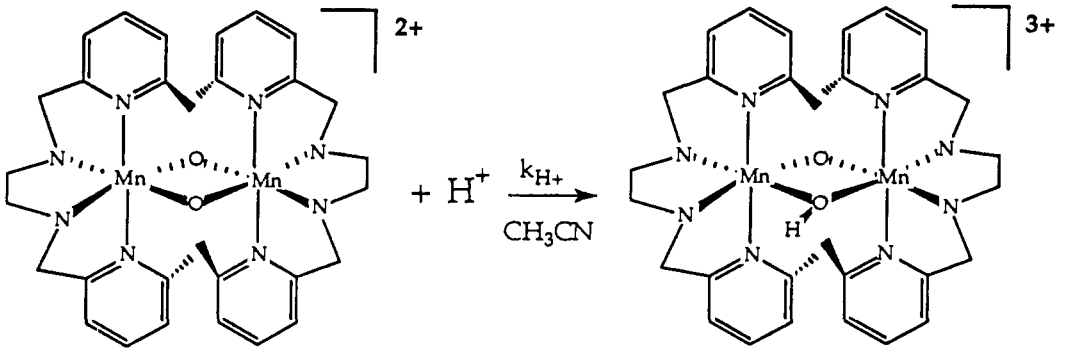
Scheme I



[3] [3H]+

two consecutive first-order reactions. We thus, after taking into account the fact that $HClO_4$ is a strong acid in CH_3CN,[17] obtained a value of 5440 M^{-1} s^{-1} at 25 °C for k_{H+}, the second-order rate constant in Scheme I. The temperature dependence of k_{H+} showed that the slowness of this protonation reaction is due to the activation enthalpy ($\Delta H^{\ddagger}$ = 16 kcal/mol, $\Delta S^{\ddagger} \approx 0$ eu).

Spectrophotometric titration[18] of $3H^+$ with the triflate salt of 2,6-lutidinium[19] showed its CH_3CN pK_a to be 16.2 (5), implying[8d] a pK_a of approximately 8,7 in water. The protonation in Scheme I is thus thermodynamically downhill by over 16 pK_a units. With ordinary oxygens diffusion-controlled rates are observed when ΔpK_a is downhill by more than four pK_a units,[5a] so k_{H+} is more than 10^6 slower than the rate constant expected for such an oxygen.

We have obtained measurable rate constants at reduced temperatures (see Table I) for two other oxo-bridged manganese complexes, $[(TACN)_4Mn^{(IV)}{}_4(\mu\text{-}O)_6][Br]_4$ (**4**)[7a] and $[(Salpn)Mn^{(IV)}(\mu\text{-}O)]_2$ (**2**).[20] As before, rapid scan data on the protonation of **4** in excess $HClO_4$ showed the formation and decay of the known[7b,c,21] $4H^+$. The protonation of **2** with pyH^+ gave a stable product identified by its UV-vis spectrum[22] as $2H^+$. In all three cases the rate constants are *substantially slower* than those for the protonation of organic oxygens with comparable equilibrium constants.

We have been unable to measure rate constants for the protonation of $[(bispicen)Mn^{(III)}(\mu\text{-}O)_2Mn^{(III)}(bispicen)][ClO_4]_3$ (**1**)[11] (the (III,III) compound could not be generated from the reduction of the (III,IV) precursor fast enough to allow measurement of k_{H^+}), $[(HB(Pz)_3)Fe^{(III)}(\mu\text{-}O)(\mu\text{-}O_2CCH_3)_2Fe^{(III)}(HB(Pz)_3)]$ (**5**)[23] (even at −30 °C the formation of $5H^+$ [7d] was too fast to observe), and $[(bipy)_2Mn^{(III)}(\mu\text{-}O)_2Mn^{(IV)}(bipy)_2][ClO_4]_3$ (**6**)[24] ($6H^+$ decayed to a known trimer[4] faster than the mixing time of our stopped-flow; k_{obs} = 25.2 s^{-1} at 25 °C, pH 2,3).

The slow protonation rates we have observed suggest that proton transfers could be rate-determining in the action of oxo-bridged metalloproteins. We are now investigating the effects of various structural features of oxo-bridged complexes on the rates at which they accept protons.

