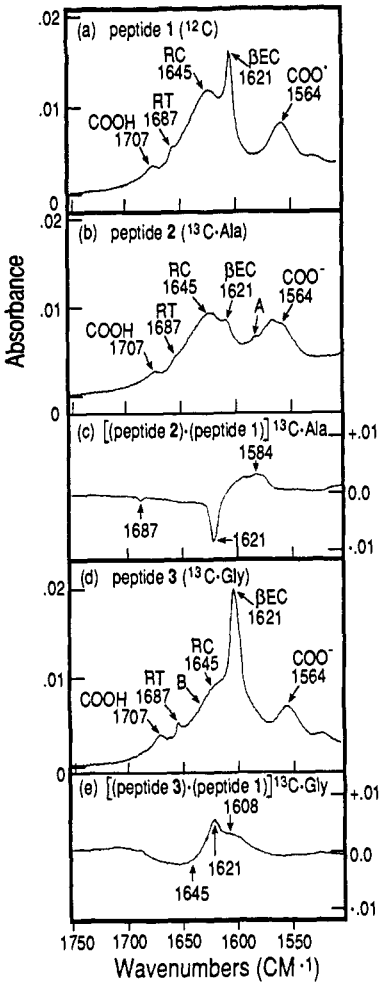

Figure 1. Infrared spectra (at 2-cm^{-1} resolution) of the amide I region for peptides **1**, **2**, and **3** are shown in (a), (b), and (d), respectively. RC represents "random coil"; RT, reverse turn; βEC, β-extended chain. The peptide [**2**-**1**] and [**3**-**1**] difference spectra are shown in (c) and (e), respectively. The 4 mM peptide samples were examined by attenuated total reflectance in phosphate-buffered D_2O (pD = 7.0; 23 °C) containing 1% sodium dodecyl sulfate (SDS) to ensure substantial amounts of random coil peptide. (Measuring small amounts of ordered conformations in the presence of abundant random coil is an important aspect of the current work, since it is difficult to do this with other spectroscopic methods.) Additional details of the experimental conditions are available in the supplementary material.

The peptide **3** spectrum shows a significant decrease in absorption at ~1645 cm^{-1} (disorder), see arrow **B** in Figure 1d, with a shift of area to lower energy causing a relative increase in the maximum height of the 1621-cm^{-1} peak. This appears as a broad nonsymmetrical negative band at ~1645 cm^{-1} in the difference spectrum, Figure 1e, with a corresponding positive band centered at ~1608 cm^{-1} ($\Delta \approx 37$ cm^{-1}). Therefore, it is apparent that the glycines at positions 17-21 of peptide **1** are predominantly disordered.

These results show that isotopically enhanced FTIR can be used to examine the secondary structure(s) of residues at specific locations in conformationally heterogeneous peptides. With a relatively simple model for bond vibrations, i.e., isolated harmonic motion, it is possible to understand the major isotopic shifts observed in three model peptides. Quantitative analyses of complex structures will be possible when additional details of vibrational transitions are considered. For example, molecular vibrations, rather than being truly harmonic, are actually anharmonic.[21,22] This is especially characteristic of functional groups that participate in hydrogen bonding, such as the amide carbonyl. Other factors that may cause complex isotopic effects are the interactions that can take place between neighboring oscillators during vibrational transitions. In effect, phase-dependent *summation* transition dipoles can exist, causing splitting of the carbonyl absorption bands that ordinarily would be associated with isolated oscillators (transition dipole coupling). The degree of splitting and the relative intensities of the split bands is highly dependent upon the geometry of the interacting transition dipoles.[1,23,24] When these additional factors are considered, the data provided by mathematical deconvolutions[16,17,25-27] of isotopically shifted infrared spectra, together with normal mode calculations and systematic assignments of labeled residues to secondary structures, will allow detailed conformational analyses of peptides and proteins in solution, in the solid state, and at interfacial surfaces.

Acknowledgment. The authors thank their colleagues Jeffrey Skolnick, Peter E. Wright, and M. Reza Gadhiri for valuable discussions. We especially acknowledge the enthusiastic support of Richard Lerner, Peter Wright, and William Beers in the creation of a vibrational spectroscopy facility at The Scripps Research Institute. We also thank W. C. Johnson and Araz Toumadje for generously sharing the program VARIABLE SELECTION, used in the analysis of the circular dichroism spectra presented in the supplementary material.

