Synthesis of Enantiopure C_2-Symmetric VERDI Disulfonamides and Their Application to the Catalytic Enantioselective Addition of Diethylzinc to Aromatic and Aliphatic Aldehydes

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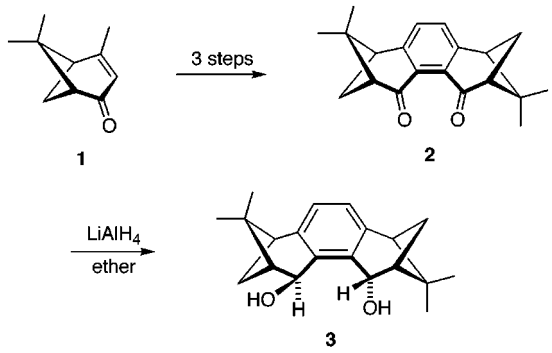
The enantiopure disulfonamides **7a**−**c** have been prepared from the C_2-symmetric diketone **2**, a starting material conveniently accessible from the "dimerization" of (+)-verbenone. These ligands, when treated with titanium isopropoxide and diethylzinc, function as catalysts for the enantioselective alkylation of aldehydes. Stereoselectivity levels ranging from 72 to 98% ee are seen depending on the structural characteristics of the aldehyde. In all cases, the absolute configuration of the carbinol product is *R*. A working mechanistic model is advanced for the purpose of rationalizing the high levels and direction of asymmetric induction exhibited by these VERDI catalysts.

Asymmetric synthesis, when realized by means of molecular catalysis, is a rich, fundamental, and attractive area of investigation. Although various strategies and methodologies have been developed,[1,2] enantioselective bond formation remains one of the more vigorously pursued areas of investigation because of a continuing quest for improvement.[3−8] The necessary discrimination between enantiotopic atoms, groups, or faces in achiral molecules requires the development of efficient and effective catalyst systems. In this connection, the possibility of bringing together two molecules of inexpensive, enantiopure (+)-verbenone (**1**)[9] in a manner that leads conveniently to C_2-symmetric aryl-conjoined "dimers" has recently been realized in this laboratory.[10] The new molecular scaffolds represented by **2** and **3**, referred to as VERDI reagents to reflect their origin (VERbenone DImers), are currently being crafted into catalysts that will hopefully have broad-ranging potential application for high-level enantioselection in a variety of reactions.

So extensively studied has been the addition of diethylzinc to aldehydes in the presence of small quantities of chiral ligands that this particular reaction has come to be regarded as a good first test of the serviceability of new catalyst systems.[11−16] Mechanistic studies of this broadly useful reaction have revealed an appreciable sensitivity to the steric and electronic properties of the various ligand types.[17] Ample consideration has also been accorded to transition state models for a variety of



examples.[18] In this paper, we report on the structural features of diol **3**, the preparation of several structurally related disulfonamides, and the ability of titanium isopropoxide complexes of the latter VERDI ligands to bring about the title reaction in an enantiocontrolled manner.

Results and Discussion

Structural Considerations. In general terms, the tetrasubstitution pattern of the central benzene ring in VERDI systems can be expected to introduce substantial

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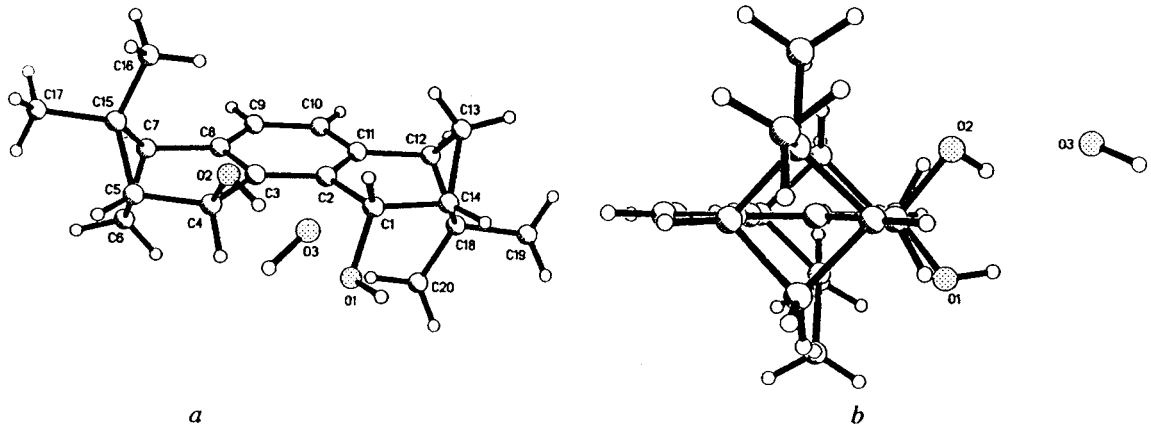


