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. For overviews, see: (b) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200. (c) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (d) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167. (e) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

(2) (a) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982. (c) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990. (d) Denmark, S. E.; Pham, S. M. *Helv. Chim. Acta* **2000**, *83*, 1846. (e) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021. (f) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488. (g) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. See also the reference section in ref 7.

(3) (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (b) Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2000**, *48*, 306. See also: (c) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 8827.

(4) (a) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799. (b) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329.

(5) For a complementary approach, relying on chiral Lewis acids, see e.g.: (a) Mikami, K.; Matsukawa, S. *Tetrahedron Lett.* **1994**, *35*, 3133. (b) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453. (c) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620. (d) Kobayashi, S.; Nishio, K. *Chem. Lett.* **1994**, 1773. (e) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351.

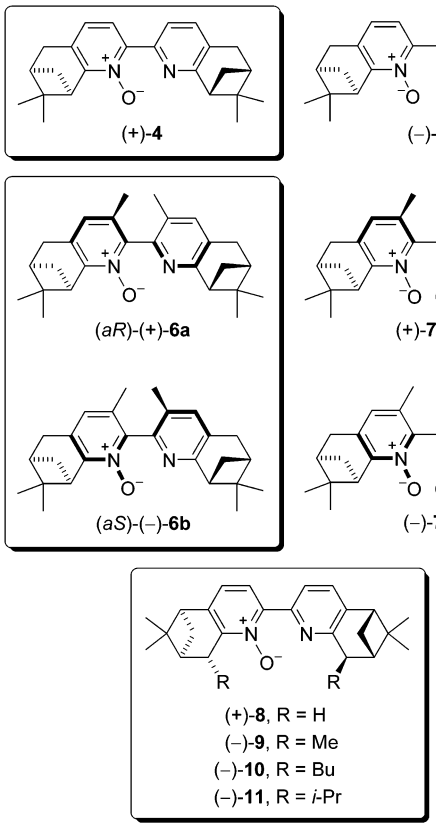
(6) For the use of other types of chiral Lewis bases, see ref 2 and the following. Phosphoramides: (a) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett.* **1996**, *37*, 5149. (b) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513. Tartrates: (c) Wang, Z.; Wang, D.; Sui, X. *Chem. Commun* **1996**, 2261. (d) Wang, D.; Wang, Z. G.; Wang, M. W.; Chen, Y. J.; Liu, L.; Zhu, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 327. (2-Pyridinyl)oxazolines (stoichiometric): (e) Angell, R. M.; Barrett, A. G. M.; Braddock, D. C.; Swallow, S.; Vickery, B. D. *Chem. Commun.* **1997**, 919.

(7) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047.

(8) For our syntheses of the core 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.; Russel, D. R.; Langer, V.; Mansfield, D. J.; Valko, M.; Kočovský, P. *Organometallics* **2001**, *20*, 673. (c) Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 4727.

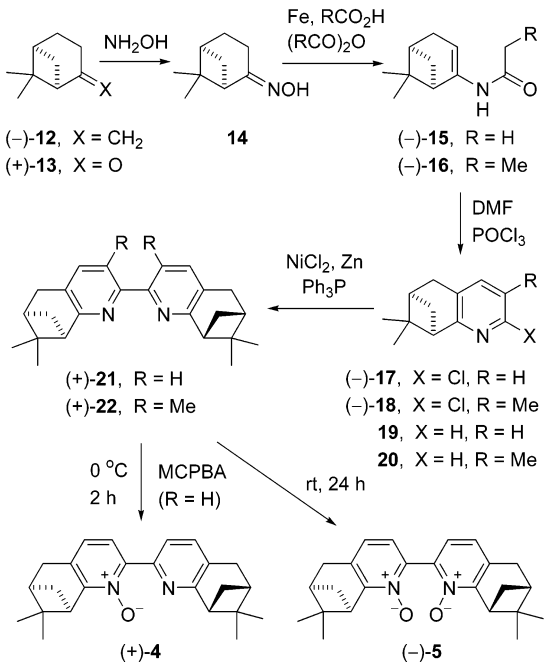
10.1021/jo035074i CCC: $25.00
Published on Web 11/11/2003

CHART 1



oxidation[8b] or by ozonolysis,[8c] was first converted into oxime **14**. Reductive acetylation of the latter oxime (Fe, Ac_2O, AcOH, rt, 10 min, 90%),[8a,b,11] afforded enamide (−)-**15**, which was converted into chloropyridine derivative (−)-**17** on Vilsmeier−Haack reaction (DMF, $POCl_3$, 0 °C, 2 h; 70%).[8a,b,12] Finally, the Ni(0)-mediated coupling of the latter chloride ($NiCl_2$, Ph_3P, Zn, DMF, 60 °C, 18 h) produced the bipyridine PINDY (+)-**21** (50%), contaminated by the reduction product **19** (32%), which was removed from the desired bipyridine by evaporation in high vacuum.[8] Oxidation of PINDY (+)-**21** with MCPBA (1 equiv) in CH_2Cl_2 at 0 °C for 45 min afforded selectively the desired *N*-monoxide (+)-**4** (96%); only traces of the corresponding *N*,*N*-dioxide (−)-**5** could be detected by TLC in the crude reaction mixture. By contrast, oxidation with 2 equiv of MCPBA, carried out at room temperature for 24 h, produced *N*,*N*-dioxide (−)-**5** (62%). The selectivity in the former case can be understood as follows: since PINDY (+)-**21** has an unrestricted rotation about the py−py axis, the molecule can assume the conformation in which the two pyridine rings are positioned in the same

SCHEME 2



plane (or near to), so that the two aromatic systems are conjugated.[13] Oxidation of one of the nitrogens automatically lowers the electron density of that pyridine ring, and this effect is conveyed through conjugation to the other pyridine ring, whose nitrogen becomes less prone to oxidation. Although this effect can hardly be expected to be strong, it appears to be sufficient to allow selective *N*-mono-oxidation under controlled conditions.

We envisaged that the free rotation about the py−py axis in **4** could be restricted by introducing two methyl groups, as in **6a**,**b**. To this end, we set out to synthesize the parent bipyridine **22**, which we planned to oxidize in a similar manner as in the case of **4**.[7] Oxime **14** was submitted to the same strategy, this time employing propionic (instead of acetic) anhydride in the reductive acylation [Fe, $(EtCO)_2O$, DMF, rt, 4 h], to obtain enamide **16** (80%). Owing to the increased steric bulk, the Vilsmeier−Haack reaction **16** → **18** required rather harsher conditions (DMF, $POCl_3$, 75 °C for 18 h, then 100 °C for 10 h; 63%), and so did the final coupling **18** → **22** [$(Ph_3P)_2$-$NiCl_2$, Zn, Me_4NI, THF, 50 °C, 72 h]. The desired bipyridine **22** (65%) thus formed was accompanied by a small amount of the reduction product **20** (as revealed by the ^1H NMR spectrum of the crude product), which was again removed by evaporation in high vacuum followed by crystallization.

Unlike with PINDY (+)-**21**, *N*-oxidation of Me_2PINDY (+)-**22** (Scheme 3) could not be controlled in favor of *N*-monoxide; with 1 equiv of MCPBA at 0 °C for 2 h, the reaction produced two atropoisomeric pairs of *N*-monoxides and *N*,*N*-dioxides (+)-**6a** (17%), (−)-**6b** (30%), (+)-**7a** (14%), and (−)-**7b** (27%), accompanied by unreacted bipyridine **22** (∼10%). While the *N*-monoxides **6a** and **6b** were readily separated from the *N*,*N*-dioxides **7a** and **7b**

(9) For similar or alternative syntheses of the core bipyridines, see: (a) Lötscher, D.; Rupprecht, S.; Stoeckli-Evans, H.; von Zelewsky, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4341. (b) Kolp, B.; Abeln, D.; Stoeckli-Evans, H.; von Zelewsky, A. *Eur. J. Inorg. Chem.* **2001**, 1207. (c) Lötscher, D.; Rupprecht, S.; Collomb, P.; Belser, P.; Viebrock, H.; von Zelewsky, A.; Burger, P. *Inorg. Chem.* **2001**, *40*, 5675.

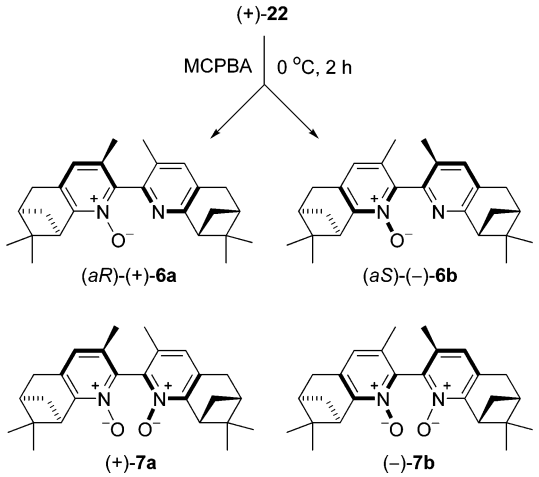
(10) For recent overviews on the synthesis of terpenoid bipyridines, see: (a) Knof, U.; von Zelewsky, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 303. (b) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. (c) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831. (d) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737.

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

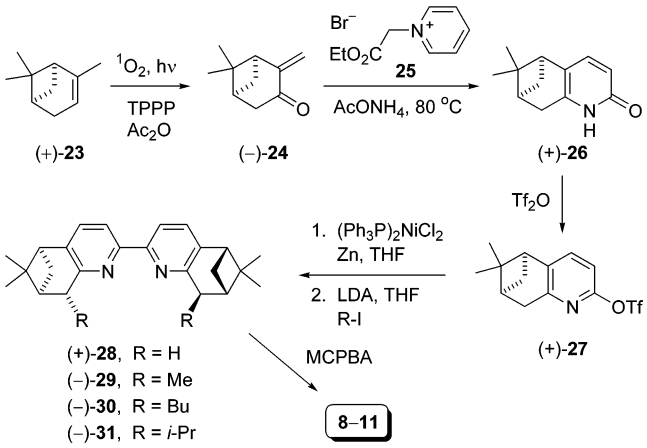
(12) An alternative, more robust synthesis of the triflate analogue of **17** was developed by us recently.[8c]

(13) Crystallographic analysis of several terpene-derived bipyridines[8b] revealed the *s-trans* disposition of the nitrogen atoms of the pyridine rings. PINDOX (+)-**4** showed bending from planarity by ∼25° in the crystal.[7]

SCHEME 3



SCHEME 4



by chromatography, separation of individual atropoisomers required more careful chromatographic technique.[14] This lack of sensitivity in the *N*-oxidation of (+)-**22** can be rationalized as follows: while in PINDY **21**, the two pyridine rings are conjugated, which is the prerequisite for selective *N*-mono-oxidation (vide supra), and this effect cannot be attained with Me_2PINDY **22**. Here, the two pyridine rings cannot assume a planar conformation about the py−py axis, so that they cannot be conjugated and therefore behave as independent units, which leads to the formation of a mono- and bisoxide mixture.

