Monocrystals of (2*R*)-**3bCr** were submitted to an X-ray crystallographic study[12] in order to determine not only the exact conformation of this new complex in the solid state but also to confirm the assignment of the aminalic proton chemical shift of this diastereomer by ^{1}H NMR. The ORTEP plot of aminal (2*S*)-**3bCr** is shown in Figure 1 and indicates, as expected,[13-16] an eclipsed chromium carbonyl bond versus the methoxy group.

Chromium transfer from (naphthalene)tricarbonylchromium is known to allow the introduction of the tricarbonylchromium moiety with higher diastereoselectivity and under milder conditions,[17] and the major diastereomer is still the same as the one obtained under thermic conditions.[18] In our case, reaction of **3a** with (naphthalene)tricarbonylchromium (1 mol equiv), at room temperature for 4 days, gives an 80% yield of the diastereomeric aminals (2*R*)-**3aCr** and (2*S*)-**3aCr** in a 3/97 ratio. Thus, the opposite diastereomer (2*S*)-**3aCr** is, now, the major one, with very high de (94%)! This inversion of selectivity is unprecedented, to our knowledge, and might be due either to a chelation by one of the nitrogen atoms of the imidazolidine ring or to the steric requirements of the aminal group itself. Heating of the above mixture at 140 °C for 20 h allowed a "thermodynamic" equilibrium to be reached,[19] and we obtained as the major diastereomer the aminal (2*R*)-**3aCr** with the same 76% de as found previously, in 95% isolated yield. This surprising "isomerization" presumably involves dissociation and recomplexation of the arene to the opposite diastereoface.[19]

For aminal **3b**, these "kinetic" conditions ((naphthalene)tricarbonylchromium) worked as well, and we obtained the diastereomeric aminals (2*R*)-**3bCr** and (2*S*)-**3bCr** in a 2/98 ratio. The isolation of the homochiral aldehydes **1aCr** and **1bCr** is achieved quantitatively by hydrolysis of the corresponding chiral aminals. Thus, for the first time, an efficient method exists for the *enantioselective* introduction of the Cr moiety on aromatic aldehydes.

In conclusion, our preliminary results show that chiral diamines having a C_2 axis of symmetry can be considered as an original and efficient tool for the asymmetric formation and resolution of aminals of ortho-substituted (benzaldehyde)tricarbonylchromium complexes, which is achieved very easily on a preparative scale with high yields.

Supplementary Material Available: A listing of complete crystallographic data of compound (2*R*)-**3bCr**, ^{1}H NMR spectral data of (2*R*)-**3aCr**, (2*S*)-**3aCr**, (2*R*)-**3bCr**, and (2*S*)-**3bCr**, and full experimental procedures with analytical data (3 pages). Ordering information is given on any current masthead page.

(12) Crystal data for (2*R*)-**3bCr** (from ether/petroleum ether): $CrC_{19}H_{24}O_4N_2$, fw 396.41, triclinic, space group $P\bar{1}$; a = 8.071 (2) Å, b = 10.722 (2) Å, c = 11.414 (2) Å, V = 934 (5) Å^3, Z = 2, ρ(calcd) = 1.41 g cm^{-3}, μ (Mo Kα) = 6.21 cm^{-1}, T = 296 K. The structure was solved by direct methods; 3286 measured reflections in which 2963 are considered as observed ($I > 3\sigma(I)$). All coordinates of H atoms were calculated. Final residuals: R = 0.0308, R_w = 0.0319.

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(19) A referee suggested that the pure "thermodynamic" diastereomer should also be submitted to these equilibration conditions. Thus, a pure sample of (2*R*)-**3aCr** was heated for 20 h at 140 °C in Bu_2O and was recovered unchanged. It might be speculated whether the 88/12 ratio reflects a true "thermodynamic" equilibrium or whether 20 h are not enough to attain the complete equilibration. However, heating for more prolonged periods gives rise to partial decomposition and extensive decomplexation. Further work is underway which is beyond the scope of this communication.

