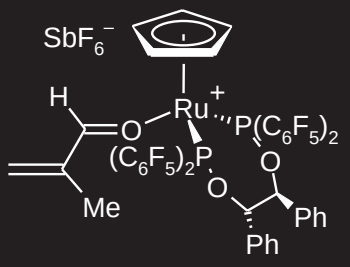
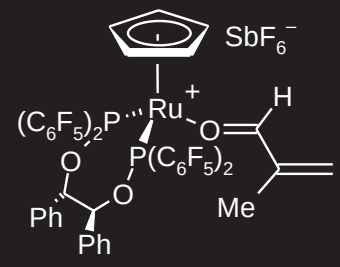
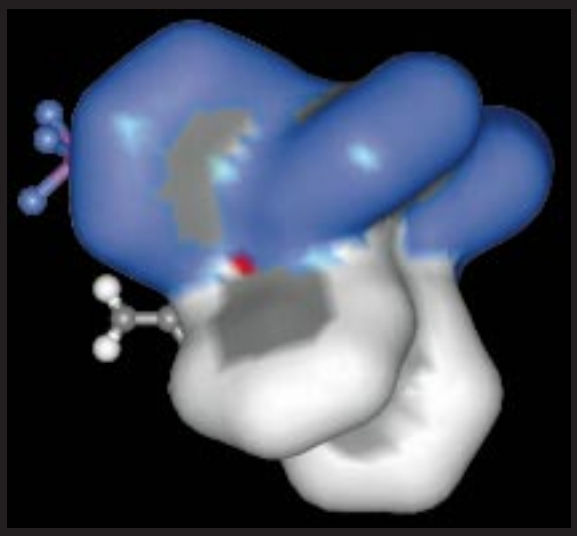
Many chiral Lewis acids catalyze asymmetric Diels–Alder reactions between enals and dienes, but a new readily accessible and thermally stable Ru Lewis acid also provides valuable structural information about catalyst–substrate interactions. Of particular interest is an X-ray structure that shows cooperative binding of the dienophile by the catalyst and the anion.

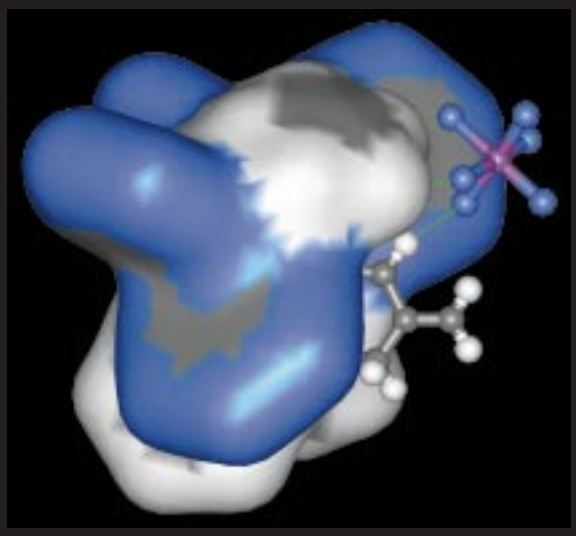


C_α-*si*-face view



C_α-*re*-face view





C_α-*si* face less accessible

C_α-*re* face more accessible

4 : 96

Find out more about this catalyst on the following pages.

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A Stable and Recoverable Chiral Ru Lewis Acid: Synthesis, Asymmetric Diels–Alder Catalysis and Structure of the Lewis Acid Methacrolein Complex**

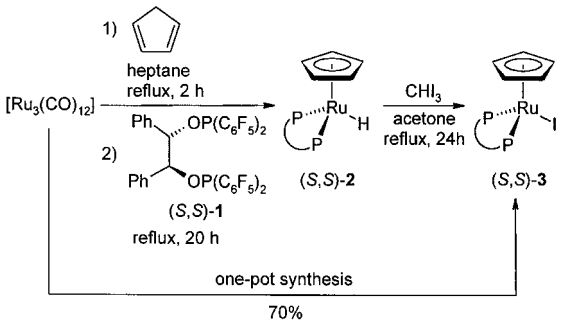
E. Peter Kündig,* Christophe M. Saudan, and Gérald Bernardinelli