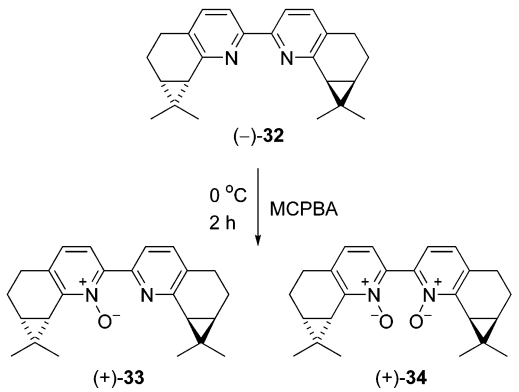
The configuration at the chiral axis of (−)-**6b** was found to be (*S*) by single-crystal X-ray analysis,[7] so that (+)-**6a** must have (*R*)-configuration. The axial configuration of dioxides (+)-**7a** and (−)-**7b** has not been rigorously established and is only assumed by analogy with the configuration of related *N*,*N*′-dioxides, e.g., (*S*)-(−)-1,1′-bisisoquinoline *N*,*N*′-dioxide[3a] and (*R*)-(+)-3,3′-bis(methoxymethyl)-6,6′-diphenyl-2,2′-bipyridine *N*,*N*′-dioxide.[4]

The synthesis of the *iso*-PINDY series **8**−**11** (Scheme 4) commenced with the ene-reaction of (+)-α-pinene with singlet oxygen[15] (+)-**23** → (−)-**24** (99%),[8c,15] followed by

(14) The synthetic impracticality of **6a** and **6b** is further enhanced by the slow isomerization of the two atropoisomers to reach a thermodynamic equilibrium (**6a**:**6b** ∼1:2) at room temperature within ca. 3 weeks in $CDCl_3$.

(15) Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135.

SCHEME 5



Kröhnke annulation[16] (−)-**24** + **25** → (+)-**26** (43%).[8c] Triflate **27**, obtained from pyridone (+)-**26** (99%), was then dimerized via the Ni-mediated coupling[8c,17] to give *iso*-PINDY (+)-**28** (51%).[18] Although this route represents a substantial short-cut with respect to the procedure developed by von Zelewsky,[9b] it has been found to work well only on a relatively small scale.[8c] For large-scale syntheses, the von Zelewsky protocol[9b] is more robust and reliable.

Deprotonation of (+)-**28**[9] with LDA, followed by the reaction with MeI, BuI, and *i*-PrI, respectively, afforded the bis-alkylated derivatives Me_2-*iso*-PINDY (−)-**29** (99%), Bu_2-*iso*-PINDY (−)-**30** (93%), and *i*-Pr_2-*iso*-PINDY (−)-**31** (56%), respectively.[9,19] Controlled oxidation of the latter bipyridines with ∼0.8 equiv of MCPBA (CH_2Cl_2, 0 °C, 45 min; 4 h for **31**) afforded the corresponding monoxides (+)-**8**, (−)-**9**, (−)-**10**, and (−)-**11** (43%, 67%, 66%, and 61%, respectively) along with the unreacted **28**−**31** (48%, 21%, 18%, and 25%, respectively) and traces of the corresponding *N*,*N*-dioxides (<5%).

Finally, to further probe the impact of the architecture of the terpene moiety on the catalyst reactivity, we utilized CANDY (−)-**32**, available from (+)-2-carene in several steps,[8c] as a precursor of CANDOX (+)-**33** (Scheme 5). Oxidation of (−)-**32** with MCPBA (CH_2Cl_2, 0 °C, 2 h) proved less selective than that in the PINDY and *iso*-PINDY series and afforded a mixture of *N*-monoxide (+)-**33** (53%) and the corresponding *N*,*N*-dioxide (+)-**34** (39%), which were separated by chromatography.

Allylation of Aldehydes with Allyltrichlorosilanes Catalyzed by Chiral Bipyridine *N*-Monoxides. Addition of allyltrichlorosilane (**2**) to benzaldehyde (**1a**) (Scheme 1), carried out in the presence of PINDOX (+)-**4**

(16) For the Kröhnke annulation, see: (a) Kröhnke, F. *Chem. Ber.* **1937**, *70*, 864. For a review, see: (b) Kröhnke, F. *Synthesis* **1976**, 1. For recent overviews of its application in the synthesis of terpenoid bipyridines, see refs 8−10.

(17) For the method of an analogous dimerization of α-chloropyridines, see refs 8 and the following: (a) Hayoz, P.; von Zelewsky, A. *Tetrahedron Lett.* **1992**, *33*, 5165. (b) Dehmlow, E. V.; Sleegers, A. *Liebigs Ann. Chem.* **1992**, *9*, 953. (c) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2881.

(18) 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 ^{1}H NMR spectrum of the bipyridine (+)-**8** thus obtained showed no peaks corresponding to the minor *meso*-diastereoisomer.[8c]

(19) (a) Slightly lower yields have previously been reported for these alkylations.[9b] (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.[8c]

TABLE 1. Allylation of Aldehydes 1 with Trichloroallylsilane 2 (Scheme 1)[a]

entry	catalyst	aldehyde	R	solvent	temp (°C)	time (h)	yield (%)[b]	% ee[c]	configuration of **3**[d]
1	(+)-**4**	**1a**	Ph	CH_2Cl_2	−90	24	67[f]	92	(*S*)-(−)
2	(+)-**4**	**1a**	Ph	CH_2Cl_2	−60	24	78[g]	90	(*S*)-(−)
3	(+)-**4**	**1a**	Ph	CH_2Cl_2	−40	6	65[g]	87	(*S*)-(−)
4	(+)-**4**[e]	**1a**	Ph	MeCN	−20	24	95[g]	84	(*S*)-(−)
5	(+)-**4**[e]	**1a**	Ph	$CHCl_3$	−20	18	47[f]	80	(*S*)-(−)
6	(+)-**4**	**1b**	*p*-Me-C_6H_4	CH_2Cl_2	−60	24	71[g]	87	(*S*)-(−)
7	(+)-**4**	**1c**	*p*-MeO-C_6H_4	CH_2Cl_2	−60	24	68[f]	87	(*S*)-(−)
8	(+)-**4**	**1d**	*p*-Cl-C_6H_4	CH_2Cl_2	−60	24	62[f]	89	(*S*)-(−)
9	(+)-**4**	**1e**	*p*-NO_2-C_6H_4	CH_2Cl_2	−60	24	58[f]	65	(*S*)-(−)
10	(+)-**4**	**1f**	PhCH=CH_2	CH_2Cl_2	−90	48	52[f]	83	(*S*)-(−)[h]
11	(+)-**4**[e]	**1f**	PhCH=CH_2	MeCN	−20	24	96[g]	53	(*S*)-(−)[h]
12	(+)-**4**[i]	**1g**	$PhCH_2CH_2$	CH_2Cl_2	−60	48	23[f]	56[j]	(*R*)-(+)
13	(+)-**4**[i]	**1g**	$PhCH_2CH_2$	CH_2Cl_2	−40	48	44[f]	49[j]	(*R*)-(+)
14	(+)-**4**	**1h**	2-furyl	CH_2Cl_2	−60	48	63[g]	85	(*S*)-(−)
15	(+)-**4**[e]	**1i**	2-thiopheneyl	CH_2Cl_2	−60	18	40[f]	83	(*S*)-(−)[k]
16	(+)-**4**[e]	**1i**	2-thiopheneyl	CH_2Cl_2	−40	18	45[f]	81	(*S*)-(−)[k]
17	(+)-**4**[e]	**1i**	2-thiopheneyl	CH_2Cl_2	−20	24	40[f]	78	(*S*)-(−)[k]
18	(+)-**4**[e]	**1i**	2-thiopheneyl	MeCN	−40	58	50[f]	83	(*S*)-(−)[k]
19	(+)-**4**[e]	**1i**	2-thiopheneyl	MeCN	−20	18	57[f]	82	(*S*)-(−)[k]
20	(−)-**5**	**1a**	Ph	CH_2Cl_2	−90	48	18[f]	41	(*R*)-(+)
21	(+)-**6a**	**1a**	Ph	CH_2Cl_2	−60	12	72[g]	98	(*S*)-(−)
22	(−)-**6b**	**1a**	Ph	CH_2Cl_2	−60	24	67[f]	82	(*R*)-(+)
23	(+)-**7a**	**1a**	Ph	CH_2Cl_2	−60	24	52[f]	14	(*R*)-(+)
24	(−)-**7b**	**1a**	Ph	CH_2Cl_2	−60	24	57[f]	10	(*S*)-(−)
25	(+)-**8**[i]	**1a**	Ph	CH_2Cl_2	−60	18	72[g]	46	(*S*)-(−)
26	(−)-**9**[i]	**1a**	Ph	CH_2Cl_2	−60	18	75[g]	88	(*S*)-(−)
27	(−)-**9**	**1a**	Ph	$CHCl_3$	−20[l]	18	73[g]	80	(*S*)-(−)
28	(−)-**9**[i]	**1f**	PhCH=CH_2	CH_2Cl_2	−60	18	75[g]	83	(*S*)-(−)
29	(−)-**10**[i]	**1a**	Ph	CH_2Cl_2	−60	18	72[g]	84	(*S*)-(−)
30	(−)-**10**	**1a**	Ph	$CHCl_3$	−20[l]	18	84[g]	80	(*S*)-(−)
31	(−)-**10**[i]	**1f**	PhCH=CH_2	CH_2Cl_2	−60	18	73[g]	84	(*S*)-(−)
32	(−)-**11**	**1a**	Ph	CH_2Cl_2	−60	18	15[f]	97	(*S*)-(−)
33	(−)-**11**	**1a**	Ph	CH_2Cl_2	−20	18	23[g]	93	(*S*)-(−)
34	(−)-**11**[e]	**1a**	Ph	$CHCl_3$	−20[l]	18	75[g]	85	(*S*)-(−)
35	(−)-**11**[e]	**1a**	Ph	MeCN	−40	18	75[g]	96	(*S*)-(−)
36	(−)-**11**[e]	**1c**	*p*-MeO-C_6H_4	MeCN	−40	18	41[f]	91	(*S*)-(−)
37	(−)-**11**[e]	**1j**	*p*-CF_3-C_6H_4	MeCN	−40	18	88[g]	96	(*S*)-(−)
38	(−)-**11**[e]	**1k**	2-naphth	MeCN	−40	18	73[g]	95	(*S*)-(−)
39	(−)-**11**	**1f**	PhCH=CH_2	CH_2Cl_2	−60	18	25[f]	96	(*S*)-(−)
40	(−)-**11**[e]	**1f**	PhCH=CH_2	MeCN	−40	18	78[g]	92	(*S*)-(−)
41	(+)-**33**[e]	**1a**	Ph	CH_2Cl_2	−60	18	90[g]	22	(*S*)-(−)