The Origin of Greater Than 200:1 Enantioselectivity in a Catalytic Diels-Alder Reaction As Revealed by Physical and Chemical Studies

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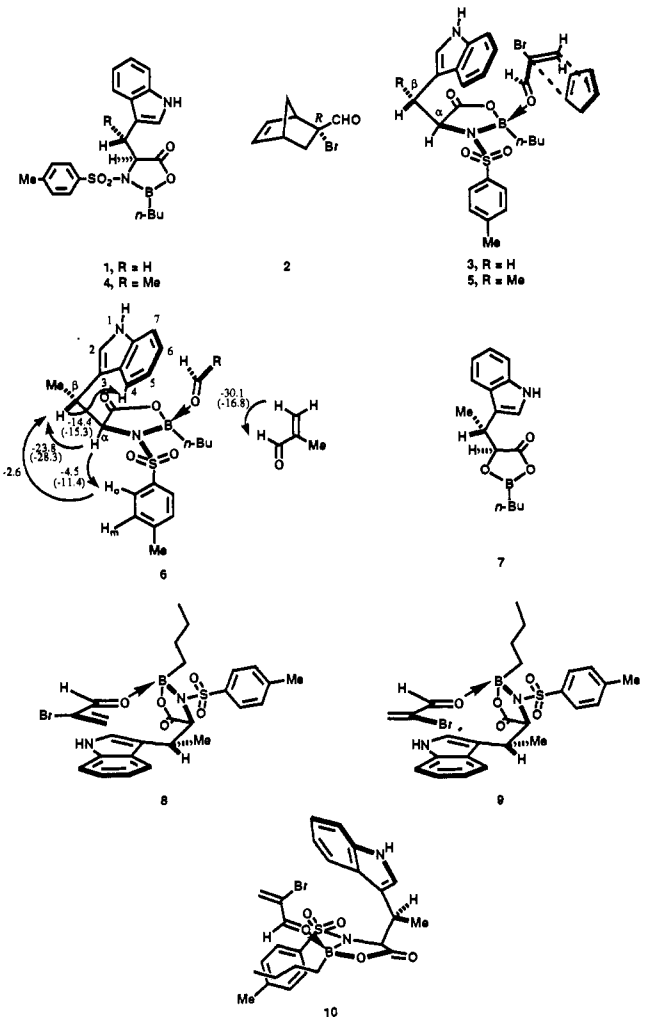
The (*S*)-tryptophan-derived oxazaborolidine **1** catalyzes the Diels-Alder reaction between 2-bromoacrolein and cyclopentadiene to form the chiral adduct **2** with unprecedented (>200:1) enantioselectivity (5 mol % **1**, CH_2Cl_2, -78 °C, 30 min),[1] a result consistent with the working hypothesis of a preferred transition state assembly **3**. The interlocking physical and chemical studies reported herein provide experimental support for **3**.

Chart I



A. Catalyst **4**, derived from ($\alpha S,\beta R$)-β-methyltryptophan[2] and *n*-butylboronic acid as described for **1**,[1] also catalyzes the reaction of cyclopentadiene and 2-bromoacrolein to form **2** with >200:1

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(2) Racemic *N*-tosyl-β-methyltryptophan was synthesized (see: Behforouz, M.; Zarrinmayeh, H.; Ogle, M. E.; Riehle, T. J.; Bell, F. W. *J. Heterocycl. Chem.* **1988**, *25*, 1627-1632) and resolved to the ($\alpha S,\beta R$) enantiomer by recrystallization of the diastereomeric 1:1 salts with (-)-norephedrine from ethanol. This chiral *N*-tosyl derivative and that of (*S*)-tryptophan each had $[\alpha]^{25}_D$ -42° (c = 1 in EtOH). The structure of *N*-tosyl-($\alpha S,\beta R$)-β-methyltryptophan was also verified by a single-crystal X-ray diffraction study (paper in preparation). The study of catalyst **4** was advantageous for NMR measurements and especially for determination of the $HC_\alpha C_\beta H$ dihedral angle.