The asymmetric Diels–Alder reaction between enals and dienes has become the test reaction for chiral Lewis acids with a single coordination site. In these reactions chiral B, Cu, and Ti compounds are often the catalysts of choice.[1] We have recently found that the iron Lewis acid catalysts [CpFe(cyclop-F)][BF_4] and [CpFe(biphop-F)][BF_4] (cyclop-F = 1,2-bis[bis(pentafluorophenyl)phosphanyloxy]cyclopentane; biphop-F = 1,2-bis[bis(pentafluorophenyl)phosphanyloxy]-1,2-diphenylethane) can give competitive enantioselectivities.[2] Herein we focus on Ru catalysts for this reaction, present an efficient one-pot synthesis of the catalyst precursor, and report details of reactivity and structural data of the catalyst–methacrolein complex.

The perfluoroaryldiphosphinite ligands cyclop-F[3] and biphop-F[2b] (**1**) used for the chiral Fe and Ru Lewis acids create the chiral environment around the coordination site of the enal. Since they are electron-poor, they offset the donor properties of the Cp ligand and thus contribute to the Lewis acidity of the metal center. An attractive feature of this family of Lewis acids is that the immediate catalyst precursors are amenable to structural characterization.[2, 4] Interpretation of observed enantioselectivities is thereby placed on firmer ground than those advanced for in situ prepared catalysts.

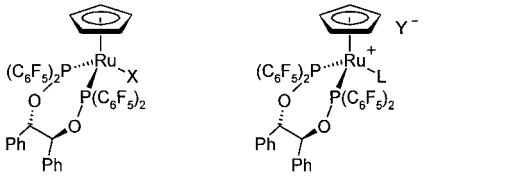
Lewis acids based on the fragment $CpRu^+$ are known[5] but they have not previously found application in Diels–Alder catalysis of enals—presumably because they tend to coordinate the alkene rather than the carbonyl function.[6] We note, however, recent reports on Diels–Alder catalysis with structurally closely related complexes containing the isoelectronic (η^6-arene)Ru^{2+} fragment.[4b,c] The more highly charged metal center thus prefers to bind to the enal oxygen atom to form a M–O σ bond.

The iodoruthenium complex (*S*,*S*)-**3** was prepared in a one-pot procedure from [$Ru_3(CO)_{12}$].[7] (Scheme 1; details in Experimental Section). Crucial to the success was the hydride-labilizing effect[8] that enabled CO substitution in the in situ formed [$CpRu(CO)_2H$].[9] The intermediate hydrido complex (*S*,*S*)-**2** was initially isolated. Its ^{1}H NMR spectrum (in C_6D_6) showed a triplet (J = 33.5 Hz) at δ = −11.08 for the Ru–H proton. Reflux in acetone in the presence of iodoform[10] afforded the air-stable iodo complex (*S*,*S*)-**3**. In subsequent preparations, complex (*S*,*S*)-**2** was not isolated.



Scheme 1. One-pot synthesis of (*S*,*S*)-**3**.

Reaction of a solution of (*S*,*S*)-**3** in acetone with the appropriate silver salt generated the cationic complexes (*S*,*S*)-**4a–d**.[11] The cationic complex (*S*,*S*)-**4e** was obtained from (*S*,*S*)-**4d** by metathesis[12] with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB).[13] In CH_2Cl_2, methacrolein readily displaced the coordinated acetone in (*S*,*S*)-**4d** to give complex (*S*,*S*)-**5d** (Scheme 2). In contrast to the corresponding Fe Lewis acid aldehyde complexes, which slowly



(*S*,*S*)-**2** (X = H)
(*S*,*S*)-**3** (X = I)
(*S*,*S*)-**7** (X = Cl)
(*S*,*S*)-**12** (X = Br)