[a] The reaction was carried out at 1.0 mmol scale in CH_2Cl_2 with 1.1 equiv of **2**, in the presence of the catalyst (10 mol %) and Bu_4NI (1 equiv). [b] Isolated yield (note that some of the products are fairly volatile). [c] Determined by chiral HPLC or GC. [d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data.[3] [e] Carried out in the absence of Bu_4NI. [f] Incomplete conversion. [g] Complete conversion. [h] **3f** is dextrorotatory in Et_2O[3] and levorotatory in $CHCl_3$. [i] With 20 mol % of the catalyst. [j] The reaction is too slow at lower temperatures. [k] The configuration was assigned by Brown[32] and Cozzi[33] by analogy with their other results. [l] The components were mixed at ca. −60 °C and then allowed to warm to −20 °C, and the reaction was run for the specified period.

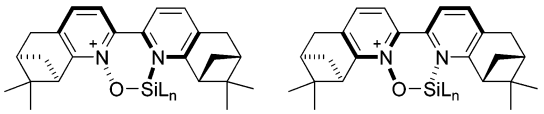
(7 mol %) as organocatalyst and Bu_4NI[20] at −90 °C, produced (*S*)-(−)-**3a** (92% ee; Table 1, entry 1). In the absence of Bu_4NI, the reaction was slower and marginally less selective.[7] Raising the temperature led to acceleration, accompanied by a very minor decrease of enantioselectivity (entries 2 and 3). Changing the solvent from CH_2Cl_2 to MeCN led to a quantitative conversion and had little effect on the enantioselectivity (entry 4). On the other hand, in chloroform, both enantioselectivity and conversion were reduced (entry 5), whereas practically no reaction was observed in THF or acetone. Marginal difference in selectivity was observed for *p*-substituted benzaldehydes **1b**−**d**, except for the *p*-nitro derivative **1e** (entries 6−9). 1- and 2-Naphthaldehydes exhibited high asymmetric induction (88% and 79% ee, respectively, at −60 °C),[7] and so did cinnamaldehyde **1f** (entries 10 and 11). However, saturated aldehydes, such as dihydrocinnamaldehyde **1g**, gave low enantioselectivities and reaction rates (entries 12 and 13), demonstrating the beneficial effect of the π-conjugation. High enantioselectivity was also attained for furan and thiophene derivatives **1h**,**i** (entries 14−19), showing the compatibility of this asymmetric reaction with a heteroaromatic system. Here again, switching from CH_2Cl_2 to MeCN as the solvent resulted in increasing the yields, whereas the enantioselectivities remained practically identical (compare entries 16 with 18, and 17 with 19).

Whereas PINDOX (+)-**4** proved to be a fairly efficient catalyst for allylation of benzaldehyde and its congeners **1a**−**i**, as shown above, the reaction catalyzed by *N*,*N*-dioxide (−)-**5** (7 mol %) at −90 °C, was found to be considerably less selective, producing the opposite enantiomer, i.e., (*R*)-(+)-**3a**, in only 41% ee (entry 20). The latter result contrasts with the report by Nakajima, who showed that when (*S*)-3,3-dimethyl-2,2′-biquinoline *N*,*N*′-dioxide was employed as catalyst, (*R*)-(+)-**3a** was obtained in 88% ee.[3a,21]

(20) For the accelerating effect of Bu_4NI, see ref 5e.

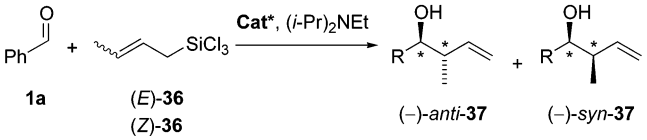
(21) Since both our and Nakajima *N*,*N*-dioxides produced the same enantiomer of alcohol **3a**, it can be assumed that the configuration at the chiral axis in the intermediate arising from (−)-**5** is the same as that in Nakajima's catalyst, i.e., (*S*).

CHART 2



(*aR*)-**35** (*aS*)-**35**

SCHEME 6



Assuming a bidentate coordination of the Lewis-basic catalyst to the allyl silane, two atropoisomeric intermediates (*aR*)-**35** and (*aS*)-**35** (Chart 2) can be considered.[22] Obviously, the configuration at the chiral axis should be controlled by the chiral centers of the terpene framework. To shed more light on the mechanism and, in particular, to establish the sense of the axial chirality in the reactive intermediate, we employed atropoisomeric Me_2PINDOX catalysts (+)-**6a** and (−)-**6b**, where the rotation about the py−py bond is restricted.

Allylation of benzaldehyde (**1a**) with allyltrichlorosilane (**2**), catalyzed by Me_2PINDOX (*aR*)-(+)-**6a**, resulted in the formation of (*S*)-(−)-**3a**, which exhibited the same configuration as that observed for the PINDOX-catalyzed reaction but with increased enantioselectivity (98% ee; entry 21). 2-Naphthaldehyde reacted similarly (91% ee).[7] By contrast, the atropoisomeric catalyst (*aS*)-(−)-**6b** induced the formation of the opposite enantiomer, i.e., (*R*)-(+)-**3a**, though with a slightly lower enantioselectivity (82% ee; entry 22). These results clearly demonstrate the decisive role of the chiral axis on the sense of the asymmetric induction. Furthermore, since (+)-**6a**, where the axial configuration is known to be (*aR*) (vide supra), gave rise to the same enantiomer of the product as that formed with (+)-**4**, the twist about the py−py axis assumed by (+)-**4** during the reaction must be the same, i.e., (*aR*). Whereas the *N*-monoxides **6a** and **6b** gave very high asymmetric induction, the corresponding atropoisomeric *N*,*N*-dioxides **7a** and **7b** proved inefficient, affording almost racemic products (entries 23 and 24).

Me_2PINDOX (+)-**6a** was found to be the most enantioselective catalyst to date. However, its preparation was not easy (vide supra) and it was configurationally unstable,[14] and thus it could hardly become a popular, shelf-type catalyst. Therefore, we endeavored to find an alternative that would exhibit similar efficiency but would be easier to synthesize and store. To this end, we focused on the *iso*-PINDOX series **8**−**11** (Chart 1), whose parent bipyridines **28**−**31** proved effective in other catalytic reactions.[8c]

The basic *iso*-PINDOX (+)-**8** did catalyze the allylation reaction but with only modest enantioselectivity (46% ee; entry 25), which was not unexpected since the chiral centers had been moved further away from the pyridine rings. By contrast, the methylated analogue (−)-**9**, where the chirality was brought closer again to the reaction center, improved the enantioselectivity considerably (up to 88% ee; entries 26−28). The dibutyl congener (−)-**10** exhibited similar efficiency, both for benzaldehyde (84% ee; entry 29) and cinnamaldehyde (84% ee; entry 31). At −20 °C in chloroform, marginal loss of enantioselectivity was observed (80% ee; entry 30). A dramatic improvement in asymmetric induction was attained with the more congested *i*-Pr_2-*iso*-PINDOX (−)-**11**: 97% ee at −60 °C in CH_2Cl_2 (entry 32), which puts this catalyst in the league of Me_2PINDOX (+)-**6**. However, the reaction rate and conversion was rather low in this case (entries 32 and 33). To amend this flaw, we explored the effect of the solvent and temperature. Thus, in chloroform at −20 °C the reaction proved to occur much faster and afforded the product in good yield, although at some expense of the enantioselectivity (85% ee; entry 34). An optimum was found in acetonitrile, where high asymmetric induction was restored at −40 °C (96% ee) and the product was obtained in good yield (entry 35). Both electron-rich *p*-methoxybenzaldehyde (**1c**) and electron-poor *p*-trifluoromethylbenzaldehyde (**1j**) exhibited high enantioselectivity (91% and 96% ee, respectively; entries 36 and 37), showing that electronic effects are unimportant in this system. 2-Naphthaldehyde (**1k**) was found to be in the same range (95% ee; entry 38). The power of the solvent effect can again be seen in the case of cinnamaldehyde (**1f**): although the reaction was slow in dichloromethane (entry 39), a much faster process was observed in acetonitrile (entry 40), both with high yield and high asymmetric induction (92% ee). Hence, the combination of *i*-Pr_2-*iso*-PINDOX (−)-**11** as catalyst and acetonitrile as solvent appears to be a well-balanced choice, characterized by good conversion rates, very high enantioselectivities (≤96% ee), and acceptable catalyst loading (7−10 mol %).[23,24] In contrast to most of these catalysts, CANDOX (+)-**33** exhibited substantially lower enantioselectivity (22% ee, entry 41).