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enantioselectivity, as predicted for geometry **3**/**5**. Studies with various dienophiles and cyclopentadiene reveal that enantioselectivities with catalyst **4** are very similar to those with **1**: for example, in CH_2Cl_2 at −78 °C, 2-chloroacrolein (200:1); 2-methylacrolein or 2-ethylacrolein (96:4). With both catalysts (**1** and **4**), the corresponding reaction with acrolein exhibits low enantioselectivity (30:70) and the *opposite face* selectivity predominates.

B. Catalysts **1** and **4** were characterized by ^1H, ^{11}B, and ^{13}C NMR studies which confirmed both purity and the correctness of the assigned structures. ^1H 2-D NOESY studies of **4** at 500 MHz and temperatures down to 210 K in CD_2Cl_2 revealed a conformationally mobile structure with NOE effects only between vicinal protons on the aromatic rings. However, an equimolar mixture of 2-methylacrolein and **4** in CD_2Cl_2 at 210 K showed a number of very informative nonvicinal NOE effects (all negative) which are summarized in **6** (% NOEs as shown). ^1H NMR spectrum of **6** at 500 MHz in CD_2Cl_2 at 210 K (δ): 0.53–1.40 (m, 9 H, *n*-Bu); 1.61 (d, J = 7.0 Hz, 3 H, β-Me); 1.74 (s, 3 H, Me_a); 2.39 (s, 3 H, Ts Me); 4.12 (d, J = 3.2 Hz, 1 H, α-CH); 4.25 (qd, J = 7.0, 3.2 Hz, 1 H, β-CH); 5.95 (s, 1 H, H_c); 6.30 (s, 1 H, H_b); 7.03 (br s, In 2); 7.08 (m, 1 H, In 5); 7.11 (m, 1 H, In 7); 7.20 (m, 1 H, In 6); 7.35 (d, J = 8.0 Hz, 2 H, H_m); 7.72 (d, J = 8.0 Hz, 2 H, H_o); 7.84 (d, J = 7.7 Hz, 1 H, In 4); 8.65 (br s, 1 H, In 1 [NH]); 9.35 (s, 1 H, H_d [CHO]). These data demonstrate that the catalyst moiety of the aldehyde complex is conformationally fairly rigid and that the preferred molecular geometry approximates that depicted for **6** (ca. 55° $HC_\alpha C_\beta H$ dihedral angle). The aldehyde complexation is rapidly reversible on the NMR time scale at 210 K, as indicated by the chemical shifts for the aldehyde moiety (e.g., as compared to the static methylacrolein–BF_3 complex, which is discussed below) and its sharp spectrum. That 2-methylacrolein is complexed to the face of boron in **4** which is proximate to the indole ring is indicated by the bright orange-red color of the complex at 210 K, which fades upon warming to 250 K and reappears on cooling. This color, which corresponds to a broad absorption band in the 400–600-nm region, indicates charge-transfer complexation between the π-donor indole ring and the coordinated aldehyde, consistent with the sort of arrangement shown in **3** and **5** with a ca. 3 Å spacing between donor and acceptor elements. Further evidence for the proximity of the coordinated aldehyde and indole subunits in the complex derives from the fact that the ^1H NMR peak due to the CH_3 of 2-methylacrolein in the 1:1 mixture with **4** moves *upfield* with decreasing temperature (from δ 1.79 at 262 K to δ 1.46 at 188 K in CD_2Cl_2) in contrast to the *downfield* methyl shift of a 1:1 mixture of 2-methylacrolein and BF_3 with decreasing temperature.