a *b*

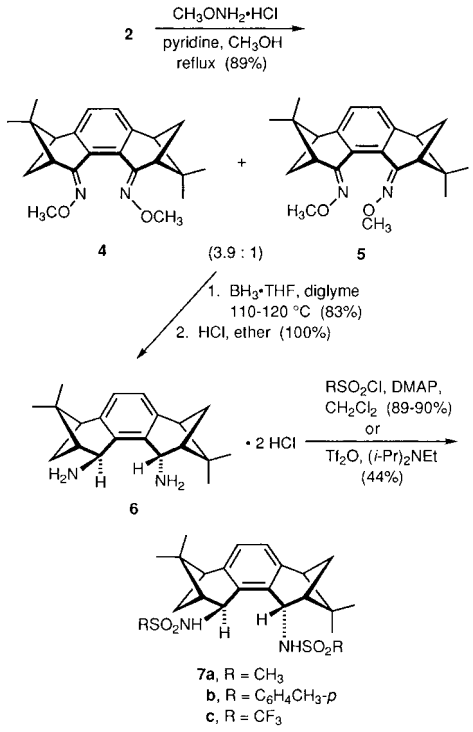
Figure 1. ORTEP diagram of **3**: (a) front view; (b) side view.

structural rigidity and a unique geometrical relationship between the ligating centers. In an effort to gain insight into the bite angle characteristic of the two hydroxyl groups in **3**, we have pursued an X-ray crystallographic analysis of this ligand. Examination of molecular models indicated that the chelate bite angle was considerably in excess of 90°. The advantages potentially associated with wide bite angles have previously been discussed.[19]

Two views of the experimentally determined structural topography of **3** are provided in Figure 1. The O1−C1−C2−O2 dihedral angle of interest is 101.95°. It will be noted that a $^1/_3$ hydrate is involved.[20] Although the resultant hydrogen bonding may affect the hydroxyl group positions to a small extent, it is quite clear that the natural bite angle exceeds 100°. Our expectation is that diamines related to **3** will share the same backbone constraints and valence angles. At issue, of course, is whether these structural features might lead to improved enantioselectivity in catalytic operations.

Synthetic Studies. When the dioxime of **2** proved to be too insoluble for convenient processing,[21] recourse was made instead to reaction with an excess of *O*-methylhydroxylamine hydrochloride in a 1:1 methanol−pyridine solvent system at the reflux temperature. These conditions gave rise to a chromatographically separable mixture of **4** and **5** (Scheme 1). The less polar major constituent **4** was easily identified since the out,out geometry conserves C_2 symmetry. None of the in,in isomer could be detected.

Scheme 1



However, equilibration between **4** and **5** was noted in $CDCl_3$ solution. On standing for two days at room temperature, approximately 10% of **4** had undergone conversion to **5**. The behavior of **5** was more dramatic in that isomerization to **4** was 90% complete. This isomer distribution may well represent the equilibrium point.