To extend the scope of the reaction and shed further light on the mechanism, allylation of benzaldehyde with *trans*-crotyltrichlorosilane (*E*)-**36** (prepared as an 87:13 *trans*/*cis* mixture via the CuCl-catalyzed reaction of crotyl chloride with $HSiCl_3$)[6b] was briefly explored (Scheme 6 and Table 2). With PINDOX (+)-**4** as catalyst, the reaction in CH_2Cl_2 produced mainly *anti*-**37** (Table 2, entries 1 and 2). *i*-Pr_2-*iso*-PINDOX (−)-**11** behaved in a similar way, producing the *anti*-isomer practically enantiopure (entry 3) but with low conversion. Changing the solvent to acetonitrile resulted in considerable improvement of the conversion rate and diastereoselectivity (98:2) with barely any loss of the level of asymmetric induction (98% ee; entry 4). The *cis*-crotyl derivative (*Z*)-**36** (prepared as a practically pure isomer on Pd-catalyzed addition of $HSiCl_3$ to butadiene)[25] reacted much more slowly than its *trans*-isomer even in acetonitrile and afforded mainly *syn*-**37** (87% ee; entry 5).

(22) Note that chelation of Si by an *N*-monoxide catalyst, such as PINDOX, would generate a six-membered ring [as in (*aR*)-**35**/(*aS*)-**35**], which is in contrast to the *N*,*N*-dioxides, such as **5** and those reported by Nakajima[3] and Hayashi,[4] where chelation leads to a seven-membered ring.

(23) Note that, unlike with transition metal catalysts, the organocatalytic reactions currently require higher catalyst loading, with 10−20 mol % being more the rule than an exception. Reactions that work in the presence of 1 mol % or less of the catalyst are rare.[4,24]

(24) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674.

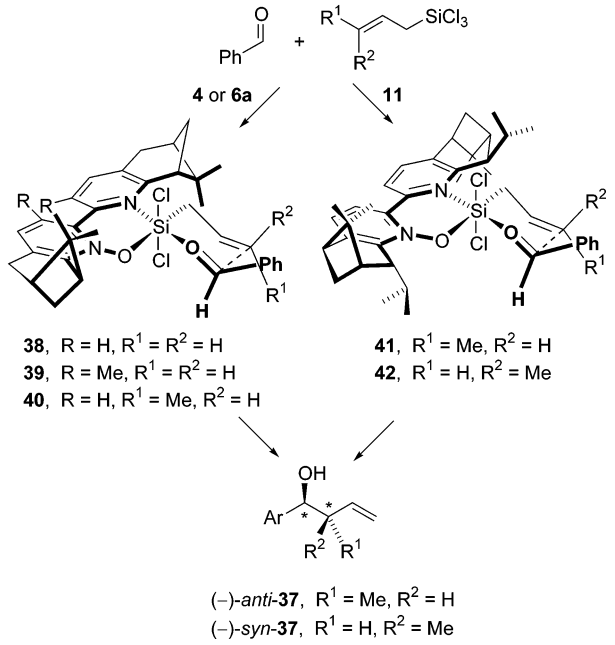
(25) Tsuji, J.; Hara, M.; Ohno, K. *Tetrahedron* **1974**, *30*, 2143.

TABLE 2. Reaction of Benzaldehyde (1a) with (*E*)- and (*Z*)-Crotyltrichlorosilane 36 (Scheme 6)[a]

entry	catalyst	crotyl	solvent	temp (°C)	time (h)	yield (%)[b]	*anti*-**37** (% ee)[c]:*syn*-**37** (% ee)[c]	configuration of **37**[d]
1	(+)-**4**	(*E*)-**36**[f]	CH_2Cl_2	−60	24	54[h]	93 (87):7	(1*S*)-(−)
2	(+)-**4**[e]	(*E*)-**36**[f]	CH_2Cl_2	−60	15	44[h]	96 (87):4	(1*S*)-(−)
3	(−)-**11**	(*E*)-**36**[f]	CH_2Cl_2	−60	18	27[i]	93 (≥99):7	(1*S*)-(−)
4	(−)-**11**[e]	(*E*)-**36**[f]	MeCN	−40	18	88[i]	98 (98):2	(1*S*)-(−)
5	(−)-**11**[e]	(*Z*)-**36**[g]	MeCN	−40	18	37[h]	10:90 (87)	(1*S*)-(−)

[a] The reaction was carried out at 1.0 mmol scale in CH_2Cl_2 with 1.1 equiv of **36**, in the presence of the catalyst (10 mol %) and Bu_4NI (1 equiv). [b] Isolated yield. [c] The *anti*/*syn* ratio was determined by GC. The enantiopurity was determined by chiral GC. [d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data.[3] [e] Carried out in the absence of Bu_4NI. [f] The *E*/*Z* ratio was 87:13. [g] Pure (*Z*)-isomer. [h] Incomplete conversion. [i] Complete conversion.

SCHEME 7

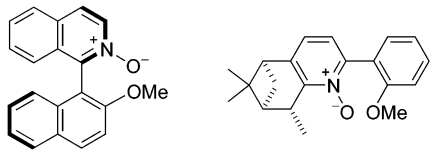


In the crotylation, noteworthy is the discrepancy between the composition of the starting crotyl derivative and the *anti*/*syn* ratio of the product. Thus, with (*E*)-**36**, which was an 87:13 mixture of geometrical isomers, the product **37** was obtained as a 93:7 to 98:2 *anti*/*syn* mixture (compare entries 1−4). Hence, the reaction of (*E*)-**36** must be kinetically preferred over that of (*Z*)-**36**, which is confirmed by the observation of a much slower reaction of pure (*Z*)-**36** (entry 5).

The high preference for the formation of *anti*-**37** from (*E*)-**36** (and *syn*-**37** from (*Z*)-**36**) is compatible with the generally accepted mechanism that involves a cyclic transition state, where the incoming aldehyde is coordinated to the Lewis-acidic site of Si (Scheme 7).[2,3,22] On the other hand, participation of the open-chain mechanism would deteriorate the homogeneity of the process, which would be manifested by a greater proportion of the opposite diastereoisomer.[24] The transition states **38**−**42**, proposed in Scheme 7, respect the stereoelectronic effect,[2,7] which dictates that the Lewis-basic *N*-oxide oxygen be positioned *trans* to the allylic group to enhance its nucleophilicity. Assuming chelation to the nitrogen of the second pyridine ring,[26] the structures **38**−**42** represent transition states that are compatible with both absolute and relative stereochemistry of the allylation.

We have shown recently that chelation to the second pyridine ring is not an absolute prerequisite to attain high enantioselectivity and good reaction rates. Thus, pyridine-type *N*-oxides lacking another pyridine ring (Chart 3) exhibited high enantioselectivity in the allylation of benzaldehyde with **2** (87% ee with **43** and 68% ee with **44**), which was attributed to arene−arene interactions as the key factor.[24,27] However, the solvent effect observed there was different from the trend shown here: in the present study, MeCN was identified as the favored solvent (higher reaction rates and excellent asymmetric induction). In our previous work, CH_2Cl_2 and $CHCl_3$ were found to be the solvents of choice, whereas MeCN proved inferior. Furthermore, the insensitivity of the present catalysts to the electronic properties of the aldehyde (Table 1, entries 36 and 37) sharply contrasts with the behavior of **43**, where the differences in enantioselectivity were dramatic (12% ee for **1c** and 96% ee for **1j**).[24] These findings show that the key factors operating in the reaction vary with the catalyst structure, and it would be premature to try to further hypothesize before more data are available.

CHART 3



(*R*)-(+)-**43** (+)-**44**

Conclusions

Whereas allylation of benzaldehyde **1a** with allytrichlorosilane **2**, catalyzed by PINDOX (+)-**4**, produced (*S*)-(−)-**3a** of 92% ee at −90 °C (Scheme 1), Me_2PINDOX (+)-**6a** gave 98% ee at −60 °C (Table 1, entries 1 and 21). The synthesis of (+)-**4** was straightforward (Scheme 2), but (+)-**6a** presented several problems, mainly associated with the poor selectivity of the final *N*-oxidation of the bipyridine precursor (Scheme 3). In this instance, bisoxidation was the main process and the *N*-monoxide was formed as a 2:1 mixture of atropoisomers, of which the minor one, (+)-**6a**, gave the highest enantioselectivities. This catalyst is further tainted by its configurational

(26) Pyridine is certainly known to be capable of coordinating Si. The propensity of various reagents to coordinate to Si and thus accelerate nucleophilic substitution decreases in the following order: F^- > *N*-methylimidazole > DMAP > HMPA > *N*-methyl-2-pyridone > pyridine *N*-oxide > Ph_3PO > 2,4-dimethylpyridine > *N*-methyl-4-pyridone > DMF > pyridine > Me_3N: (a) Bassindale, A. R.; Stout, T. *Tetrahedron Lett.* **1985**, *26*, 3403. (b) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; J. Wiley: New York, 2000; p 135.

(27) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal. A* **2003**, *196*, 179.

lability (at the chiral axis).[14] With the isomeric *N*-monoxides **8**−**11** (*iso*-PINDOX), the latter synthetic problems have been eliminated and the *N*-monoxides were formed with good selectivity (Scheme 4). The bis-*iso*-propyl derivative (−)-**11** was found to match the enantioselectivity of (+)-**6**, but the conversion rates were lower. Changing the solvent from CH_2Cl_2 to MeCN resulted in a dramatic improvement of the reaction rates, while the enantioselectivities remained high (96% ee) both for the electron-rich and electron-poor benzaldehydes (Table 1, entries 32, 35−37). Only marginal loss of enantioselectivity was observed when the reactions were carried out at the industrially acceptable temperature of −20 °C, rather than at the most common −90 or −60 °C. Stereoelectronically controlled *O*,*N*-chelation of the silicon by the catalyst and cyclic transitions states (Scheme 7) have been proposed to rationalize both absolute and relative stereochemistry of allylation and crotylation. A cyclic transition state is compatible with the stereochemical outcome.