(*S*,*S*)-**4a** (L = $(CH_3)_2CO$, Y = OTf)
(*S*,*S*)-**4b** (L = $(CH_3)_2CO$, Y = BF_4)
(*S*,*S*)-**4c** (L = $(CH_3)_2CO$, Y = PF_6)
(*S*,*S*)-**4d** (L = $(CH_3)_2CO$, Y = SbF_6)
(*S*,*S*)-**4e** (L = $(CH_3)_2CO$, Y = TFPB)
(*S*,*S*)-**5d** (L = $CH_2C(CH_3)CHO$, Y = SbF_6)
(*S*,*S*)-**8d** (L = CH_2Cl_2, Y = SbF_6)

decompose in CH_2Cl_2 above −20 °C,[2] complexes (*S*,*S*)-**4d** and (*S*,*S*)-**5d** are stable in solution at room temperature. The ^{1}H NMR and IR spectra (CD_2Cl_2) of (*S*,*S*)-**5d** showed coordinated (δ = 9.76, $\tilde{\nu}$ = 1606 cm^{-1}) and free (δ = 9.53, $\tilde{\nu}$ = 1695 cm^{-1}) methacrolein and its NOESY spectrum at −20 °C indicated an *s-trans* coordinated methacrolein with the formyl proton pointing towards the cyclopentadienyl ring.[14] This preferred structure in solution coincides with that found in the solid state by X-ray diffraction analysis (Figure 1).[15,16] The asymmetric unit contains two molecules of the same absolute configuration (*S*,*S*) and which adopt almost identical conformations. Both cationic complexes are associated in pairs with SbF_6^- ions; the Ru–Sb distances are 5.785(1) and 5.798(1) Å, respectively. In each ion pair, three fluorine atoms of the anion are involved in hydrogen bond interactions (H–F distances less than 2.6 Å[17]): two with the cyclopentadienyl ring and one with the formyl hydrogen atom[18] of the methacrolein moiety (Figure 1). These hydrogen bonds fix the substrate in the chiral pocket and impede rotation around the Ru–O bond. Other hydrogen atoms of the Cp ligand are involved in intramolecular hydrogen bond interactions with

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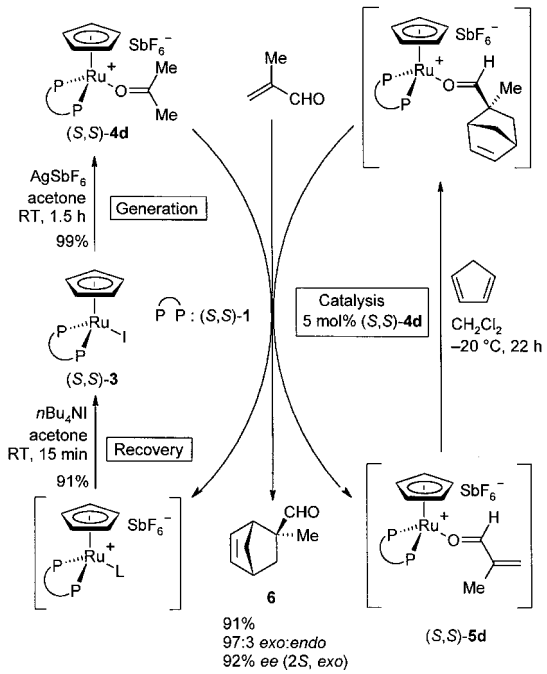

Scheme 2. Catalyst generation and recovery.

