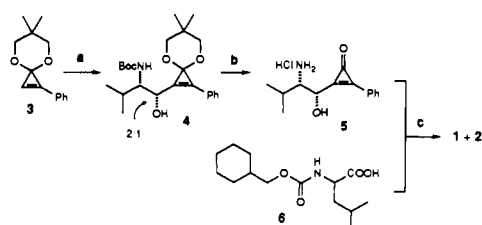


Scheme 1^a

^a (a) *n*-BuLi/TMEDA/THF and then (*S*)-*N*-Boc-valinal (46%); (b) HCl/H₂O, AcOEt/Et₂O (90%); (c) *i*-BuOCOCi/Et₃N/CH₂Cl₂ (73%).

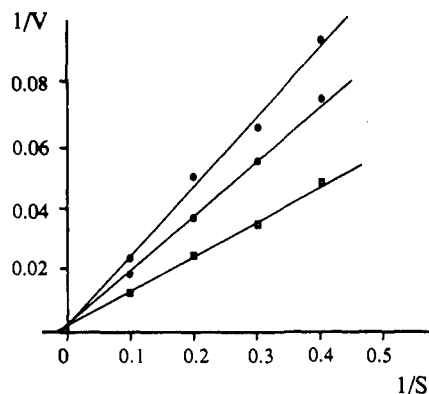


Figure 1. Lineweaver-Burk plot of papain inhibition by compound **1** with Z-Phe-Arg-NMec. The K_m of the substrate is 54.48 μM . Concentrations of the inhibitor are 0 (\square), 0.02 μM (\bullet), and 0.05 μM (\circ). The inhibitor was dissolved in dimethyl sulfoxide and was added to the Na,K-phosphate buffer (pH 6.8) containing papain, EDTA, and dithiothreitol.

added to (*S*)-*N*-(*tert*-butoxycarbonyl)valinal to obtain the alcohol **4** and its 1'*R* epimer as a 2:1 diastereomeric mixture,⁸ which was carried through to the final stage without separation. Removal of the acetal and the Boc group was achieved in a single step by the action of HCl in EtOAc-Et₂O. Condensation of the relatively stable amino alcohol hydrochloride (**5**) with the mixed anhydride obtained by the reaction of (*S*)-*N*-(cyclohexylmethoxycarbonyl)leucine **6** with isobutyl chloroformate in the presence of Et₃N then gave the target CCI **1** and its 1'*R* epimer **2** as a ~2:1 mixture readily separable by silica gel chromatography.⁹

The inhibitory activity of **1** and **2** against papain¹⁰ was assayed by using Z-Phe-Arg-NMec¹¹ as a substrate under the conditions described in the literature.¹² A Lineweaver-Burk plot for **1** is shown in Figure 1, which indicates that this compound is a competitive inhibitor with a K_i value of $0.055 \pm 0.021 \mu\text{M}$.¹³ The 1'*S* isomer **1** is a potent inhibitor of papain, whereas its *R* epimer **2** is a rather weak one as indicated by the IC₅₀ values (0.054 and 32 μM for **1** and **2**, respectively, determined under the same

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(9) **1**: mp 85–89 °C; IR (KBr, cm⁻¹) 3330, 1858, 1695, 1658, 1625; ¹H NMR (CDCl₃, δ) 0.77 (d, J = 5.0 Hz, 6 H), 0.80–1.05 (m, 2 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.10 (d, J = 6.6 Hz, 3 H), 1.10–1.80 (m, 12 H), 2.40 (m, 1 H), 3.50–3.88 (m, 3 H), 4.09 (m, 1 H), 5.11 (d, J = 4.4 Hz, 1 H), 5.31 (m, 1 H), 7.36–7.62 (m, 4 H), 7.98 (dd, J = 7.5, 1.7 Hz, 2 H). Anal. C, H, N: 2: mp 148–149 °C; IR (KBr, cm⁻¹) 3350, 3260, 1860, 1825, 1715, 1653, 1625; ¹H NMR (CDCl₃, δ) 0.80–1.00 (m, 8 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.15 (d, J = 6.7 Hz, 3 H), 1.10–1.80 (m, 12 H), 2.16 (m, 1 H), 3.68 (m, 1 H), 3.75 (m, 1 H), 4.02–4.22 (m, 2 H), 5.14 (d, J = 2.8 Hz, 1 H), 5.19 (d, J = 6.5 Hz, 1 H), 6.92 (d, J = 6.0 Hz, 1 H), 7.42–7.65 (m, 3 H), 7.99 (dd, J = 6.7, 1.5 Hz, 2 H). Anal. C, H, N.