Experimental Section

Starting Materials. (−)-Pinocarvone (−)-**24** was obtained on a 40 g scale from (+)-α-pinene (+)-**23** via the photochemical oxidation (99%) according to the Mihelich procedure.[15] The Kröhnke salt **25** was prepared from *tert*-butyl α-bromoacetate and pyridine by refluxing in ethyl acetate in the same manner as the corresponding ethyl ester.[8c,16] The trichlorosilyl enol ethers were prepared according to the literature procedures.[28]

(6*R*, 6′*R*, 8*R*, 8′*R*)-(+)-5, 5′, 6, 6′, 7, 7′, 8, 8′- Octahydro-6,6′,7,7′-tetramethylbis(6,8-methanoquinoline) *N*-Monoxide (+)-(4). *m*-Chloroperoxybenzoic acid (70%, 167 mg, 0.68 mmol) was added portion-wise to a solution of (+)-PINDY[8,9a,c] (+)-**21** (233 mg, 0.68 mmol) in dichloromethane (5 mL) at 0 °C, and the mixture was stirred at this temperature for 45 min The reaction mixture was washed successively with saturated $NaHCO_3$ (3 × 10 mL) and brine (10 mL). After drying over Na_2SO_4, the solvent was evaporated in vacuo. The resulting solid was purified by column chromatography on silica gel (10 × 2.5 cm; ethyl acetate/methanol, 25:1) to give pure (+)-**4** as a pale yellow solid (235 mg, 96%): mp 202−204 °C (toluene); $[\alpha]_D$ +56.0 (*c* 0.78, $CHCl_3$); ^{1}H NMR δ 0.69 (s, 3 H), 0.72 (s, 3H), 1.30 (d, J = 9.9 Hz, 1 H), 1.33 (d, J = 9.7 Hz, 1 H), 1.43 (s, 3 H), 1.47 (s, 3 H), 2.31−2.36 (m, 2 H), 2.99 (m, 4 H), 3.04 (t, J = 5.6 Hz, 1 H), 4.14 (t, J = 5.6 Hz, 1 H), 7.13 (d, J = 8.0 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 8.63 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (62.9 MHz) δ 21.30 (Me), 21.33 (Me), 25.8 (Me), 26.0 (Me), 30.4 (CH_2), 30.9 (CH_2), 31.1 (CH_2), 31.5 (CH_2), 39.1 (C), 39.2 (C), 39.8 (CH), 40.1 (CH), 40.3 (CH), 50.4 (CH), 123.3 (CH), 124.4 (CH), 125.5 (CH), 130.7 (C), 132.7 (C), 135.0 (CH), 145.1 (C), 146.6 (C), 157.1 (C), 166.5 (C); HRMS (EI) 360.2198 ($C_{24}H_{28}N_2O$ requires 360.2202).

(6*R*, 6′*R*, 8*R*, 8′*R*)-(−)-5, 5′, 6, 6′, 7, 7′, 8, 8′- Octahydro-6,6′,7,7′-tetramethylbis(6,8-methanoquinoline) *N*,*N*′-Dioxide (−)-(5). *m*-Chloroperoxybenzoic acid (70%, 160 mg, 0.64 mmol) was added portion-wise to a solution of (+)-PINDY[8,9a,c] (+)-**21** (100 mg, 0.29 mmol) in dichloromethane (3 mL) at 0 °C, and the mixture was stirred at room temperature for 24 h. The reaction mixture was washed successively with saturated $NaHCO_3$ (3 × 10 mL) and brine (10 mL). After drying over Na_2SO_4, the solvent was evaporated in vacuo. The resulting solid was purified by column chromatography on silica gel (10 × 2.5 cm; ethyl acetate/methanol, 5:1) to give pure (−)-**5** as a pale yellow solid (68 mg, 62%): mp 232−234 °C (ethyl acetate); $[\alpha]_D$ −22.4 (*c* 0.78, $CHCl_3$); ^{1}H NMR δ 0.77 (s, 6 H), 1.31 (d, J = 9.9 Hz, 2 H), 1.44 (s, 6 H), 2.29−2.33 (m, 2 H), 2.71−2.76 (m, 2 H), 3.01 (m, 4 H), 4.08 (t, J = 5.6 Hz, 1 H), 7.08 (d, J = 7.9 Hz, 1 H), 7.28 (d, J = 7.9 Hz, 1 H); ^{13}C NMR (62.9 MHz) δ 21.3 (Me), 25.7 (Me), 30.2 (CH_2), 31.6 (CH_2), 39.1 (C), 39.8 (CH), 40.1 (CH), 124.4 (CH), 124.5 (CH), 134.1 (C), 140.8(C), 156.0 (C); HRMS (EI) 376.2154 ($C_{24}H_{28}N_2O_2$ requires 376.2151).

Oxidation of (6*R*,6′*R*,8*R*,8′*R*)-(+)-5,5′,6,6′,7,7′,8,8′-Octahydro-3,3′,7,7,7′,7′-hexamethylbi(6,8-methanoquinoline) (+)-(22) with MCPBA. *m*-Chloroperoxybenzoic acid (70%, 93 mg, 0.38 mmol) was added portion-wise to a stirred solution of (+)-**22** (141 mg, 0.38 mmol) in dichloromethane (5 mL) at 0 °C, and the stirring was continued at this temperature for a further 2 h. Then the mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with dichloromethane (2 × 15 mL), and the organic layer was washed with $NaHCO_3$ (2 × 15 mL), dried with Na_2SO_4, and concentrated in vacuo. Flash chromatography of the residue on silica gel (15 g) with a petroleum ether/ethyl acetate mixture (1:1), followed by ethyl acetate/methanol (20:1), furnished the unreacted starting material (20 mg) and the diastereoisomeric mixtures of, respectively, the *N*-monoxides and the *N*,*N*′-dioxides as colorless oils (50 mg). The latter mixture was then placed on a preparative silica gel plate (Merck, 60 F_{254}) and eluted using a mixture of petroleum ether, diethyl ether, and acetone (8:1:1) to afford, in the following order, monoxide (+)-**6a** (25 mg, 17%), monoxide (−)-**6b** (44 mg, 30%), bisoxide (−)-**7b** (40 mg, 27%), and bisoxide (+)-**7a** (21 mg, 14%) as white, crystalline solids.

(*R*,6*R*,6′*R*,8*R*,8′*R*)-(+)-5,5′,6,6′,7,7′,8,8′-Octahydro-3,3′,7,7,7′,7′-hexamethylbi(6,8-methanoquinoline)-1-oxide (*aR*)-(+)-(6a): mp 207−209 °C (ethyl acetate-methanol); $[\alpha]_D$ +28.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 0.66 (s, 3 H), 0.67 (s, 3 H), 1.1−1.2 (m, 2 H), 1.32 (s, 3 H), 1.35 (s, 3 H), 2.23 (m, 2 H), 2.66 (m, 2H), 2.90 (m, 5 H), 3.92 (t, J = 5.6 Hz, 1 H), 6.89 (s, 1 H), 7.28 (s, 1 H); HRMS (EI) 388.5529 ($C_{26}H_{32}ON_2$ requires 388.5518).

(*S*,6*R*,6′*R*,8*R*,8′*R*)-(−)-5,5′,6,6′,7,7′,8,8′-Octahydro-3,3′,7,7,7′,7′-hexamethylbi(6,8-methanoquinoline)-1-oxide (*aS*)-(−)-(6b): mp 223−225 °C (ethyl acetate/methanol; this material spontaneously recrystallizes at 150−180 °C before reaching the mp); $[\alpha]_D$ −44.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.67 (s, 3 H), 0.78 (s, 3 H), 1.24 (d, J = 9.9 Hz, 1 H), 1.42 (s, 3 H), 1.44 (d, J = 9.9 Hz, 1 H), 1.47 (s, 3 H), 2.32 (m, 2 H), 2.71 (m, 2 H), 2.98 (m, 5 H), 4.01 (t, J = 5.6 Hz, 1 H), 6.97 (s, 1H), 7.36 (s, 1 H); ^{13}C NMR δ 17.65 (CH_3), 18.64 (CH_3), 21.47 (CH_3), 21.53 (CH_3), 26.12 (CH_3), 26.45 (CH_3), 30.88 (CH_2), 31.06 (CH_2), 31.57 (CH_2), 31.74 (CH_2), 39.50 (C), 39.62 (C), 40.39 (CH), 40.48 (CH), 40.53 (CH), 50.21 (CH), 127.61 (CH), 130.31 (C), 130.83 (C), 132.34 (2 × C), 137.47 (CH), 147.38 (C), 153.35 (2 × C), 164.15 (C); HRMS (EI) 388.5529 ($C_{26}H_{32}ON_2$ requires 388.5518).

(ξ,6*R*,6′*R*,8*R*,8′*R*)-(+)-5,5′,6,6′,7,7′,8,8′-Octahydro-3,3′,7,7,7′,7′-hexamethylbi(6,8-methanoquinoline)-1,1′-dioxide (+)-(7a): mp 229−231 °C (ethyl acetate/methanol); $[\alpha]_D$ +7.4 (*c* 0.2, $CHCl_3$); ^{1}H NMR δ 0.64 (s, 6 H), 1.28 (d, J = 9.9 Hz, 4 H), 1.37 (s, 6 H), 1.95 (s, 6 H), 2.21 (m, 2 H), 2.6−2.7 (m, 2 H), 2.8−2.9 (m, 4 H), 3.86−3.92 (q, J = 5.6 Hz, 2 H), 6.90 (s, 2 H); ^{13}C NMR δ 17.85 (2 × CH_3), 18.45 (2 × CH), 21.46 (2 × CH_3), 26.09 (2 × CH_3), 30.59 (2 × CH_2), 31.82 (2 × CH_2), 40.22 (2 × CH), 40.29 (2 × CH), 40.44 (2 × CH), 127.05 (2 × CH), 133.33 (2 × C), 136.85 (2 × C), 139.07 (2 × C), 153.43 (2 × C); HRMS (EI) 404.5523 ($C_{26}H_{32}O_2N_2$ requires 404.5508).