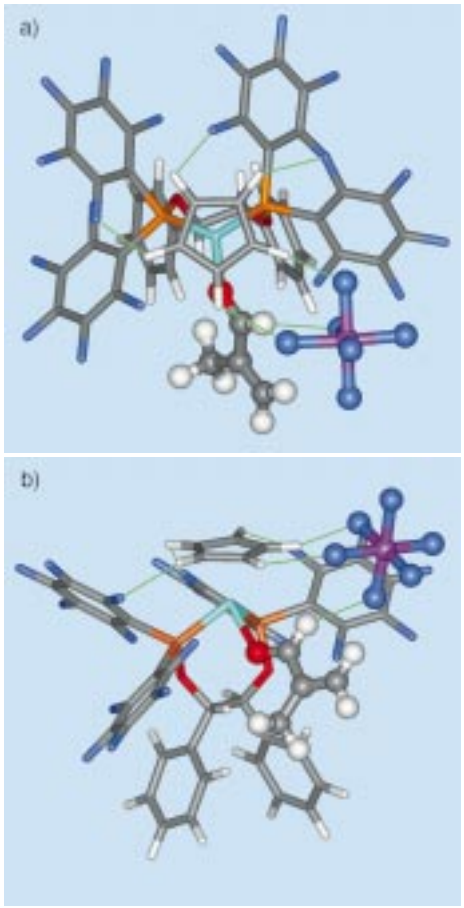

Figure 1. a) Top view and b) front view of one of the ion pairs present in the asymmetric unit of (*S*,*S*)-**5d**. The C–H···F hydrogen bonds are represented by green lines. (WebLab ViewerPro[28])

fluorine atoms of the pentafluorophenyl substituents.[19] The *s-trans* conformation of the methacrolein was determined without ambiguity.

The Diels–Alder reaction of methacrolein with cyclopentadiene catalyzed by (*S*,*S*)-**4d** (5 mol%, CH_2Cl_2, –20 °C, 22 h) gave the cycloadduct **6** in 91% yield with a diastereomeric ratio of *exo*:*endo* of 97:3 and an enantioselectivity of 92% *ee* (*exo*), and 2*S* absolute configuration (Scheme 2). We infer that product **6** was formed through a diene approach from the less hindered top side (cyclopentadienyl side) and addition to the dienophile C_α-*re* face of the *s-trans* conformer of the dienophile.[20] The methacrolein conformation found in both the solid state and in solution is close to that which we presume to lead to the transition state of the cycloaddition.

The nature of the counterion had a large effect on the rate ($TfO^- < BF_4^- < PF_6^- < SbF_6^- < TFPB^-$; TfO^- = trifluoromethanesulfonate) but not on the enantioselectivity of the reaction (Figure 2).[4a, 21] The previously advanced interpretation for a similar phenomenon in dicationic Cu catalysts

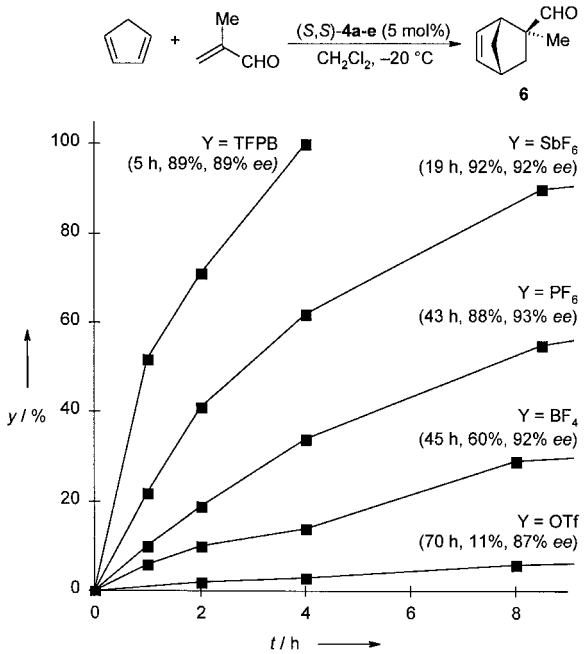

Figure 2. Plot of GC yield (*y*) as a function of reaction time (*t*) for the catalyzed reaction of methacrolein with cyclopentadiene in presence of (*S*,*S*)-**4a**–**e**. In parentheses: total reaction time, yield of isolated product and *ee* value of *exo*-cycloadduct **6**.

invoked competition of the anion and the substrate for the Lewis acid site.[21] Figure 1 prompts another explanation. By interacting simultaneously with catalyst and coordinated aldehyde, the anion slows down turnover frequency. Though weak, these hydrogen bonding interactions (green in Figure 1) must be highly sensitive to the nature of the anion.[22] With catalyst (*S*,*S*)-**4d**, a fivefold increase in diene had little effect on the rate, indicating that the rate-limiting step is not the cycloaddition reaction but may be ligand exchange.