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conditions). Thus, the configuration at the C1' carbon bearing a hydroxyl group is very important for inhibitory activity. Most interestingly, unlike typical activated carbonyl inhibitors, **1** exhibits a high level of specificity toward cysteine proteinase. Thus, it was found to be inactive toward serine proteinases (e.g., thrombin, cathepsin G) and carboxyl proteinases (e.g., cathepsin D) at 100 μM .

In summary, we have shown that **1** represents a novel class of inhibitor for papain,¹⁴ and we have demonstrated a new strategy for designing biologically active molecules by combination of a cyclopropenone reactive site and a suitable enzyme recognition site. The mechanism of action of the CCI is unclear at this time owing to the complex reactivities of cyclopropenones (vide supra). Mechanistic studies and further exploration of the concept of CCI are in progress.

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Molecular Structure and Electrochemistry of Ru₂(dpf)₄(C≡CC₆H₅)₂ (dpf = *N,N*-Diphenylformamidinate Ion): A Novel Ru(III)-Ru(III) Dimer

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Since the discovery of Ru₂(OOCCH₃)₄Cl, numerous Ru₂⁵⁺ complexes containing a variety of bridging and axial ligands have been reported.^{1–5} The electrochemical potentials for the Ru₂⁵⁺/Ru₂⁶⁺ and Ru₂⁵⁺/Ru₂⁴⁺ redox couples vary over a wide range, depending on the σ and π donor ability of the ligands. In most instances, however, the Ru₂⁵⁺ oxidation state is thermodynamically preferred. A few Ru₂⁴⁺ complexes have recently been reported,^{6–10} but to date no Ru₂⁶⁺ complex having the tetra- μ -carboxylate type structure has been isolated and structurally characterized. Two diruthenium carboxylate complexes were reported to contain a Ru₂⁶⁺ core,^{11,12} but were later shown by Cotton et al.¹³ to be Ru₂⁵⁺ compounds. The diamagnetic, air-

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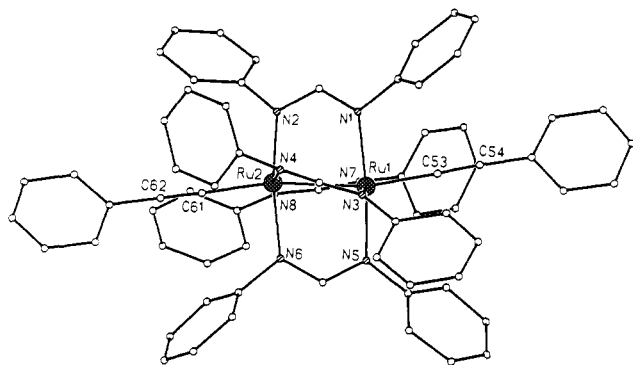


Figure 1. View of the $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ molecule.