Supplementary Material Available: CD spectra of peptide **1** (and analyses of these spectra by the methods of W. C. Johnson and colleagues) (4 pages). Ordering information is given on any current masthead page.

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Stereospecific Synthesis of Cyclobutanol Derivatives Using a 5 Minus 1 Methodology and Platinum(II)

Frederick F. Stewart and P. W. Jennings*

Department of Chemistry, Gaines Hall
Montana State University
Bozeman, Montana 59717

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The literature is replete with strategies and methods for the preparation of three-, five-, and six-membered carbocyclic ring systems. In contrast, four-membered ring construction is uniquely difficult.[1,2] The most common preparative methods for this system are 2 + 2 cycloadditions which are often facilitated by light. However, thermal cyclizations using ketene may be used in the formation of cyclobutanones.[3] A less common methodology, but one of equal validity is that of a 3 + 1 process. This has been amply demonstrated by the ring strain release reactions in which cyclopropane is ring expanded.[4]

In principle, a 5 minus 1 strategy would yield cyclobutanes. Previous results in all carbon-based systems have been reported,

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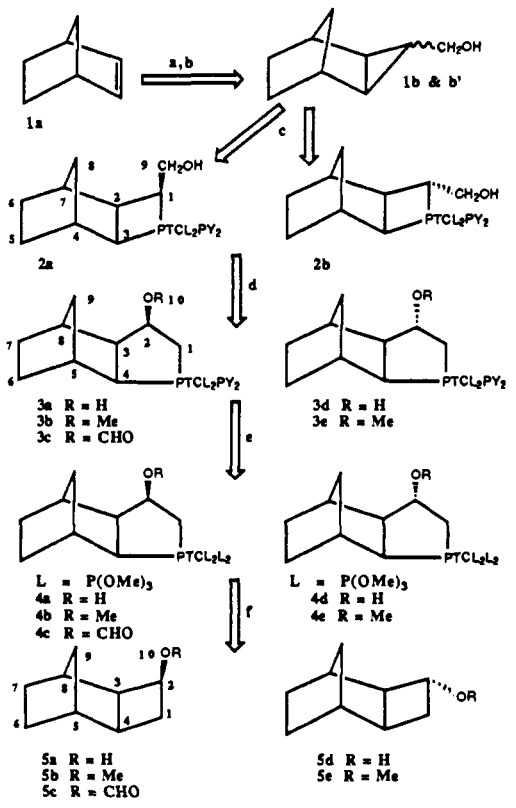
Scheme I[a]



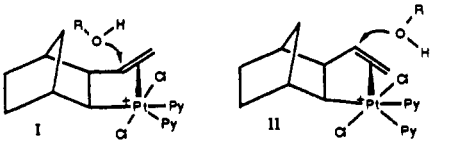
[a](a) $N_2CHCOOEt$, Rh(II), room temperature 12 h, 95%; (b) LAH, 63%; (c) kinetic resolution Pt(II) 93%; (d) H^+, ROH (R = H, Me, OHC), (70–80%); (e) $P(OMe)_3$, 100%; (f) heat, 1 h, 80–90%.

but they are discouraging since this transformation requires an increase in ring strain energy.[5] However, we felt that one might be successful in this venture using metallacyclopentanes. Ample precedent exists demonstrating that metallacyclopentanes will release cyclobutanes under proper conditions. Grubbs[6] eloquently demonstrated that Ni(II) complexes would reductively eliminate cyclobutane and that the reaction was critically dependent upon the phosphine coordination number (yields were >90%). Subsequently, Whitesides[7] showed that Pt(IV) complexes, resulting from solvent oxidative addition to the original Pt(II) complexes, were responsible for cyclobutane formation. However, in this case, it was necessary to heat the reaction to 120 °C for 17 h, and yields of cyclobutane were <40%. Pd(II) complexes also yield cyclobutane on photolysis, but the yields are <10%.[8] Osborn[9] was successful with Ir(III) and Binger[10] investigated the use of Ni(II).