C. Both the indole and *N*-tosyl subunits of catalysts **1** and **4** are crucial to enantioselectivity. Much lower enantioselectivity is observed for the 2-bromoacrolein–cyclopentadiene reaction when the β-indolylmethylene group of **1** is replaced by a β-naphthylmethylene group (a drop from >200:1 to ca. 7:1); replacement of β-indolylmethylene by phenyl, cyclohexyl, or isopropyl not only degrades enantioselectivity (to about 2:1) but also changes the absolute facial preference, causing the enantiomer of **2** to predominate with these catalysts. If the *N*-tosyl group of **1** is replaced by *N*-mesitylsulfonyl, enantioselectivity disappears, probably because the *o*-methyls of the mesityl group prevent proper positioning of the indole subunit for π-complexation with the dienophile. Further, very low enantioselectivity results when the chiral dioxaborolidine **7**[3] is used to catalyze the reaction of 2-bromoacrolein and cyclopentadiene at −78 °C in CH_2Cl_2 (1.2:1 selectivity for **2** over its enantiomer). This last result implies that the *N*-tosyl group of **1** and **4** is not only helping to fix the position of the indole ring in the catalytic complex but also blocking coordination of boron with the enal at the face trans to the indole subunit and keeping the formyl proton of the complexed α,β-enal at a distance from the sulfonyl oxygens.

The enantioselectivity of the Diels–Alder reactions which are catalyzed by **1** and **4** arises as a consequence of the following: (1) stereoselective coordination of the dienophile at the face of boron which is cis to the indole ring; (2) selective channeling of the Diels–Alder reaction along a path involving either the s-cis or s-trans α,β-enal complex (but not both), this factor being crucial since, for a given geometry of the complex, s-cis and s-trans conformers of the α,β-enal lead to enantiomeric products;[4] and (3) effective steric shielding of one face of the coordinated α,β-enal in the more reactive complex.

Since the equilibrium between catalyst, free α,β-enal, and catalyst–α,β-enal complex is very fast relative to Diels–Alder addition, the Curtin–Hammett principle applies and the relative free energies of activation for reaction from s-cis and s-trans complexes **6** will determine enantioselectivity; in consequence the ratio of the concentrations of the two coordinated α,β-enal rotamers is irrelevant. Assuming a catalyst–α,β-enal complex which has the molecular geometry represented by **6** with π-stacking of the indole ring and α,β-enal (the separation of the parallel π-nodal planes approximates the optimal separation of 3.3 Å), it must be the s-cis α,β-enal complex which gives rise to the observed predominating enantiomer **2**.[5] Although a charge-transfer interaction between the complexed α,β-enal and the indole ring should favor the s-cis conformer (better overlap), there may be some complexed s-trans enal present at equilibrium.[6,7]

Structures **8** and **9** show a different view of the s-cis and s-trans complexes **6**. Inspection of these structures reveals a very simple reason for the much higher reactivity of the s-cis complex **8** toward cyclopentadiene as compared with the s-trans complex **9**. Addition of the diene to **9** would result in $sp^2 \rightarrow sp^3$ transformation of the α and β carbons and strongly increased steric repulsion between the α-bromine substituent and the indole ring. There is no such steric problem in the addition of the diene to the s-cis complex **8**. Such differences also account for the enantioselectivity observed with 2-methylacrolein as reactant and the lack of same (and reversal of face selectivity via the s-trans pathway) for acrolein itself.

The possibility that the catalytic Diels–Alder reaction proceeds via the complex of **1** or **4** with the s-trans α,β-enal cannot be rigorously excluded, but it seems much less likely. For such a process, complex **10** appears to be the only arrangement which can reasonably be expected to produce the observed facial preference with 2-substituted acroleins. In **10** one of the sulfonyl oxygens might serve to help stabilize charge on the positive formyl carbon. However, complex **10**, which involves proximity but not π-stacking of the indole and α,β-enal subunits, explains neither the unique influence of the indole ring (e.g., relative to β-naphthyl)

(3) Catalyst **7** was synthesized from the corresponding chiral α-hydroxy acid and *n*-butylboronic acid by heating at reflux in toluene for 6 h with CaH_2 in a Soxhlet thimble for removal of water. For synthesis of the hydroxy acid from indolmycin, see: (a) Schach von Wittenau, M.; Els, H. *J. Am. Chem. Soc.* **1961**, *83*, 4678–4679; **1963**, *85*, 3425–3431. (b) Chan, T. H.; Hill, R. K. *J. Org. Chem.* **1970**, *35*, 3519–3521. (c) Dirlam, J. P.; Clark, D. A.; Hecker, S. *J. Org. Chem.* **1986**, *51*, 4920–4924.