sensitive complexes $\text{Ru}_2(\text{L})_2(\text{BF}_4)_2$ (L = dibenzotetraaza[14]-annulene ligand)¹⁴ and Ru_2L_6 (L = CH_2SiMe_3 or CH_2CMe_3)¹⁵ are examples of Ru_2^{6+} compounds that do not have bridging ligands. Trihalo-bridged $[\text{Ru}_2\text{X}_3]^{3-}$ (X = Cl or Br)¹⁶ complexes with a highly symmetrical cofacial bioctahedral arrangement have also been reported in the literature. Edge-sharing pseudo-octahedral Ru_2^{6+} complexes which contain both three-atom and single-nitrogen-atom bridges represent another structural type.^{5,17,18} In this communication, we report the synthesis, structural characterization, and preliminary spectroscopic and electrochemical studies of the novel Ru_2^{6+} complex $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ (dpf = N,N' -diphenylformamidinate ion). The work extends our knowledge of the Ru_2^{n+} ($n = 4-7$) complexes and poses questions concerning the electronic structure of this important class of compounds.

$\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ was obtained from the reaction of $\text{Ru}_2(\text{dpf})_4\text{Cl}^{19}$ with excess $\text{LiC}\equiv\text{CC}_6\text{H}_5$ in THF under an argon atmosphere at room temperature (5 h). The red solution was opened to air, solvent removed, and the purple residue dissolved in CH_2Cl_2 . The product was purified on a silica gel column using CH_2Cl_2 as eluent. A purple band was collected, and upon evaporation of CH_2Cl_2 , $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ was obtained in ca. 30% yield.²⁰ The starting material $\text{Ru}_2(\text{dpf})_4\text{Cl}$, which has not been reported previously, has a magnetic moment (3.96 μ_B , 298 K) very close to that reported for $\text{Ru}_2(\text{ap})_4(\text{C}\equiv\text{CC}_6\text{H}_5)$ (3.92 μ_B , 308 K), where ap is a 2-anilino-pyridinate ion.²¹ The magnetic moment is consistent with the presence of three unpaired electrons. $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ is unambiguously diamagnetic as determined by the ^1H and ^{13}C NMR.²²

The crystal structure of $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ reveals several unusual features (Figure 1): (i) The Ru-Ru bond distance (2.556(1) Å) is much longer than expected for a Ru_2^{6+} complex of this structural type; for example, $\text{Ru}_2(\text{DFM})_4$ (DFM = N,N' -ditolylformamidinate)⁸ and $\text{Ru}_2(\text{dpf})_4\text{Cl}$ have Ru-Ru bond distances of 2.475 and 2.339 Å, consistent with bond orders of

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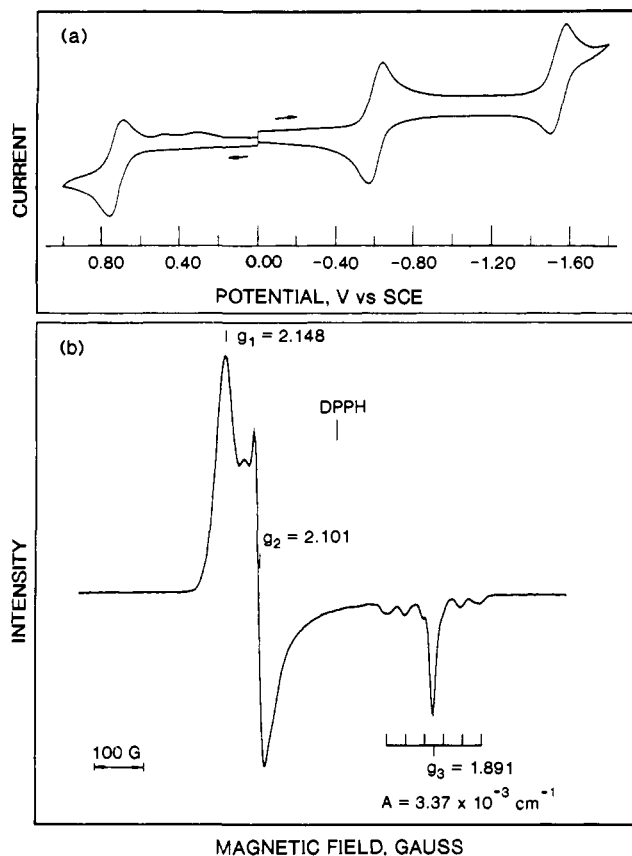


Figure 2. (a) Cyclic voltammogram of $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ in CH_2Cl_2 , 0.1 M TBAP. Scan rate = 0.10 V/s. (b) ESR spectrum at 77 K after bulk controlled-potential electroreduction of $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ at -0.90 V vs SCE in CH_2Cl_2 , 0.1 M TBAP.