Diels–Alder reactions with the Ru complex (*S*,*S*)-**4b** are slower than those with the analogous Fe complex and gives product **6** with a lower enantioselectivity (Fe: 97% *ee*, Ru: 92% *ee*). The difference in product *ee* can be attributed to the increased size of the chiral pocket on going from the first row to the second row transition metal.

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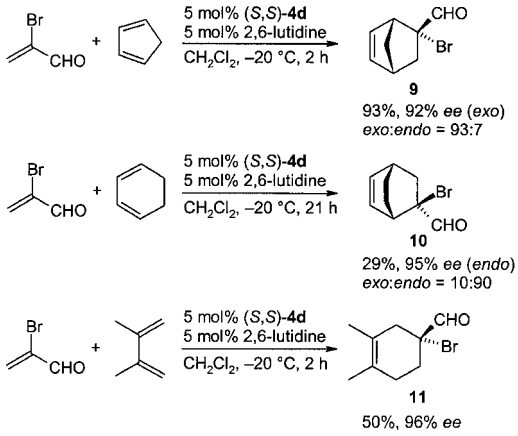
Chiral Lewis acid catalysts are generally lost during workup and at best the chiral ligand is recovered. The stability of our catalyst makes recovery straightforward. Addition of nBu$_4$NI to the reaction mixture generated the catalyst precursor complex (*S*,*S*)-**3** but separation from **6** was difficult. This reaction also afforded the chloro complex (*S*,*S*)-**7** as minor product, presumably the result of iodide attack on coordinated CH_2Cl_2 in (*S*,*S*)-**8d**.[23, 24] A more general procedure for catalyst recovery involved addition of hexane to the reaction mixture and filtration over celite. Catalyst extraction from celite with acetone followed by addition of nBu$_4$NI yielded (*S*,*S*)-**3** (91%).

A limitation of the use of our Ru Lewis acid became apparent in reactions with α-bromoacrolein. Reactions with this dienophile had to be carried out in the presence of a base (2,6-lutidine). Without it, the catalyst decomposed and a racemic cycloadduct was obtained. More importantly, while the reaction with cyclopentadiene afforded cycloadduct **9** in good yield and enantioselectivity (Scheme 3), with the less



Scheme 3. Diels–Alder reactions of α-bromoacrolein with dienes catalyzed by (*S*,*S*)-**4d**: catalyst deactivation by the product (see text).

reactive cyclohexadiene and dimethylbutadiene, yields of **10** and **11** dropped to 29% and 50%, respectively, although *ee* values remained high. The isolation of the bromo complex (*S*,*S*)-**12** as sole Ru product recovered (in 83% and 91%, respectively) from these reactions points to catalyst deactivation by the cycloaddition products **10** and **11**.[25] The highly acidic organic cation formed by bromide abstraction from **10** and **11** may explain the formation of racemic Diels–Alder product in the absence of the amine.

To summarize, the key features of the new chiral Ru Lewis acid described here are its straightforward synthesis, a well defined structure, and high stability which makes easy recycling possible. First results in its use as Diels–Alder catalyst are promising and cycloadduct enantioselectivities are high although limitations exist with brominated cycloadducts.