(4) The s-trans form of the uncomplexed α,β-enal is known to be more stable for acrolein (ΔE, 1.4 kcal/mol), 2-methylacrolein (ΔE, 2.2 kcal/mol), and 2-bromoacrolein (ΔE, 0.5 kcal/mol), whereas for 2-chloroacrolein the s-cis form is somewhat more stable (ΔE, 0.6 kcal/mol), but these data are not decisive in the present context. See: (a) Bostrøn, G. O.; Bakken, P.; Stølevik, R. *J. Mol. Struct.* **1988**, *172*, 227–240. (b) Durig, J. R.; Qiu, J.; Dehoff, B.; Little, J. S. *Spectrochim. Acta* **1986**, *42A*, 89–103.

(5) The indole ring of **6** is approximately bisected by a plane passing perpendicular to the α,β-enal plane and through the enol C–O bond, with the indole nitrogen in proximity to the carbonyl carbon. This geometry corresponds electronically (in the HOMO–LUMO sense) to that observed in the crystalline indole–1,3,5-trinitrobenzene donor–acceptor complex; see: Hanson, A. W. *Acta Crystallogr.* **1964**, *17*, 559–568.

(6) This negative NOE effect refers to the complexed α,β-enal, even though the complexed and uncomplexed enals are both present and rapidly interconverting in the case of catalyst **4**, since the uncomplexed α,β-enal shows a positive NOE effect.

(7) In a separate study it has been shown (Corey, E. J.; Loh, T. P.; Sarshar, S.; Azimioara, M. D. *Tetrahedron Lett.*, in press) that complex formation between BF_3 and 2-methylacrolein in CD_2Cl_2 becomes slow below 243 K on the 500-MHz ^1H NMR time scale. The ^1H NMR spectrum of the complex at 200 K indicates complete coordination, and only the s-trans enal complex can be detected (positive 8% NOE effect between the formyl and *cis*-β-protons). In addition a crystalline 1:1 BF_3–2-methylacrolein complex has been shown by single-crystal X-ray diffraction studies to have the s-trans geometry.

nor the reversed face selectivity for 2-bromo- or 2-methylacrolein vs acrolein.

In summary, a variety of physical and chemical data point to transition-state assembly **3** as the most plausible model for the catalytic enantioselective reaction of 2-substituted acroleins with cyclopentadiene.[8,9]

(8) For another detailed study of a catalytic Diels-Alder system, see: Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794-7795.

(9) This research was assisted financially by the National Science Foundation and the National Institutes of Health.

Synthesis and DNA-Binding Properties of a Cisplatin Analogue Containing a Tethered Dansyl Group

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In the present report we describe the synthesis, fluorescence, and DNA-binding properties of a structural analogue of the platinum antitumor drug cisplatin,[1-5] [Pt(dansen)Cl_2], which contains a tethered dansyl group. The fluorescent properties of the dansyl moiety offer a viable alternative to radiolabeling[6-8] and allow one to monitor by a nondestructive technique[9-12] much lower levels of [Pt(dansen)Cl_2] than cisplatin or its ethylenediamine analogue, [Pt(en)Cl_2]. The structural changes that occur in DNA upon binding of this complex and the ability of the resulting adducts to be recognized by structure-specific recognition proteins[13] mimic properties of cisplatin. Moreover, we have been able to use the fluorescent tag in [Pt(dansen)Cl_2] to observe its covalent binding to plasmid DNA in bacterial cells.

Preparation of the platinum complex containing the dansylated ethylenediamine (dansen) ligand, dichloro((2-((3-dansylpropyl)amino)ethyl)amine)platinum(II) or [Pt(dansen)Cl_2], is outlined in Scheme I. Analytically pure samples were obtained by vapor diffusion of ether into a DMF solution of the complex. The ^{195}Pt NMR chemical shift of [Pt(dansen)Cl_2], δ -2355, is close to the value of δ -2379 for [Pt(en)Cl_2], indicating the presence of two chloride ions and two nitrogen atoms of an ethylenediamine chelate as the ligands.[14,15]