2 and 2.5, respectively, and the electronic configurations reported for Ru_2^{4+} [$(\sigma^2\pi^4\delta^2\pi^*4\delta^*0)^{8,9}$ or $(\sigma^2\pi^4\delta^2\pi^*3\delta^*1)^7$] and Ru_2^{5+} ($\sigma^2\pi^4\delta^2(\pi^*\delta^*)^3$)²¹ compounds. On this basis, $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ should have a bond order of 3 and presumably have a shorter Ru-Ru bond distance. (ii) The Ru-Ru-C axial angles are nonlinear (average 159.8°). (iii) Two long (average 2.100 Å) and two short (average 2.009 Å) Ru-N bonds are observed.²³ The longer bonds show a compressed Ru-Ru-N angle (average 80.1°) compared to the short Ru-N bond (average 92.7°). The average N-Ru-Ru-N torsion angle is 14.6° .

Figure 2a shows the cyclic voltammogram of $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ in CH_2Cl_2 with 0.1 M TBAP. There are two reversible one-electron reductions at $E_{1/2} = -0.61$ and -1.54 V and a reversible one-electron oxidation at $E_{1/2} = 0.73$ V. Each process appears to be metal centered, and they correspond to the formation of Ru_2^{5+} , Ru_2^{4+} , and Ru_2^{7+} complexes, respectively. Two waves observed at $E_{pc} = 0.48$ and 0.32 V apparently result from a chemical reaction involving an unstable Ru_2^{7+} complex.

The ESR spectrum of $[\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2]^-$ generated electrochemically gives a rhombic signal as shown in Figure 2b.²⁴ The shape of the signal supports the presence of one unpaired electron.^{3,4,25,26} This is surprising since all previous Ru_2^{5+} complexes of this structural type have three unpaired electrons with the exception of $\text{Ru}_2[(p\text{-tolyl})\text{NNN}(p\text{-tolyl})_4(\text{CH}_3\text{CN})\cdot\text{BF}_4]^{10}$. The latter complex has one unpaired electron but is ESR silent

(23) The long Ru-N bonds are the ones adjacent to the dpf phenyl rings that are closest to the axial phenyl, and flatten out against it.

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down to 77 K. The appearance of the g_3 tensor in the ESR spectrum is a result of the distribution of ruthenium isotopes of different nuclear spins in the complex and deserves further comments. The observed hyperfine coupling which makes up 29.8% of the signal (sextet, $A = 3.37 \times 10^{-3} \text{ cm}^{-1}$) is due to coupling to the ^{99}Ru ($I = 5/2$, 12.7%) and ^{101}Ru ($I = 5/2$, 17.1%) isotopes, and the remaining, more intense singlet results from that fraction of the complex that contains the other ruthenium isotopes ($I = 0$, 70.2%).

Obviously, there remain many unanswered questions regarding the electronic structure of $\text{Ru}_2(\text{dpf})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$. A thorough investigation of the chemical, electrochemical, and spectroscopic properties of this complex as well as the synthesis of other Ru_2^{6+} complexes²⁷ is under way.

Acknowledgment. The support of the Robert A. Welch Foundation (Grant E-918) is gratefully acknowledged.

(27) $\text{Ru}_2(\text{ap})_4(\text{C}\equiv\text{CC}_6\text{H}_5)_2$ has been synthesized by a modification of the procedure described in ref 21. The crystal structure and other properties are currently under investigation.