Since the catalytic hydrogenation of the **4/5** mixture over 10% palladium on charcoal did not proceed up to 1000 psi, reduction was effected alternatively with the borane•THF complex in diglyme.[22] After 5 days at 110−120 °C, the diamine was obtained in 83% yield. Its

(16) Disulfonamides: (a) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657. (b) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095. (c) Takashashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691. (d) Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956. (e) Hwang, C.-D.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979. (f) Rozema, M. J.; Eisenberg, C.; Lütjens, H.; Ostwald, R.; Belyk, K.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 3115. (g) Brieden, W.; Ostwald, R.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 582. (h) Lütjens, H.; Nowotny, S.; Knochel, P. *Tetrahedron Asymmetry* **1995**, *6*, 2675. (i) Zhang, X.; Guo, C. *Tetrahedron Lett.* **1995**, *36*, 4947. (j) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700. (k) Qiu, J.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 2665. (l) Guo, C.; Qui, J.; Zhang, X.; Verdugo, D.; Larter, M. L.; Christie, R.; Kenney, P.; Walsh, P. J. *Tetrahedron* **1997**, *53*, 4145. (m) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895. (n) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423.

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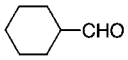
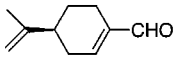
(20) Interestingly, the water molecule in **3** resides on a 3-fold axis, and the three molecules that surround it appear to behave almost as a calixarene.

(21) Morris, J. C. M.S. Thesis, The Ohio State University, 1997.

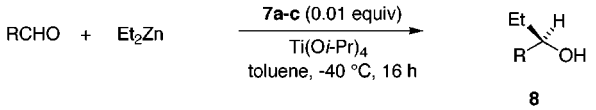
Table 1. Enantiomeric Excesses Resulting from the Asymmetric Addition of Diethylazinc to Several Aldehydes as Catalyzed by Disulfonamides 7a−c in the Presence of Titanium Isopropoxide

entry	aldehyde	disulfonamide (0.01 equiv)	$Ti(O\textit{i}\text{-}Pr)_4$, equiv	$(C_2H_5)_2Zn$, equiv	yield, %	ee, %	config
1	PhCHO	**7a**	1.2	1.2	93	98	*R*
2		**7b**	1.2	1.2	93	89	*R*
3		**7c**	1.2	1.2	90	95	*R*
4	4-FC_6H_4CHO	**7a**	1.2	1.2	97	81	*R*
5		**7b**	1.2	1.2	83	81	*R*
6		**7c**	1.2	1.2	83	86	*R*
7	$CH_3(CH_2)_4CHO$	**7a**	0.6	2.2	87	98	*R*
8		**7b**	0.6	2.2	77	92	*R*
9	PhCH=CHCHO	**7a**	0.6	2.2	81	72	*R*
10		**7b**	0.6	2.2	90	72	*R*
11	$PhCH_2CH_2CHO$	**7a**	0.6	2.2	86	97	*R*
12		**7b**	0.6	2.2	74	96	*R*
13		**7a**	1.2	1.2	65	96	*R*
14		**7b**	1.2	1.2	64	88	*R*
15		**7a**	1.2	1.2	75	82	*R*
16		**7b**	1.2	1.2	83	81	*R*

purification was most readily accomplished by crystallization of the dihydrochloride salt **6**.

The optimal conditions for preparing disulfonamides **7a** and **7b** involved the use of DMAP as the acid scavenger. Ligand **7c** was not obtained by comparable reaction with triflyl chloride. Success was realized instead with triflic anhydride and Hunig's base, although the yield was only modest.

Asymmetric Catalysis. After a brief scan of reaction conditions, those developed by Yoshioka[23] were found to be optimal and were therefore adopted. The results of catalyzed diethylzinc additions to seven aldehydes are compiled in Table 1. For all 16 entries, the level of **7** was maintained constant at 0.01 equiv. For *n*-hexanal, cinnamaldehyde, and hydrocinnamaldehyde (entries 7−12), somewhat lesser amounts of titanium isopropoxide and more elevated proportions of diethylzinc led to modestly improved chemical yields and are therefore cited. Without exception, all three disulfonamides were seen to function as efficient precatalysts for the formation of **8**.