(ξ,6*R*,6′*R*,8*R*,8′*R*)-(−)-5,5′,6,6′,7,7′,8,8′-Octahydro-3,3′,7,7,7′,7′-hexamethylbi(6,8-methanoquinoline)-1,1′-dioxide (−)-(7b): mp 233−235 °C (ethyl acetate/methanol); $[\alpha]_D$ −15.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 0.78 (s, 6 H), 1.25 (m, 4 H), 1.37 (s, 6 H), 1.91 (m, 2 H), 2.05 (s, 6 H), 2.29 (m, 2 H), 2.73 (m, 2 H), 2.97 (m, 4 H), 3.98 (t, J = 5.6 Hz, 2 H), 6.96 (s, 2 H); ^{13}C NMR δ 14.58 (2 × CH), 18.25 (2 × CH_3), 21.71 (2 × CH_3), 26.12 (2 × CH_3), 30.89 (2 × CH_2), 31.84 (2 × CH_2), 40.33 (2 × CH), 40.45 (2 × CH), 62.23 (2 × C), 126.99 (2 × CH), 133.09 (2 × C), 133.24 (2 × C), 140.08 (2 × C), 153.87 (2 × C); HRMS (EI) 404.5501 ($C_{26}H_{32}O_2N_2$ requires 404.5508).

(28) Denmark, S. E.; Stavenger, R. A.; Winter, S. B. D.; Wong, K.-T.; Barsanti, P. A. *J. Org. Chem.* **1998**, *63*, 9517.

***N*-Oxidation of *iso*-PINDY Derivatives 28−31.** *m*-Chloroperoxybenzoic acid (70%, 167 mg, 0.68 mmol) was added portion-wise to a solution of the respective *iso*-PINDY derivative **28**−**31**[8c,9,29,30] (0.68 mmol) in dichloromethane (5 mL) at 0 °C, and the mixture was stirred at this temperature for 45 min (**28**−**30**) or for 4 h (**31**). The reaction mixture was then diluted with ether and washed successively with saturated $NaHCO_3$ (3 × 10 mL) and brine (10 mL). After drying over Na_2SO_4, the solvent was evaporated in vacuo. The resulting solid was purified by column chromatography on silica gel (10 × 2.5 cm) with a mixture of petroleum ether and ethyl acetate (10:1) to elute the unreacted starting material, followed by ethyl acetate, to give pure **8**−**11**, respectively as pale yellow solids.

***iso*-PINDOX (+)-8** (43%): mp 171−172 °C (ethyl acetate/hexane); $[\alpha]_D$ +102.3 (*c* 1.03, CH_2Cl_2); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 0.69 (s, 3H), 0.71 (s, 3H), 1.31 (d, *J* = 9.6 Hz, 2H), 1.43 (s, 6H), 2.37−2.42 (m, 1H) 2.44−2.48 (m, 1H) 2.71 (dt, *J* = 9.6 and 5.8 Hz, 2 H), 2.82 (dt, *J* = 9.6 and 5.8 Hz, 2 H), 3.15−3.22 (m, 4 H), 6.98 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 8.53 (d, *J* = 7.8 Hz, 1H); ^{13}C NM δ ($CDCl_3$, 100 MHz) 21.4 (CH_3), 21.7 (CH_3), 26.2 (CH_3), 26.4 (CH_3), 31.5 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 37.0 (CH_2), 39.7 (CH), 39.9 (C), 40.6 (CH), 46.5 (CH), 46.8 (CH), 122.6 (CH), 123.7 (CH) 124.7 (CH), 133.1 (CH), 142.6 (C), 144.9 (C), 146.1 (C), 147.0 (C), 147.8 (C), 156.8 (C); MS (EI) *m*/*z* 360 (M, 100%), 344 ($M^{\bullet+}$ − CH_3 61%); HRMS (EI) 360.2203 ($C_{24}H_{28}ON_2$ requires 360.2202).

Me-*iso*-PINDOX (−)-9 (66%): mp 166−169 °C (ethyl acetate−hexane); $[\alpha]_D$ −4.4 (*c* 1.05, CH_2Cl_2); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 0.53 (d, *J* = 9.8 Hz, 6H), 0.85 (m, 1H), 1.13 (m, 1H) 1.29 (d, *J* = 6.6 Hz, 3H), 1.36 (s, 6H), 1.48 (d, *J* = 6.6 Hz, 3H), 2.07−2.11 (m, 2H) 2.45 (dt, *J* = 9.6 and 5.8 Hz, 2 H), 2.71 (t, *J* = 5.8 Hz, 2 H), 3.15 (dq, *J* = 7.2 and 2.4 Hz, 1 H), 3.39 (dq, *J* = 7.2 and 2.4 Hz, 1 H), 6.90 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 15.3 (CH_3), 18.7 (CH_3), 20.9 (CH_3), 21.3 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 28.6 (CH_2), 28.9 (CH_2), 35.3 (CH), 39.2 (CH), 41.8 (C), 42.0 (C), 47.2 (CH), 47.3 (CH), 47.5 (CH), 47.9 (CH), 122.7 (CH), 123.5 (CH), 124.9 (CH), 132.8 (CH), 142.4 (C), 144.9 (C), 146.9 (C), 147.8 (C), 150.5 (C), 160.6 (C); MS (EI) *m*/*z* 388 ($M^{\bullet+}$, 15%), 372 [$M^{\bullet+}$ − O, 20%], 357 [$M^{\bullet+}$ − (O + Me), 32%]; HRMS (EI) 388.2514 ($C_{26}H_{32}ON_2$ requires 388.2515).

Bu-*iso*-PINDOX (−)-10 (67%): mp 51−53 °C (ethyl acetate−hexane); $[\alpha]_D$ −22.6 (*c* 1.02, CH_2Cl_2); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 0.53 (s, 3H), 0.57 (s, 3H), 0.81−0.88 (m, 6H), 1.15 (m, 2H), 1.36−1.39 (m, 12H), 1.49 (s, 6H), 2.20 (m, 1H), 2.25−2.28 (m, 1H), 2.30−2.32 (m, 1H), 2.47 (dt, *J* = 9.5 and 5.0 Hz, 2H), 2.65 (m, 1H) 2.72 (t, *J* = 5.0 Hz, 2 H), 2.95 (d, *J* = 9.5 Hz, 1H) 3.10 (m, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 14.6 (CH_3), 21.0 (CH_3), 21.3 (CH_3), 21.4 (CH_3), 23.2 (CH_2), 23.4 (CH_2), 26.4 (CH_3), 26.8 (CH_3), 28.0 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 30.4 (CH_2), 30.6 (CH_2), 32.7 (CH_2), 40.8 (CH), 41.3 (C), 41.4 (C), 43.7 (CH), 44.3 (CH), 44.6 (CH), 47.1 (CH), 47.2 (CH), 122.5 (CH), 122.7 (CH) 124.8 (CH), 132.8 (CH), 142.3 (C), 144.7 (C), 147.0 (C), 147.7 (C), 150.0 (C), 160.2 (C); MS (EI) *m*/*z* 472 ($M^{\bullet+}$, 16%), 415 (M − Bu, 72%); HRMS (EI) 472.3454 ($C_{32}H_{44}ON_2$ requires 472.3454).

***i*-Pr-*iso*-PINDOX (−)-11** (61%): mp 69−71 °C (ethyl acetate/hexane); $[\alpha]_D$ −21.9 (*c* 1.00, CH_2Cl_2); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 0.51 (s, 3H), 0.55 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.54−1.57 (m, 2H) 2.28−2.33 (m, 2H) 2.44−2.54 (m, 2H) 2.67−2.71 (m, 2H), 2.75−2.81 (m, 1H), 2.89−2.90 (m, 1H), 3.07−3.15 (m, 1H), 3.19 (t, *J* = 1.6 Hz, 1 H), 6.86 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 8.58 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 20.4 (CH_3), 21.0 (CH_3), 21.3 (CH_3), 21.4 (CH_3), 22.1 (CH_3), 22.6 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 28.6 (CH_3), 28.8 (CH_2), 29.7 (CH_2), 30.7 (CH_3), 41.5 (CH), 42.3 (C), 42.8 (C), 43.7 (CH), 45.9 (CH), 46.9 (C), 47.1 (CH), 49.5 (CH), 122.5 (CH), 123.4 (CH) 124.8 (CH), 132.9 (CH), 142.9 (C), 145.3 (C), 147.0 (C), 147.7 (C), 149.6 (C), 159.0 (C); MS (EI) *m*/*z* 444 ($M^{\bullet+}$, 8%), 429 ($M^{+\bullet}$ − CH_3, 19%); HRMS (EI) 467.3041 ($C_{30}H_{40}ON_2Na$ requires 467.3038).

(4*S*,6*R*)-(−)-5,5-Dimethyl-4,6-methano-1-propionamidocyclohexene (−)-(16). Iron powder (12.5 g, 224 mmol) was added to a stirred solution of nopinone oxime **14**[8] (3.8 g, 25 mmol) and propionic anhydride (25 mL, 195 mmol) in DMF (60 mL). Then, a few drops of chlorotrimethylsilane were added under nitrogen to initiate the reaction, and the mixture was stirred at room temperature for 4 h (until TLC showed that the reaction was complete). The reaction mixture was diluted with ether, and the solid was filtered off through a short column of Celite. The filtrate was washed with NaOH (20% aqueous solution), dried with $NaSO_4$, and concentrated in vacuo to afford sufficiently pure (−)-**16**, as a yellow oil (3.9 g, 80%): $[\alpha]_D$ −40.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.91 (s, 3 H), 1.18 (t, *J* = 7.8 Hz, 3 H), 1.29 (s, 3 H), 1.36 (d, *J* = 8.7 Hz, 1 H), 2.02 (dt, *J* = 6.3 Hz, *J* = 1.6 Hz, 1 H), 2.10 (m, 1 H), 2.24 (q, *J* = 7.8 Hz, 2 H), 2.27−2.44 (m, 2 H), 5.93 (s, 1 H), 6.45 (br s, 1 H); HRMS (EI) 193.2890 ($C_{12}H_{19}ON$ requires 193.2881).