The [Pt(dansen)Cl_2] complex binds covalently to DNA to form bifunctional 1,2-intrastrand cross-links, adducts that display structures analogous to those formed upon binding of cisplatin to duplex DNA.[16] Covalent binding to calf thymus and other

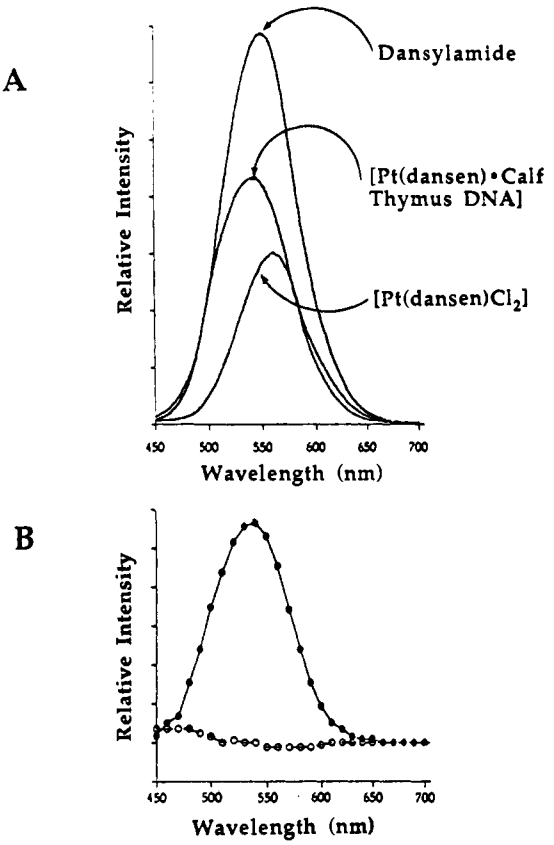
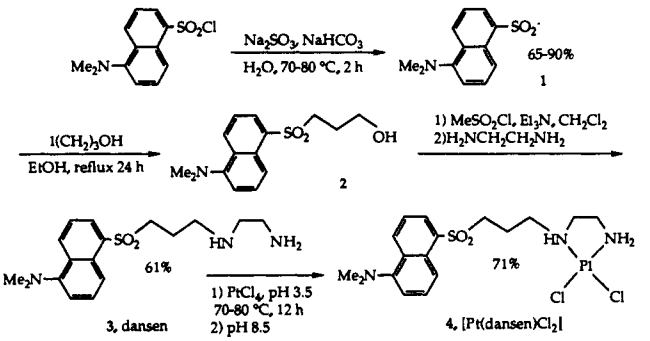


Figure 1. (A) Emission spectra (excitation, 344 nm; excitation bandpass, 5 nm; emission bandpass, 5 nm) of [Pt(dansen)Cl_2], [Pt(dansen)Cl_2] bound to calf thymus DNA at r_b = 0.032, and dansylamide. For all three spectra, the platinum concentration was 3.64×10^{-7} M and the excitation wavelength, 344 nm. (B) Emission spectra (excitation, 344 nm; excitation bandpass, 20 nm; emission bandpass, 20 nm) of pUC19 plasmid DNA recovered from XL1-Blue bacterial cells treated with [Pt(dansen)Cl_2] (●) or free dansen ligand (○). Data were manually digitized and the displayed spectra obtained following subtraction of the typically weak fluorescent background of DNA that becomes significant at the low r_b values used in this experiment.

Scheme I



double-stranded DNAs was demonstrated by platination reactions followed by precipitation or dialysis and subsequent quantitation by atomic absorption or fluorescence spectroscopic analysis. Bifunctional coordination was revealed by analyzing reactions of the diaqua form with the dodecanucleotide d(TCTAGGCCTTCT), which contains a single d(GpG) platinum binding site. Four products having a 1:1 platinum-to-strand ratio were observed (Figure S1, supplementary material) and purified by HPLC. Nuclease and phosphatase digestion analysis[17] revealed the three nucleosides dA, dC, and dT in a 1:4:5 ratio and the absence of unmodified dG (Figure S1). Four peaks corresponding to platinated d(GpG) were also observed. These digestion products

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