8

While high asymmetric induction (89−98% ee) was observed with benzaldehyde (entries 1−3), the addition of a 4-fluoro substituent decreased enantioselectivity (entries 4−6), in line with an anticipated dropoff in the tightness with which the sulfonamide nitrogens bind to the titanium center in the transition state. While saturated cyclic (entries 13 and 14) and acyclic aldehydes (entries 7 and 8, and 11 and 12) continue to provide *R*-carbinols at a comparably high level of enantioselectivity (88−98% ee), the presence of a conjugated double bond brings on a 10−20% reduction in the level of asymmetric induction. This decrease likely results from the fact that the enforced coplanarity of the α- and β-trigonal centers with the carbonyl π-bond causes the two possible planar orientations to have diminished energy differences once complexed. The least well-behaved substrate of this family (entries 9 and 10 and 15 and 16) is cinnamaldehyde. Although the aromatic aldehydes share similar structural features, they appear more capable of adjusting their geometry, perhaps with some loss of conjugation, to better fit into the catalytic complex for ethyl group transfer, which occurs predominantly to the Re face.

While the enantioselectivities are in most cases close to those published earlier,[16] the results with $CH_3(CH_2)_4$-CHO seem to be better than those observed previously.[14b,16k]

Mechanistic Analysis. Studies by three other research groups have an important bearing on the possible means by which the VERDI disulfonamide catalysts proceed to bring about titanium-mediated ethylzincation. Ohno and co-workers established that these addition reactions do not proceed at a reasonable rate when either the disulfonamide or the titanium isopropoxide is omitted.[16a−c] Parallel studies with **7a−c** in this laboratory

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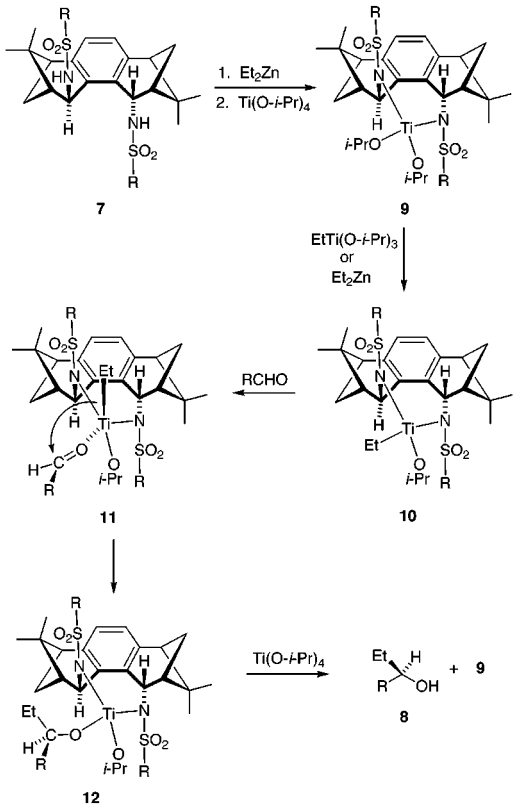
Scheme 2



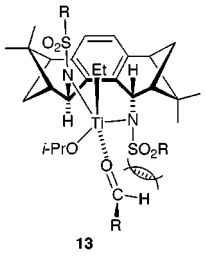
clearly demonstrated the existence of powerful catalytic efficiency with these compounds.

In a somewhat later development, Knochel reported that the realization of high enantioselectivities is dependent on the nature of the titanium alkoxide.[23] Ti(O*i*-Pr)$_4$ and Ti(O*t*-Bu)$_4$ proved notably effective.

More recently, Walsh demonstrated that titanium isopropoxide does not react directly with disulfonamides to give bis(alkoxide) complexes.[16n] By making recourse to the more reactive Ti(NMe)$_2$(O*i*-Pr)$_2$ reagent, they could obtain X-ray quality crystals, establish the tetradentate nature of the ligand (coordination through the sulfonamide nitrogen and oxygen) so as to maintain a C_2-symmetric environment, and demonstrate that these complexes qualify potentially as the catalytically active species.

In light of the well-established fact that dialkylzinc reagents react with disulfonamides to generate the expected complexes,[24] we propose for consideration the possibility that the first-formed intermediate is the zinc complex to **7**. Introduction of titanium isopropoxide can be considered to allow for the intervention of an alkyltitanium species **10**, quite possibly via the titanate complex **9**. To coordinate **10** to an aldehyde, for which ample precedence exists,[25,26] we suggest that the ethyl substituent migrates to an "apical" position. This option, which would presumably result in ligation of titanium to the oxygen lone pair as shown in **11** in order to minimize steric congestion,[27] offers improved π-facial discrimination relative to "apical" coordination of the aldehyde. Once the ethyl group is transferred to the Re face with generation of **12**, further reaction with titanium isopropoxide establishes the catalytic cycle.