New Route to Substituted Piperidines via the Stevens [1,2]-Shift of Ammonium Ylides

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Piperidine rings are frequently encountered structural components in alkaloid natural products. Recently, we have investigated an approach to functionalized cyclic amines via ammonium ylides. The Stevens rearrangement of ammonium ylides has often been the subject of mechanistic studies since its initial observation,¹ yet it has been only sporadically applied to organic synthesis.² Potential problems include competing Hofmann eliminations³ or Sommelet-Hauser rearrangements,⁴ as well as controllable generation of the ylide intermediate. However, we felt that the benefits of the reaction (successive formation of strategic carbon-nitrogen and carbon-carbon bonds) demanded a closer examination of its applicability to synthesis.

An attractive method for direct generation of the requisite cyclic ylides involves rhodium(II)-catalyzed decomposition of diazo carbonyl compounds⁵ bearing dialkylamino substituents six centers away from the carbenoid center (eq 1).⁶⁻⁸ Stevens [1,2]-shift

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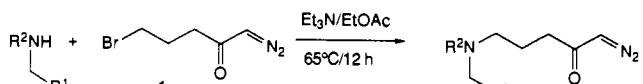
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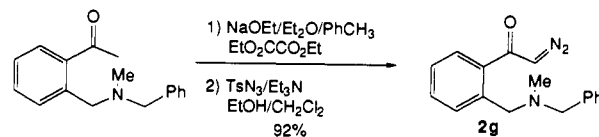
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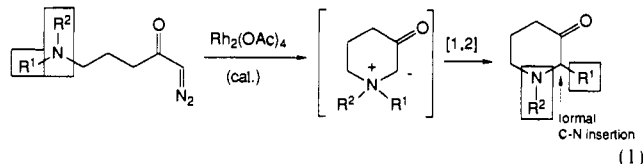
Scheme I



Substrate	R ¹	R ²	Yield
2a	Ph	Me	95%
2b	Ph	Et	83%
2c	CO ₂ Et	Me	72%
2d	p-Ac-C ₆ H ₄	Me	51%
2e	p-MeO-C ₆ H ₄	Me	82%
2f	p-NO ₂ -C ₆ H ₄	Me	60%



of one of the exocyclic groups would result in a new nitrogen heterocycle in which the carbenoid carbon had formally undergone insertion between N and R¹. Although competing C-H insertion might be a concern in those cases where a five-centered transition state was accessible,⁹ we felt that the electron deficient carbenoid would preferentially react at the site of greatest electron density, the amino lone pair. We report here the successful implementation of this strategy and its utility in the synthesis of 2-substituted piperidin-3-ones.



The most convenient route to the desired substrates proved to be direct alkylation of secondary amines with 5-bromo-1-diazo-2-pentanone (1)¹⁰ (Scheme I). In this way, diazo ketone substrates 2a-f were prepared in 51-95% yield. Compound 2g was efficiently obtained from 2'-acetyl-N-benzyl-N-methylbenzylamine via deacylative diazo transfer on the oxalacetyl derivative.¹¹

Table I lists the results obtained from addition of compounds 2a-g to a catalytic amount of $\text{Rh}_2(\text{OAc})_4$ in dichloromethane. A major concern was the known high affinity of amines for the empty coordination sites on the dimeric catalyst.¹² The only prior successful example of ammonium ylide generation from Rh-carbenoids overcame this problem by use of extremely long addition times.^{3a} In the event, substrates 2a-f gave good to excellent yields of the desired 3-piperidone [1,2]-shift products 3a-f without resort to high-dilution conditions or slow addition. Benzo-fused

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(12) (a) Felthouse, T. R. *Prog. Inorg. Chem.* **1982**, 29, 73. (b) Similar difficulties in effecting the Rh(II)-catalyzed decomposition of diazo carbonyl compounds in the presence of amines were encountered in our labs: West, F. G.; Glaeske, K. W.; Naidu, B. N. Manuscript in preparation.