Thus, in this communication, we wish to report our preliminary results using a scenario which not only successfully validates this basic concept but also emphasizes its utility for stereocontrol. The synthetic sequence is shown as Scheme I and relies on three key stereospecific transformations.[11] They are (1) kinetic resolution of the epimeric mixture (**1** → **2**), (2) stereospecific ring expansion (**2** → **3**), and (3) stereospecific reductive-elimination from the platina(IV)cyclopentane complex (**4** → **5**).

The initial step of the sequence (**1a** → **1b** and **1b'**) requires reduction of the carboxylates to hydroxylmethyl derivatives as Pt(II) will not oxidatively add cyclopropanes bearing electron-withdrawing substituents.[12,13] This reduction is the poorest yield step (63%) in the entire sequence. In the kinetic resolution step (**1** → **2**), platinum(II) preferentially reacts with the syn hydroxymethyl derivative by a rate factor of ≈2 orders of magnitude.[11] Oxidative insertion of Pt(II) to yield **2a** and **2b** is quantitative by NMR analysis (isolated 93%).

The acid-catalyzed ring expansion (70–80%) is stereospecific affording the platina(IV)cyclopentanes, **3a–e**.[11] Intermediates I and II are suggested to rationalize the stereospecific formation of **3a–e**.[14,15]



Finally, reductive-elimination (**3** → **5**) results from the reaction of the pyridine complex with trimethylphosphite. The reaction is quantitative by NMR analysis but drops to 80–85% yield during isolation (see supplementary material). NMR data for **2a**, **3a–c**, **4a–e**, and **5a–e** were garnered from 1D spectra supplemented by DEPT 135 and C–H coupling constants[16] with a Bruker AM 500 spectrometer. These proposed structures are consistent with these data.

The last step in the transformation sequence (**3** → **5**) deserves comment. In contrast to platina(IV)*cyclobutanes* which readily undergo reductive-elimination when the pyridines are replaced by tBuNC, Ph_3P, or $(MeO)_3P$, the *cyclopentane* analogues are more robust. The cyclopentane complexes are thermally stable at temperatures up to 100°C, whereas the cyclobutanes readily decompose at 60 °C. At the present time, and without detailed optimization of conditions, 2 mol of phosphite gave the best yield of cyclobutane.[17] Finally, an observation which may be useful in predicting the tendency for reductive-elimination in similar cases is the ^1J platinum–carbon coupling constant. These data show that for the less stable cyclobutane complexes, the constant is generally in the range of 350–400 Hz, whereas a constant of 520–560 Hz is observed for the more stable cyclopentane complexes. However, when the pyridine ligand is replaced with trimethylphosphite in the cyclopentane derivative, the coupling constant drops again to 350–400 Hz, and reductive-elimination proceeds.[18] Thus, it appears that the observable NMR trans influence which is exhibited by the ^1J (Pt–C) coupling constant may be useful for predicting reactivity.

In summary, the 5 minus 1 strategy has been elaborated in a sequence of reactions for the formation of four-membered carbocycles via the reductive-elimination of platinum from platina(IV)cyclopentanes. The strategy also provides for predictable stereocontrol. Finally, measurement of the Pt–C coupling constant may be useful in predicting reductive elimination.

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(15) Our contribution in 1988 (ref 11) not only demonstrateed that the cationic complex could be made by solvolysis of the alcohol in acid but also that the product was stereospecifically formed.
(16) In addition to all of the chemical shift data for compounds **5a–e**, it is important to note that the $^1J_{C-H}$ coupling constants for the cyclobutane carbons are in the range 130–145 Hz which is typical of cyclobutane ring systems.
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Supplementary Material Available: Experimental details and complete NMR spectroscopic data for **4a–e** and **5a–e** (3 pages). Ordering information is given on any current masthead page.