We emphasize that while the exact structures of the active species are presently unclear, the working model advanced in Scheme 2 provides reasonable mechanistic insight. For the proposed mechanism, enantioselectivity is determined during ethyl transfer from Ti to C in the lower-energy complex **11**. On the basis of the observed results, it is possible to conclude that disulfonamides **7** are highly capable of generating a chiral environment that usefully distinguishes the Re and Si faces of aldehydes. The unfavored interactions[28] between the R group of the aldehyde and the VERDI backbone in complex **13** render matters unfavorable for transfer of the ethyl group to the Si face.



Conclusions. The enantiopure VERDI disulfonamides **7** in combination with titanium isopropoxide and diethylzinc are effective chiral promoters for enantioselective 1,2 alkyl addition to structurally varied aldehydes. The methodology is simple and operationally practical to implement, requires no removal of liberated isopropyl alcohol, and functions as a typical ligand-accelerated catalytic process.[28]

The VERDI ligand system, by virtue of its inherent structural rigidity, sulfonamide spacing, and bite angle, draws the metal center closer to the chirality. These features may be at the heart of the very high selectivities. The success realized with aliphatic aldehydes is of particular interest. Investigations aimed at defining the utility of other VERDI catalyst systems are expected to be the subject of future reports.

Experimental Section

General Methods. All reactions were carried out under a nitrogen or argon atmosphere. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230−400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high field ^{1}H and ^{13}C NMR. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at Atlantic Microlab, Inc. Norcross, GA.

(1*S*,3*R*,6*R*,8*S*)-1,2,3,6,7,8-Hexahydro-2,2,7,7-tetramethyl-1,3:6,8-dimethanophenanthrene-4,5-dione (*E*,*E*)-Bis(*O*-

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methyloxime) (4) and (1*S*,3*R*,6*R*,8*S*)-1,2,3,6,7,8-Hexahydro-2,2,7,7-tetramethyl-1,3:6,8-dimethanophenanthrene-4,5-dione (*E,Z*)-Bis(*O*-methyloxime) (5). A solution of diketone **2**[10] (0.27 g, 0.92 mmol) and *O*-methyhydroxylamine hydrochloride (0.50 g, 6.0 mmol) in a mixture of pyridine (18 mL) and methanol (18 mL) was refluxed overnight under N_2. Removal of the volatiles afforded a white solid. After ample trituration with hexanes/ethyl acetate (2:1), the combined solutions were concentrated and chromatographed on silica gel. Elution with the same solvent system afforded 226 mg of **4** and 58 mg of **5** (combined yield of 89%).

For **4**: white solid, mp 57−58.5 °C; IR (KBr, cm^{-1}) 1466, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 2 H), 3.89 (s, 6 H), 3.82 (t, J = 6.1 Hz, 2 H), 2.80 (t, J = 5.3 Hz, 2 H), 2.69 (t, J = 5.4 Hz, 1 H), 2.64 (t, J = 5.4 Hz, 1 H), 1.63 (d, J = 9.3 Hz, 2 H), 1.48 (s, 6 H), 0.64 (s, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 146.7, 127.8, 126.0, 61.5, 50.0, 48.3, 42.9, 33.4, 26.2, 22.8; HRMS (EI) m/z (M^+) calcd 352.2151, obsd 352.2163; $[\alpha]^{21}_D$ +929 (*c* 0.417, C_6H_6).

Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01. Found: C, 74.85; H, 8.12.

For **5**: white solid, mp 102−103.5°C; IR (KBr, cm^{-1}) 1459, 1248, 1065; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 2 H), 3.86 (s, 6 H), 3.73 (t, J = 5.8 Hz, 1 H), 3.05 (t, J = 0.6 Hz, 1 H), 2.89−2.66 (m, 4 H), 1.70−1.61 (m, 2 H), 1.48 (s, 3 H), 1.46 (s, 3 H), 0.70 (s, 3 H), 0.57 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 156.7, 146.7, 144.7, 131.7, 126.3, 125.2, 122.3, 61.6, 61.3, 50.6, 50.4, 49.4, 49.3, 48.8, 42.7, 35.2, 33.3, 26.7, 26.3, 22.9 (2 C); HRMS (EI) m/z (M^+) calcd 352.2151, obsd 352.2151; $[\alpha]^{21}_D$ +588 (*c* 0.64, C_6H_6). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01. Found: C, 74.76; H, 8.07.