Experimental Section

(*S*,*S*)-**3**: Cyclopentadiene (11 mL, 134 mmol) was added to $[Ru_3(CO)_{12}]$ (1.065 g, 1.67 mmol) in refluxing heptane (300 mL). After 2 h, (*S*,*S*)-**1** (5.187 g, 5.50 mmol) was added and the reaction mixture was refluxed for 20 h. The solution was concentrated and maintained at 0°C overnight. After decantation and drying of the pale yellow solid under vacuum, iodoform (2.166 g, 5.50 mmol) and acetone (50 mL) were added and the mixture was refluxed for 24 h. Volatiles were removed under vacuum and the residue was washed in air with MeOH. Recrystallization from CH_2Cl_2/MeOH afforded (*S*,*S*)-**3** as red-orange crystals (4.389 g, 70%). M.p. >250°C; $[\alpha]_D^{20} = -126.3$ ($c = 1.0$ in CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6, 20°C, TMS): $\delta = 7.49$ (d, $J = 7.9$ Hz, 2H; H_{ar}), 6.60–7.00 (m, 9H; H_{ar}, CH), 5.22 (t, $J = 7.4$ Hz, 1H; CH), 4.61 (s, 5H; C_5H_5); ^{31}P NMR (162 MHz, C_6D_6, 20°C, H_3PO_4): $\delta = 123.9$ (br. d_{AB}, $^2J(P,P) = 72$ Hz, 1P), 116.4 (br. d_{AB}, $^2J(P,P) = 71$ Hz, 1P); elemental analysis calcd for $C_{43}H_{17}F_{20}IO_2P_2Ru$ (%): C 41.80, H 1.39; found: C 41.79, H 1.60.

(*S*,*S*)-**4d**: 11.8 mL (1.17 mmol) of $AgSbF_6$ (695 mg, 1.98 mmol) in CH_2Cl_2 (20 mL) were added to (*S*,*S*)-**3** (1.235 g, 1.00 mmol) in acetone (15 mL). The mixture was stirred for 90 min. After filtration through celite and evaporation of the solvent under vacuum the residue was twice purified by dissolution in acetone, precipitation by addition of Et_2O, decantation, dissolution in acetone, and filtration through celite. (*S*,*S*)-**4d** was obtained as a yellow solid (1.392 g, 99%). M.p. >170°C (decomp); $[\alpha]_D^{20} = -81.5$ ($c = 0.60$ in CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2, 20°C, TMS): $\delta = 7.23$–6.94 (m, 6H; H_{ar}), 6.85–6.45 (m, 2H; H_{ar}), 6.77 (d, $J = 7.1$ Hz, 2H; H_{ar}), 5.27 (dd, $J = 7.9$, 14.3 Hz, 1H; CH), 5.01 (t, $J = 8.1$ Hz, 1H; CH), 4.92 (s, 5H; C_5H_5), 2.56 (s, 6H; CH_3); ^{31}P NMR (162 MHz, CD_2Cl_2, 20°C, H_3PO_4): $\delta =$ 130.1 (br. d_{AB}, $^2J(P,P) = 71$ Hz, 1P), 124.9 (br. d_{AB}, $^2J(P,P) = 66$ Hz, 1P); IR (CH_2Cl_2): $\tilde{\nu} = 1657$ cm^{-1}.

(*S*,*S*)-**5d**: (*S*,*S*)-**4d** (141 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (2 mL), and methacrolein (160 µL, 1.95 mmol) was added. After stirring the mixture for 5 min, volatiles were removed under vacuum. This treatment was repeated twice to give (*S*,*S*)-**5d** as a yellow solid (142 mg, 99%). M.p. >150°C (decomp); $[\alpha]_D^{20} = -17.7$ ($c = 0.60$ in CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2, 20°C, TMS): $\delta = 9.76$ (s, 1H; CHO), 6.95–6.25 (m, 8H; H_{ar}), 6.89–6.83 (m, 2H; H_{ar}, CH_2), 6.76–6.70 (m, 2H; H_{ar}, CH_2), 5.20 (dd, $J =$ 7.9, 14.8 Hz, 1H; CH), 5.03 (t, $J = 7.9$ Hz, 1H; CH), 4.96 (s, 5H; C_5H_5), 1.90 (s, 3H; CH_3); ^{31}P NMR (162 MHz, CD_2Cl_2, 20°C, H_3PO_4): $\delta = 127.4$ (br. d_{AB}, $^2J(P,P) = 71$ Hz, 1P), 125.4 (br. d_{AB}, $^2J(P,P) = 70$ Hz, 1P); IR (CH_2Cl_2): $\tilde{\nu} = 1606$ cm^{-1}.