(6*R*,8*R*)-(−)-2-Chloro-5,6,7,8-tetrahydro-3,7,7-trimethyl-[6,8-methanoquinoline] (−)-(18). Dimethylformamide (4.9 g, 80 mmol) was added dropwise to stirred phosphoryl chloride (27.5 g, 180 mmol) at 0 °C, followed by a solution of the enamide (−)-**16** (5.0 g, 25.9 mmol) in dimethylformamide (5 mL). After being stirred for 2 h at room temperature, the mixture was heated at 75 °C for 18 h and at 100 °C for a further 10 h. The resulting dark brown solution was poured into ice−water (500 mL) to give a clear orange solution, which was basified with aqueous 40% NaOH and extracted with dichloromethane (3 × 200 mL), and the extract was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (120 g), using hexane and then a hexanes/ethyl acetate mixture (9:1), to give (−)-**18** as a yellowish oil: 3.6 g (63%): $[\alpha]_D$ −17.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.65 (s, 3 H), 1.20 (d, *J* = 9.6 Hz, 1 H), 1.39 (s, 3 H), 2.04 (m, 1 H), 2.30 (s, 3 H), 2.62 (dt, *J* = 8.4 Hz, *J* = 8.0 Hz, 1 H), 2.87 (s, 2 H), 2.94 (t, *J* = 6.0 Hz, 1H), 7.23 (s, 2 H); HRMS (EI) 221.7297 ($C_{13}H_{16}NCl$ requires 221.7294).

(6*R*,6′*R*,8*R*,8′*R*)-(+)-5,5′,6,6′,7,7′,8,8′-Octahydro-3,3′,7,7,7′,7′-hexamethylbi(6,8-methanoquinoline) (+)-(22). A 50-mL, round-bottomed, two-necked flask containing a magnetic stirring bar was charged with $NiCl_2(PPh_3)_2$ (1.077 g, 1.65 mmol), zinc dust (0.54 g, 8.25 mmol), and Me_4NI (1.658 g, 8.25 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 (15 mL) was added via syringe through the septum, and the mixture was stirred at room temperature. After the dark green catalyst had formed (30 min), a nitrogen-purged solution of (−)-**18** (1.215 g, 5.5 mmol) in THF (5 mL) was added via syringe. After stirring at 50 °C for 72 h, the mixture was poured into 2 M aqueous ammonia (30 mL). Chloroform (100 mL) was added, and the precipitate was removed by filtration. The aqueous layer was extracted with chloroform (2 × 50 mL). 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 (60 g), using a hexanes/ethyl acetate mixture (9:1) and then ethyl acetate, to give (+)-**22** as a colorless viscous oil (0.69 g, 65%) that crystallized on standing: mp 127−129 °C (hexanes/ethyl acetate); $[\alpha]_D$ +72.3 (*c* 0.7,

(29) A synthesis of the enantiomer of **28** was first described by us;[8] it relied on the conversion of pyridone (−)-**26** into the corresponding chloride (40%), followed by Ni(0)-catalyzed coupling (90%). An alternative and rather lengthy procedure has been mentioned several times in the literature,[9] but the experimental procedures have not been revealed.

(30) Enantiomers of **29**−**31** have been reported earlier but no optical rotations had been given.[9c]

$CHCl_3$); ^1H NMR, δ 0.61 (s, 6 H), 1.20 (d, J = 9.6 Hz, 2 H), 1.31 (s, 6 H), 2.01 (s, 6 H), 2.23 (m, 2 H), 2.60 (dt, J = 9.6 Hz, J = 5.8 Hz, 2H), 2.85 (m, 4 H), 2.93 (t, J = 5.5 Hz, 2 H), 7.24 (s, 2 H); ^{13}C NMR δ 18.62 (2 × CH_3), 21.67 (2 × CH_3), 26.45 (2 × CH_3), 31.40 (4 × CH_2), 40.56 (2 × CH), 50.18 (2 × CH), 60.73 (2 × C), 129.19 (2 × C), 129.31 (2 × C), 137.95 (2 × CH), 153.50 (2 × C), 163.2 (2 × C); HRMS (EI) 372.5535 ($C_{26}H_{32}N_2$ requires 372.5528).

(7*R*,7′*R*,8*R*,8′*R*)-(+)-5,5′,6,6′,7,7′,8,8′-Octahydro-6,6′,7,7′-tetramethylbi(7,8-methanoquinoline)-*N*-oxide (+)-33 (CANDOX). *m*-Chloroperoxybenzoic acid (170 mg, 0.70 mmol) was added portion-wise to a stirred solution of CANDY (−)-**32**[8c] (135 mg, 0.39 mmol) in dichloromethane (15 mL) at 0 °C, and the stirring was continued at this temperature for a further 2 h. The mixture was then poured into a saturated aqueous $NaHCO_3$ (15 mL), and the product was extracted into dichloromethane (2 × 15 mL). The organic layer was washed with $NaHCO_3$ (2 × 15 mL), dried with Na_2SO_4, and concentrated in vacuo. Flash chromatography of the residue on silica gel (15 g) with a petroleum ether/ethyl acetate mixture (1:1) furnished *N*-mono-oxide (+)-**33** (74 mg, 53%) as a white, crystalline solid. Continued elution with an ethyl acetate/methanol mixture (20:1) furnished *N*,*N*′-dioxide (+)-**34** (57 mg, 39%), also as a white crystalline solid. Data for (+)-**33**: mp 118−120 °C (petroleum ether); $[\alpha]_D$ +25.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.71 (s, 3 H), 0.82 (s, 3 H), 1.17 (s, 3 H), 1.28 (s, 3 H), 1.39 (dt, J = 8.7 and 5.4 Hz, 1 H), 1.49−1.56 (m, 1 H), 1.81−1.87 (m, 1 H), 1.91−2.01 (m, 2 H), 1.95 (d, J = 8.4 Hz, 1 H), 2.00 (d, J = 8.3 Hz, 1 H), 2.11−2.18 (m, 1 H), 2.44−2.54 (m, 2 H), 2.69−2.79 (m, 2 H), 6.98 (d, J = 8.1 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 8.43 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.89 (CH_3), 16.8 (CH_3), 18.8 (CH_2), 20.21 (CH_2), 23.28 (CH_3), 24.43 (CH), 25.56 (CH), 25.70 (C), 26.17 (C), 28.17 (CH), 28.36 (CH_2), 29.06 (CH), 29.54 (CH_2), 29.62 (CH_3), 122.66 (CH), 124.28 (CH), 125.14 (CH), 132.26 (C), 135.95 (CH), 136.87 (C), 138.66 (C), 147.53 (C), 148.59 (C), 156.86 (C); IR ($CHCl_3$) ν 3027, 2965, 1528, 1486, 1452, 1321, 1257, 718 cm^{-1}; HRMS (EI) 360.2196 ($C_{24}H_{28}N_2O$ requires 360.2202).

(7*R*,7′*R*,8*R*,8′*R*)-(+)-5,5′,6,6′,7,7′,8,8′-Octahydro-6,6′,7,7′-tetramethylbi(7,8-methanoquinoline)-(+)-*N*,*N*′-dioxide (+)-(34). Obtained by continued elution after the isolation of (+)-**33** (CANDOX). Data for (+)-**34**: mp 210−212 °C (petroleum ether); $[\alpha]_D$ +13.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74 (s, 6 H), 1.22 (s, 6 H), 1.37 (dt, J = 5.4 and 5.3 Hz, 2 H), 1.50−1.60 (m, 2 H), 2.08 (d, J = 8.3 Hz, 2 H), 2.11−2.17 (m, 2 H), 2.47 (dt, J = 8.5 and 5.0 Hz, 2 H), 2.73 (m, 2 H), 7.08 (d, J = 7.9 Hz, 2 H), 7.28 (d, J = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.07 (2 × CH_3), 20.05 (2 × CH_2), 22.98 (2 × CH), 24.46 (2 × CH), 26.43 (2 × C), 28.12 (2 × CH_3), 29.41 (2 × CH_2), 124.01 (2 × CH), 124.36 (2 × CH), 138.04 (2 × C), 142.08 (2 × C), 148.85 (2 × C); IR ($CHCl_3$) ν 3028, 2934, 1427, 1221, 727, 668 cm^{-1}; HRMS (EI) 376.2144 ($C_{24}H_{28}N_2O_2$ requires 376.2151).

General Procedure for Reaction of Allyltrichlorosilane with Aldehydes. Allyltrichlorosilane (75 μL, 0.47 mmol) was added to a solution of the catalyst (**4**, **6a,** or **8**−**11**) (0.04 mmol), diisopropylethylamine (0.35 mL, 2 mmol), tetra-*n*-butylammonium iodide (175.4 mg, 0.47 mmol), and aldehyde (0.4 mmol) in dichloromethane (2 mL) under nitrogen at −60 °C (or −90 or −40 °C). The mixture was stirred at the same temperature until completion (TLC monitoring; see Table 1 for the reaction time) and then quenched with aqueous saturated $NaHCO_3$ (1 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel [15 × 2 cm; petroleum ether/ethyl acetate, 95:5]. Products **3** were either identical with the authentic samples[7] or their NMR data corresponded to those published.[3]

(*S*)-(−)-1-Phenyl-but-3-en-1-ol (*S*)-(−)-(3a): $[\alpha]_D$ −61.2 (*c* 1.05, $CHCl_3$); ^1H NMR δ 2.06 (br s, 1 H), 2.48−2.56 (m, 2 H), 4.77 (dd, J = 7.7, 5.2 Hz, 1 H), 5.15−5.22 (m, 2 H), 5.79−5.89 (m, 1 H), 7.28−7.39 (m, 5 H); chiral GC (Supelco β-DEX 120 column, oven 100 °C for 5 min, then 1 deg/min to 200 °C, 10 min at that temperature) showed 92% ee (t_R = 31.06 min, t_S = 31.49 min).

(*S*)-(−)-1-(4-Methyl-phenyl)-but-3-en-1-ol (*S*)-(−)-(3b): $[\alpha]_D$ −31.1 (*c* 0.9, $CHCl_3$); ^1H NMR δ 1.62 (br s, 1 H), 2.34 (s, 3 H), 2.45−2.54 (m, 2 H), 4.70 (t, J = 7.0, 1 H), 5.11−5.18 (m, 2 H), 5.75−5.86 (m, 1 H), 7.16 (d, J = 7.4, 2 H), 7.25 (d, J = 7.4, 2 H); chiral GC (Supelco β-DEX 120 column, oven 100 °C for 5 min, then 1 deg/min to 200 °C, 10 min at that temperature) showed 87% ee (t_R = 37.53 min, t_S = 38.26 min).