(1*S*,3*R*,4*S*,5*S*,6*R*,8*S*)-1,2,3,4,5,6,7,8-Octahydro-2,2,7,7-tetramethyl-1,3:6,8-dimethanophenanthrene-4,5-diamine Dihydrochloride (6). A clear solution of **4** (0.50 g, 1.4 mmol) in dry diglyme (150 mL) was cooled to 0 °C and treated slowly with borane in THF solution (40 mL of 1 M, 40 mmol). The reaction mixture was heated at 110−120 °C for 5 days, cooled to 0 °C, treated cautiously with a solution of KOH (10 g) in water (70 mL), and reheated to 120 °C for 3 h. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were treated with aqueous hydrochloric acid. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 in advance of basification with aqueous KOH solution. A fine white precipitate appeared. This mixture was extracted with CH_2Cl_2, dried, and concentrated to leave the diamine as an off-white solid (350 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (s, 2 H), 4.71 (d, J = 2.9 Hz, 1 H), 2.63 (m, 4 H), 2.34 (m, 2 H), 2.00 (s, 4 H), 1.40 (s, 6 H), 1.36 (d, J = 9.0 Hz, 2 H), 0.90 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 136.2, 124.3, 55.9, 50.8, 49.4, 38.9, 34.7, 26.9, 23.6; HRMS (EI) m/z (M^+) calcd 296.2252, obsd 296.2271.

Reduction of **5** under parallel conditions afforded the diamine in a comparable yield.

Dry HCl gas was slowly introduced into an ethereal solution of the diamine, the white solid was collected, and colorless needles were obtained by recrystallization from methanol and ether; mp 252 °C; IR (KBr, cm^{-1}) 3448, 1597, 1518; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 2 H), 4.92 (d, J = 3.6 Hz, 2 H), 2.84 (m, 4 H), 2.74 (m, 2 H), 1.62 (d, J = 9.6 Hz, 2 H), 1.52 (s, 6 H), 0.81 (s, 6 H) (NH_3^+ signals not seen); HRMS (EI) m/z (M^+ − 2HCl) calcd 296.2252, obsd 296.2271; $[\alpha]^{21}_D$ +162 (*c* 0.5, CH_3OH). Anal. Calcd for $C_{20}H_{30}Cl_2O_2 \cdot CH_3OH$: C, 62.83; H, 8.54. Found: C, 62.48; H, 8.39.

***N,N′*-[(1*S*,3*R*,4*S*,5*S*,6*R*,8*S*)-1,2,3,4,5,6,7,8-Octahydro-2,2,7,7-tetramethyl-1,3:6,8-dimethanophenanthren-4,5-ylene]bis[methanesulfonamide] (7a).** A solution of **6** (120 mg, 0.325 mmol) and DMAP (400 mg, 3.27 mmol) in CH_2Cl_2 (45 mL) was treated with methanesulfonyl chloride (60 μL, 0.78 mmol). After the reaction mixture had been stirred for 5 h, 50 mL of 1 N hydrochloric acid was introduced. Thirty minutes later, the product was extracted into CH_2Cl_2, and the combined organic phases were washed with water, dried, and concentrated to leave 135 mg (90%) of **7a** as a white solid, mp 195 °C dec; IR (KBr, cm^{-1}) 3381, 1405, 1146; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 2 H), 5.47 (dd, J = 3.4, 9.3 Hz, 2 H), 4.33 (d, J = 9.4 Hz, 2 H), 3.22 (s, 6 H), 2.86 (m, 2 H), 2.75 (m, 2 H), 2.66 (m, 2 H), 1.44 (s, 6 H), 1.35 (d, J = 9.7 H, 2 H), 0.86 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 131.8, 126.0, 57.1, 48.5, 46.8, 43.4, 39.5, 34.5, 26.8, 23.9; HRMS (EI) m/z (M^+) calcd 452.1804, obsd 452.1761; $[\alpha]^{21}_D$ +35 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{22}H_{32}N_2O_4S_2$: C, 58.38; H, 7.13. Found: C, 58.54; H, 7.15.