6: Methacrolein (82 µL, 1.00 mmol) and cyclopentadiene (100 µL, 1.22 mmol) were successively added to (*S*,*S*)-**4d** (69.9 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) at −20°C. After stirring the mixture at −20°C for 22 h, hexane (10 mL) was added and the mixture filtered through celite. Chromatography of the filtrate on silica gel (pentane:$CH_2Cl_2 = 8$:1 to 2:1) gave cycloadduct **6** as a deliquescent white solid (127 mg, 91%) with 97:3 *exo*:*endo* ratio (determined before chromatography) and 92% *ee* (*exo*). Catalyst recovery: celite was eluted with acetone and nBu$_4$NI (32 mg, 0.09 mmol) was added. After the mixture had been stirred for 15 min, evaporation of the solvent and chromatography on silica gel (hexane:$CH_2Cl_2 = 4$:1 to 2:1) gave (*S*,*S*)-**3** (56 mg, 91%).

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[15] Crystal structure determination of (*S*,*S*)-**5d**: $[C_{47}H_{23}F_{20}O_3P_2Ru][SbF_6]$; $M_r = 1414.4$; $\mu = 1.018\ mm^{-1}$, $F(000) = 1376$, $\rho_{calcd} = 1.844\ g\,cm^{-3}$, triclinic, $P1$, $Z = 2$, $a = 13.021(1)$, $b = 13.189(1)$, $c = 15.167(2)$ Å, $\alpha = 89.68(1)$, $\beta = 89.22(1)$, $\gamma = 78.05(1)^\circ$, $V = 2548.0(4)$ Å^3, yellow plate $0.18 \times 0.38 \times 0.64$ mm mounted on a quartz fiber with RS3000 perfluoropolyether oil. Intensities were measured at 150 K on a STOE IPDS diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å). $2\theta_{max} = 56^\circ$. A total of 43036 measured reflections, 21885 unique reflections (R(int.) = 0.033) of which 21123 were observable ($|F_o| > 4\sigma(F_o)$). Data were corrected for Lorentz and polarization effects and for absorption (T_{min}, T_{max} = 0.6212, 0.8437). The structure was solved by direct methods using MULTAN 87,[26] all other calculations used XTAL[27] system and WebLab ViewerPro[28] program. The absolute configuration was determined and the Flack parameter[29] converged to $x = -0.01(2)$. Full-matrix least-squares refinement based on F using weight of $1/[\sigma^2(F_o) + 0.0003(F_o^2)]$ gave final values $R = 0.045$, $\omega R = 0.055$, and $S = 2.61(2)$ for 1436 variables and 21123 contributing reflections. Hydrogen atoms were placed in calculated positions and other non-disordered atoms were refined with anisotropic displacement parameters. The final difference electron density map showed a maximum of +1.60 and a minimum of −1.47 e Å^{-3}. One of the two molecules shows an *in-plane* disorder of a phenyl group (angle between the two phenyl mean planes = 3.0(6)°). This disorder was resolved by refinement of two tilted positions (tilt angle of about 12°) with population parameters of 0.60 and 0.40, respectively, and restraints on bond lengths, bond angles, and torsional angles (40 restraints). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-112276. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Synthesis and Biological Evaluation of a Cyclo-β-tetrapeptide as a Somatostatin Analogue

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In contrast to small α-peptides, short-chain β-peptides (oligomers of β-amino acids) show a remarkable ability to fold into well defined secondary structures in solution as well as in the solid state.[1] The main three structural elements of proteins (helices, pleated sheets, and turns) have been identified in β-hexapeptides in solution.[2] Cyclic β-peptides arrange in the solid state as tubular structures with a tight net of pleated-sheet-type hydrogen bonds ("nanotubes").[3] The second fundamental difference between natural peptides and β-peptides is the latter's excellent stability against degradation by proteases and peptidases, including the most aggressive ones, such as pronase and proteinase K.[4]

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