Facile Nucleophilic Substitution on Coordinated η^5-Cyclopentadienyl

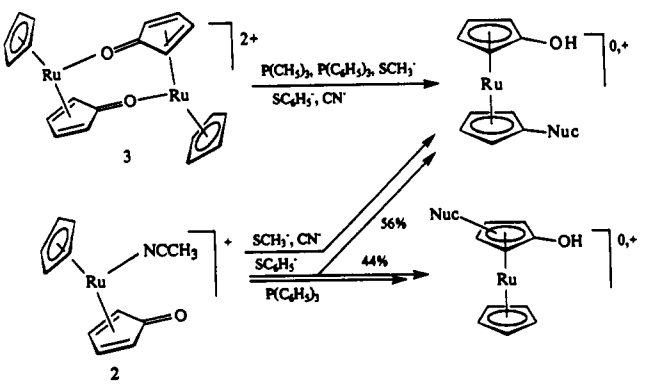
Karl Kirchner and Henry Taube*

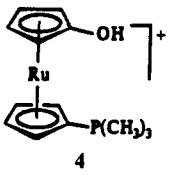
Department of Chemistry, Stanford University
Stanford, California 94305
Received March 1, 1991

Substitution in η^5-cyclopentadienyl (Cp) is acknowledged to be difficult.[1] It is reasonable to expect that on coordination to a metal cation in the η^5 mode, this difficulty would be alleviated. There are numerous examples of nucleophilic addition to η^5-cyclopentadienyl ligands,[2] and one example[3] featuring substitution on coordinated Cp, but, even so, the examples cited involve very powerful nucleophiles such as H^- or carboanions. Considerable work has also been devoted to preparing derivatives of coordinated Cp by starting with iodoferrocene and subjecting it to the action of the Cu(I) salt of the desired anions as the entering ligand.[4,5] Reactions are slow and typically require refluxing in pyridine as a solvent, for 1 h or more.

In the course of exploring the chemistry of $[Ru(\eta^5\text{-}C_5H_5)(\eta^4\text{-}C_5H_4O)]^+$ (**1**)[6] we undertook to study the action on it of a variety of nucleophiles. The experiments were done in nitromethane as solvent, at room temperature. Species **1** was introduced into the reaction solution either as the salt $[Ru(\eta^5\text{-}C_5H_5)(\eta^4\text{-}C_5H_4O)(CH_3CN)]PF_6$ (**2**)[7] or as the salt $[Ru(\eta^5\text{-}C_5H_5)(\eta^4\text{-}C_5H_4O)]_2(PF_6)_2$ (**3**).[8] With the nucleophiles Cl^-, Br^-, I^-, pyridine, isocyanides, thioketones, and several others, substitution at the metal center takes place, and a rough affinity order has been established.[9] But, to our astonishment, we noted that, with $P(CH_3)_3$ as the nucleophile, substitution takes place at the Cp ring, the η^4-cyclopentadienone ring (C_5H_4O) being reduced to η^5-hydroxycyclopentadienyl (C_5H_4OH), yielding

Scheme I





4

With **3** as the starting material, in all cases studied thus far, substitution takes place solely on the Cp ring, but, with **2** as the starting material, in some cases substitution takes place also at the ketone (see Scheme I).

To our knowledge, facile nucleophilic substitution on coordinated C_p such as we have observed with much weaker nucleophiles is unprecedented. Here we report on the reactions of **2** and **3** with $P(CH_3)_3$ and $P(C_6H_5)_3$ and give some preliminary results of the reaction of **2** and **3** with SCH_3^-, $SC_6H_5^-$, and CN^-. All reactions were carried out in CH_3NO_2 or CD_3NO_2 at room temperature under an argon atmosphere.

With equimolar amounts of each reagent (ca. 20–40 mM), in the case of the tertiary phosphines, reaction appears to be complete on mixing. By use of ^1H NMR spectroscopy on the product solution (CD_3NO_2) resulting from the action of the phosphines on **3**, reaction is found to be essentially quantitative (recovered yield as the PF_6^- salts, 50–60%). The identity of the product was established by ^1H and ^{13}C NMR spectroscopies and elemental analysis, as well as by its chemical reactivity.