***N,N′*-[(1*S*,3*R*,4*S*,5*S*,6*R*,8*S*)-1,2,3,4,5,6,7,8-Octahydro-2,2,7,7-tetramethyl-1,3:6,8-dimethanophenanthren-4,5-ylene]bis[*p*-toluenesulfonamide] (7b).** Reaction of **6** (25 mg, 0.068 mmol) with *p*-toluenesulfonyl chloride (32 mg, 0.17 mmol) and DMAP (120 mg, 0.098 mmol) in CH_2Cl_2 (15 mL) under the predescribed conditions furnished 40 mg (89%) of **7b** as a white solid, mp 128 °C dec; IR (KBr, cm^{-1}) 3311, 1599, 1342, 1160; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (m, 4 H), 7.30 (m, 4 H), 6.70 (s, 2 H), 5.69 (dd, J = 3.1, 8.4 Hz, 2 H), 4.52 (d, J = 8.5 Hz, 2 H), 2.58 (m, 2 H), 2.49 (m, 4 H), 2.43 (s, 6 H), 1.27 (d, J = 9.2 Hz, 2 H), 0.84 (s, 6 H), 0.52 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 142.8, 140.5, 131.8, 129.4, 127.3, 125.5, 57.0, 48.1, 43.9, 38.7, 25.8 23.6, 21.4; HRMS (EI) m/z (M^+) calcd 604.2430, obsd 604.2450; $[\alpha]^{21}_D$ +186 (*c* 0.407, $CHCl_3$). Anal. Calcd for $C_{34}H_{40}N_2O_4S_2$: C, 67.52; H, 6.67. Found: C, 67.72; H, 6.73.

***N,N′*-[(1*S*,3*R*,4*S*,5*S*,6*R*,8*S*)-1,2,3,4,5,6,7,8-Octahydro-2,2,7,7-tetramethyl-1,3:6,8-dimethanophenanthren-4,5-ylene]bis[1,1,1-trifluoromethanesulfonamide] (7c).** To a cold (−5 °C), magnetically stirred solution of **6** (150 mg, 0.41 mmol) and diisopropylethylamine (1.8 mL, 10.3 mmol) in CH_2Cl_2 (15 mL) was added triflic anhydride (138 μL, 0.82 mmol). The reaction mixture was stirred at this temperature for 1 h, allowed to warm to 20 °C for 1.5 h, diluted with 1 N HCl (50 mL), and agitated another 30 min before being extracted with CH_2Cl_2. The combined organic phases were washed with water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 5:1 hexanes/ethyl acetate) afforded **7c** as a white solid (102 mg, 44%), mp 215 °C dec; IR (KBr, cm^{-1}) 3215, 1438, 1368; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 2 H), 5.58 (dd, J = 2.4, 6.8 Hz, 2 H), 5.10 (d, J = 6.9 Hz, 2 H), 2.70 (m, 6 H), 1.43 (d, J = 8.3 Hz, 2 H), 1.42 (s, 6 H), 0.76 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 130.1, 126.8, 57.5, 48.1, 45.8, 39.3, 34.1, 26.1, 23.3 (CF_3 signal not observed); HRMS (EI) m/z (M^+) calcd 560.1238, obsd 560.1202; $[\alpha]^{21}_D$ +141 (*c* 0.233, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}F_6N_2O_4S_2$: C, 47.14; H, 4.67. Found: C, 47.57; H, 4.82.