(*S*)-(−)-1-(4-Methoxy-phenyl)-but-3-en-1-ol (*S*)-(−)-(3c): $[\alpha]_D$ −48.0 (*c* 1.0, $CHCl_3$); ^1H NMR δ 2.01 (br s, 1 H), 2.49 (t, J = 8.0, 2 H), 3.80 (s, 3 H), 4.68 (t, J = 6.5, 1 H), 5.10−5.17 (m, 2 H), 5.74−5.84 (m, 1 H), 6.88 (d, J = 8.7, 2 H), 7.27 (d, J = 8.7, 2 H); chiral HPLC (Chiralcel OD-H, hexane/2-propanol 97:3, 1.0 mL/min) showed 87% ee (t_R = 14.73 min, t_S = 17.19 min).

(*S*)-(−)-1-(4-Chloro-phenyl)-but-3-en-1-ol (*S*)-(−)-(3d): $[\alpha]_D$ −60.6 (*c* 1. 5, $CHCl_3$); ^1H NMR δ 1.59 (br s, 1 H), 2.41−2.54 (m, 2 H), 4.72 (dd, J = 7.8, 5.0 Hz, 1 H), 5.14−5.19 (m, 2 H), 5.73−5.83 (m, 1 H), 7.28−7.33 (m, 4 H); chiral GC (Supelco β-DEX 120 column, oven 100 °C for 5 min, then 1 deg/min to 200 °C, 10 min at that temperature) showed 89% ee (t_R = 51.70 min, t_S = 52.43 min).

(*S*)-(−)-1-(4-Nitro-phenyl)-but-3-en-1-ol (*S*)-(−)-(3e): $[\alpha]_D$ −33.2 (*c* 0. 5, $CHCl_3$); ^1H NMR δ 2.19 (br s, 1 H), 2.42−2.49 (m, 1 H), 2.54−2.60 (m, 1 H), 4.86 (dd, J = 8.0, 4.6 Hz, 1 H), 5.17−5.22 (m, 2 H), 5.74−5.84 (m, 1 H), 7.54 (d, J = 8.6, 2 H), 8.21 (d, J = 8.6, 2 H); chiral GC (Supelco β-DEX 120 column, oven 100 °C for 5 min, then 1 deg/min to 200 °C, 10 min at that temperature) showed 65% ee (t_R = 85.21 min, t_S = 85.77 min).

(*S*)-(−)-1-Phenyl-hexa-1,5-dien-3-ol (*S*)-(−)-(3f): $[\alpha]_D$ −36.9 (*c* 1.06, $CHCl_3$) and +10.3 (*c* 1.31, Et_2O); ^1H NMR δ 1.74 (br s, 1 H), 2.28−2.40 (m, 2H), 4.27−4.32 (m, 1 H), 5.09−5.15 (m, 2 H), 5.74−5.84 (m, 1 H), 6.18 (dd, J = 15.9, 6.3 Hz, 1 H), 6.55 (d, J = 15.8 hz, 1 H), 7.15−7.33 (m, 5 H); chiral HPLC (Chiralcel OD-H, hexane/2-propanol 9:1, 0.75 mL/min) showed 83% ee (t_R = 10.2 min, t_S = 14.9 min).

(*R*)-(+)-1-Phenyl-hex-5-en-3-ol (*R*)-(+)-(3g): $[\alpha]_D$ +1.8 (*c* 0.9, $CHCl_3$) [lit.[31] $[\alpha]_D$ +11.1 (*c* 3.14, $CHCl_3$)]; ^1H NMR δ 1.56 (br s, 1 H), 1.73−1.85 (m, 2 H), 2.15−2.22 (m, 1 H), 2.29−2.36 (m, 1 H), 2.65−2.73 (m, 1 H), 2.78−2.85 (m, 1 H), 3.65−3.71 (m, 1 H), 5.14 (J = 15.2 Hz, 2 H), 5.77−5.87 (m, 1 H), 7,17−7.21 (m, 3 H), 7.26−7.30 (m, 2 H); chiral HPLC (Chiralcel OD-H, hexane/2-propanol 95:5, 1 mL/min) showed 49% ee (t_S = 8.1 min, t_R = 10.9 min).

(*S*)-(−)-1-(2-Furyl)-but-3-ene-1-ol (*S*)-(−)-(3h): $[\alpha]_D$ −4.9 (*c* 1.4, EtOH); ^1H NMR δ 1.99 (br s, 1 H), 2.61−2.65 (m, 2 H), 4.65−4.85 (m, 1 H), 5.14−5.21(m, 2 H), 5.76−5.86 (m, 1 H), 5.74−5.84 (m, 1 H), 6.21−6.34 (m, 2 H), 7.38 (m, 1 H); chiral HPLC (Chiralcel OD-H, hexane/2-propanol 97.5:2.5, 0.75 mL/min) showed 85% ee (t_R = 15.3 min, t_S = 16.8 min).

(*S*)-(−)-(2-Thiopheneyl)-but-3-ene-1-ol (*S*)-(−)-(3i): $[\alpha]_D$ −19 (*c* 1.0, $CHCl_3$) [lit.[32] −5.2 (*c* 1.1, EtOH); ^1H NMR δ 2.62 (br t, J = 6.8 Hz, 2H), 4.98 (t, J = 6.8 Hz, 1H), 5.19 (m, 2H), 5.85 (m, 1H),; 6.99 (m, 2H), 7.26 (m, 1H); ^{13}C NMR δ 42.7 (CH2), 68.3 (CH), 117.7 (CH2), 122.7 (CH), 123.5 (CH), 125.6 (CH), 132.8 (CH), 146.8 (C). chiral GC (Supelco β-DEX 120 column, oven 80 °C for 2 min, then 1 deg/min, showed 83% ee (t_{minor} = 49.6 min, t_{major} = 49.8 min). The absolute configuration was assigned by Brown[32] and Cozzi[33] by analogy with their other results.

(31) Minova, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3697.

(32) Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614.

(*S*)-(−)-1-[(4-Trifluoromethyl)-phenyl]-but-3-en-1-ol (*S*)-(−)-(3j):[34] $[\alpha]_D$ −33.6 (*c* 0.25, CH_2Cl_2); ^1H NMR δ 2.07 (br s, 1H), 2.33−2.51 (m, 2H), 4.72 (dd, J = 7.8, 3.1 Hz, 1H), 5.09−5.14 (m, 2H), 5.67−5.78 (m, 1H), 7.41(d, J = 8.4, 2H), 7.54 (d, J = 8.4, 2H); chiral GC (Supelco β-DEX 120 column, oven: 100 °C for 2 min, then 0.5 deg/min showed 91% ee (t_S = 30.9 min, t_R = 31.9 min).

(*S*)-(−)-1-(Naphthalen-2-yl)-but-3-en-1-ol (*S*)-(−)-(3k): $[\alpha]_D$ −55.0 (*c* 1.16, $CHCl_3$); ^1H NMR δ 2.09 (br s, 1 H), 2.47−2.58 (m, 2 H), 4.84 (dd, J = 7.6, 5.3 Hz, 1 H), 5.07−5.14 (m, 2 H), 5.71−5.82 (m, 1 H), 7.37−7.43 (m, 3 H), 7.74−7.78 (m, 4 H); chiral HPLC (Chiralcel OD-H, hexane/2-propanol, 9:1, 0.75 mL/min) showed 90% ee (t_S = 12.6 min, t_R = 14.4 min).

(1*S*,2*S*)-(−)-2-Methyl-1-phenyl-but-3-en-1-ol (1*S*,2*S*)-(−)-(37): $[\alpha]_D$ −34.7 (*c* 1.7, $CHCl_3$) [lit. $[\alpha]_D$ −97.0 (*c* 1.11, $CHCl_3$)[2f] or +75.0 (*c* 1.0, $CHCl_3$)[2a] for the opposite enantiomer of 66% ee]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J = 6.8 Hz, 3H), 2.14 (d, J = 2.5 Hz, 1H), 2.44−2.53 (m, 1H), 4.36 (dd, J = 7.9 and 2.4 Hz, 1H), 5.17−5.22 (m, 2H) 5.74−5.86 (m, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.93, 40.71, 78.27, 117.24, 127.23, 128.05, 128.63, 141.04, 142.80; chiral HPLC [Chiralpak OD-H, hexane/2-propanol, 95:5, flow rate 0.5 mL/min, t_1 = 14.57 min (major), t_2 = 15.98 min (minor), UV detection at 220 nm]; chiral GC [Supelco γ-CD 120, t_1 = 35.23 min (minor), t_2 = 35.58 min (major)].

(1*S*,2*R*)-(−)-2-Methyl-1-phenyl-but-3-en-1-ol (1*S*,2*R*)-(−)-(37): $[\alpha]_D$ −15.7 (*c* 0.29, CH_2Cl_2) [lit. $[\alpha]_D$ −23.55 (*c* 1.15, $CHCl_3$)[2f] or +17.1 (*c* 1.0, $CHCl_3$) for the opposite enantiomer of 60% ee[2a]]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 7.2 Hz, 3H), 1.87 (br s, 1 H), 2.51−2.54 (m, 1H), 4.55 (d, J = 5.2 Hz, 1H), 5.13−5.16 (m, 2H), 5.65−5.74 (m, 1H), 7.19−7.27 (m, 5H); chiral GC (Supelco β-DEX 120 column, oven 100 °C for 2 min, then 0.5 deg/min showed 87% ee for the major product (t_1 = 42.7 min (*anti*), t_2 = 43.9 min (minor *syn*), t_3 = 45.0 min (major *syn*).

Acknowledgment. We thank the University of Glasgow for a studentship to M.B., AstraZeneca for a fully funded studentship to D.P., University of Rome for a fellowship to M.O., University of Salerno for a fellowship to A.M., the Socrates exchange program for a fellowship to P.H., Degussa for a research grant, and Dr. Alfred Bader for additional support.

Supporting Information Available: General experimental methods and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035074I

(33) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3357.

(34) Doucet, H.; Santelli, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4163.