The ^1H NMR spectrum of product **5** ($P(C_6H_5)_3$ as nucleophile) features six signals (d, acetone-d_6, 20 °C): a multiplet pattern from 7.95 to 7.77 ppm (15 H), two apparent quartets centered at 5.20 ppm (2 H) and 4.95 ppm (2 H), two apparent triplets centered at 4.62 ppm (2 H) and 4.19 (2 H), and a broad singlet at 3.74 ppm (1 H) that is readily exchanged by deuterium. The ^1H NMR spectrum of **4** similarly shows that $P(CH_3)_3$ has attacked the Cp ring.[10] The absence of a sharp singlet arising from η^5-coordinated Cp, as well as the absence of the characteristic multiplet pattern of η^4-coordinated C_5H_4O, such as in **2** and **3**, along with the peak integrations, shows that, in both **4** and **5**, the Cp rings are monosubstituted and coordinated in a η^5 fashion. Selective homonuclear decoupling experiments show that decoupling of one of the quartets converts the other to a doublet (doublet ascribable to the coupling of the α and β ring protons with ^{31}P of the phosphine moiety) without affecting the triplets, while decoupling of one of the triplets converts the other to a singlet without affecting the quartets. The ^{13}C NMR spectra support the conclusions as to the structures of **4** and **5**.

That the ketone has been reduced to an alcohol has also been established by its chemical reactivity. Both **4** and **5** readily react

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(7) **2**. 1.2 g of $[RuCp_2Br]PF_6$ and 1.4 g of Ag_2O were added to 50 mL of acetonitrile, and the mixture was stirred at 70 °C for 1 h. The brownish solution was filtered, and the crude product was precipitated with diethyl ether, then dissolved in 10 mL of acetonitrile, and chromatographed with acetonitrile on an alumina column. Reduction of the volume of the solvent, under vacuum, to about 10 mL and addition of diethyl ether gave bright yellow microcrystals. After filtration the product was washed with diethyl ether and air-dried. Yield: 0.22 g (20%). Anal. Calcd for $C_{12}NOPF_6Ru$: C, 33.34; H, 2.79; N, 3.24; P, 7.16; F, 26.37. Found: 33.54; H, 2.73; N, 3.05; P, 7.42; F, 26.77. ^1H NMR (δ, ppm, acetone-d_6, 20 °C): 6.49 (m, 2 H), 5.82 (s, 5 H), 4.68 (m, 2 H), 2.67 (s, 3 H). ^{13}C NMR (δ, ppm, acetone-d_6, 20 °C): 182.81 (C=O), 133.8 (CN), 87.6 (CpO), 87.5 (CpO), 74.3 (Cp), 5.5 (CH_3). IR (KBr, cm^{-1}): 2325.0 (m, ν_{CN}), 1698.9, 1684.5 (s, ν_{CO}).
(8) **3**. 200 mg of $RuCp(C_5H_4O)Br$ was dissolved in 5 mL of nitromethane. $AgPF_6$ was added, and the mixture was stirred at room temperature for 1 h. The resulting precipitate of AgBr was removed by filtration. The solution (dark red) was treated with diethyl ether, and the solid was filtered off, washed with diethyl ether, and air-dried. Yield: 0.23 g (94%). Anal. Calcd for $C_{20}H_{18}O_2P_2F_{12}Ru_2$: C, 30.70; H, 2.32; P, 7.92; F, 29.14. Found: C, 30.74; H, 2.35; P, 7.74; F, 29.46. ^1H NMR (δ, ppm, acetone-d_6, −50 °C): 6.45 (m, 2 H), 6.20 (m, 2 H), 6.09 (s, 10 H), 5.71 (m, 2 H), 5.27 (m, 2 H). IR (KBr, cm^{-1}): 1568.7 (s, ν_{CO}).
(9) A full report on this topic, including the X-ray structures of **2** and **3**, will be submitted separately.
(10) **4**. ^1H NMR (δ, acetone-d_6, 20 °C): 5.06 (q, 2 H), 5.00 (q, 2 H), 4.42 (t, 2 H), 4.33 (t, 2 H), 3.79 (b, 1 H), 2.04 (d, 9 H).
(11) Elemental analyses. Calcd for $C_{13}H_{18}OP_2F_6Ru$ (**4**): C, 33.42; H, 3.88; P, 13.26; F, 22.39. Found: C, 34.10; H, 3.85; P, 12.34; F, 23.82. Calcd for $C_{28}H_{24}OP_2F_6Ru$ (**5**): C, 51.46; H, 3.70; P, 9.48; F, 17.44. Found: C, 51.92; H, 3.69; P, 9.55; F, 17.36.

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