Prototypical Enantioselective Addition of Diethylzinc to Aldehydes. In a dried, 100 mL Schlenk flask was placed a 10 mg (0.022 mmol) sample of **7a** under argon. To this were added degassed toluene (20 mL) and titanium isopropoxide (0.80 mL, 2.6 mmol), and the mixture was stirred at 40 to 50 °C for 30 min prior to being cooled to −78 °C, at which point a 1.0 M hexane solution of diethylzinc (3.0 mL, 3.0 mmol) was introduced. The orange-colored solution was treated with benzaldehyde (0.224 mL, 2.21 mmol), stirred at −40 °C for 16 h, and quenched with 2 N HCl (25 mL). The separated aqueous phase was extracted with ether, and the combined organic layers were washed with saturated $NaHCO_3$ solution, dried, and concentrated. Chromatography of the residue on silica gel (elution with 2:1 hexanes/ethyl acetate) gave 28 mg (93%) of the carbinol as a colorless oil (98% ee, $[\alpha]^{21}_D$ +43.9 (*c* 5.62, $CHCl_3$)). In addition, **7a** was recovered quantitatively. The enantiomeric purity of the product was determined by chiral HPLC analysis on Daicel columns.

For these determinations, racemic carbinols were first generated by the titanium isopropoxide-promoted addition of diethylzinc to the several aldehydes at room temperature. This uncatalyzed reaction does not proceed at a measurable rate at −40 °C. The absolute configurations of the products were derived by comparison of optical rotation data with literature values.[16b,23] Some of the alcohols were converted to their benzoate derivatives in order to allow UV detection by the HPLC. The relevant data are contained in Tables 2 and 3.

Acknowledgment. Appreciation is extended to the donors of the Petroleum Research Fund, administered

Table 2. Optical Rotation Data for Carbinols 8 ($[\alpha]^{21}_D$ in $CHCl_3$ Solution

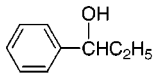
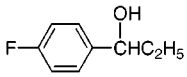
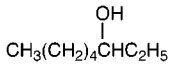
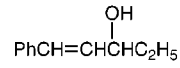
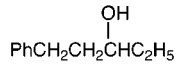
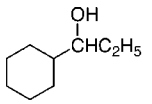
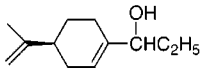
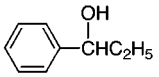
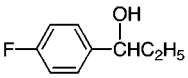
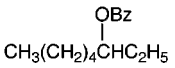
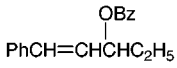
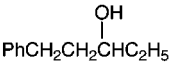
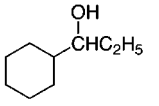
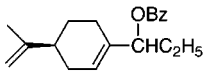
carbinol	catalyzed by **7a**	catalyzed by **7b**	catalyzed by **7c**
	+43.9 (*c* 5.615)	+43.2 (*c* 6.047)	+44.7 (*c* 5.227)
	+34.6 (*c* 2.00)	+34.3 (*c* 2.15)	+34.8 (*c* 1.067)
	-8.9 (*c* 6.12)	-8.6 (*c* 6.00)	
	+6.1 (*c* 1.09)	+6.2 (*c* 1.12)	
	-23.5 (*c* 2.45)	-23.1 (*c* 2.01)	
	+5.6 (*c* 1.09)	+4.5 (*c* 0.467)	
	-69.2 (*c* 1.973)	-78.0 (*c* 2.02)	

Table 3. Chiral HPLC Analysis Conditions (Daicel Columns)

racemic carbinol	chiral column	hexanes/*i*-PrOH	flow rate (mL/min)	retention time (min)
	OD	97.5 : 2.5	1.0	t_R = 12.10; t_S = 13.03
	AS	97.5 : 2.5	1.0	t_R = 8.43; t_S = 9.01
	OD	100 : 0	1.0	t_R = 9.29; t_S = 9.97
	OD	99 : 1	1.0	t_R = 6.38; t_S = 7.13
	OD	9 : 1	1.0	t_R = 6.13; t_S = 8.07
	AS	100 : 0	0.5	t_R = 10.63; t_S = 11.71
	OD	100 : 0	1.0	t_R = 14.63; t_S = 18.23

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Supporting Information Available: Tables giving the crystal data and structure refinement information, bond lengths and bond angles, torsion angles, atomic and hydrogen coordinates, and isotropic and anisotropic displacement coordinates for **3**. The authors have deposited the atomic coordinates for the X-ray structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. This material is available free of charge via the Internet at http://pubs.acs.org.

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