Acknowledgment. This work was supported by NSF Grant CHE-9120454. We are grateful to Holden Thorp (N.C. State) for a sample of **1**, to Vincent Pecoraro (U. of Michigan) for a sample of **2**, and to Derek Hodgson and Patricia Goodson (Wyoming) and to Stephen Lippard (MIT) for helpful discussions. We thank the University of Wyoming chemistry department for the use of its diffuse reflectance apparatus.

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(21) The fact that the relatively featureless UV-vis spectrum of $4H^+$ in CH_3CN is reproduced in the diffuse reflectance spectrum of solid $4H^+$ implies that the μ-OH structure established for $4H^+$ by X-ray crystallography (refs 7b,c) persists in solution. UV-vis observation of the reaction of **4** with $HClO_4$ gives the same two isosbestic points (530 and 620 nm) observed by Armstrong[7c] during the spectrophotometric titration of **3** with triflic acid.
(22) A μ-OH structure has been proposed for $2H^+$ on the basis of the increase (≈0.1 Å) in the Mn-Mn distance (EXAFS) of $2H^+$ over that of **2**. The UV-vis spectrum of $2H^+$ in CH_3CN agrees with that reported in ref 13.
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A Novel Pd-Catalyzed Cycloalkylation to Isoxazoline 2-Oxides. Application for the Asymmetric Synthesis of Carbanucleosides

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Received June 22, 1992

2-Ene-1,4-diols constitute useful building blocks for synthesis via Pd-catalyzed reactions because of their potential for sequential replacement of each oxygen leaving group and for enantioselective synthesis via dissymmetrization with chiral ligands.[1-4] The ambident nature of nitro-stabilized anions permits both C and O alkylation.[5,6] We wish to record an unusual Pd-catalyzed cy-

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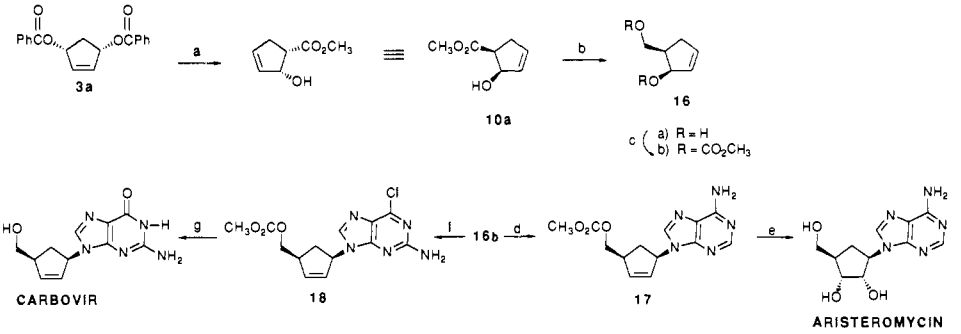
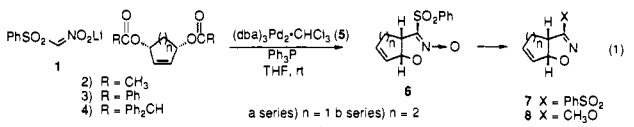
Scheme I. General Regio-, Diastereo-, and Enantioselective Synthesis of Carbanucleosides[a]



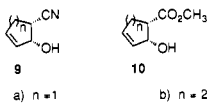
[a] (a) See text. (b) LAH, ether, room temperature, 95%. (c) n-C_4H_9Li, THF, −78 to 0 °C, recooled to −78 °C, $ClCO_2CH_3$, 98%. (d) 5% $Pd(OAc)_2$, 40% $(i\text{-}C_3H_7O)_3P$, n-C_4H_9Li, THF, room temperature, then adenine, DMSO, room temperature, 96%. (e) (i) NaOH, C_2H_5OH, room temperature; (ii) OsO_4, NMO, THF–H_2O, 0 °C, 88%, 2.4:1. (f) 10% $(C_3H_5PdCl)_2$, 40% TPP, 2-amino-6-chloropurine, THF, room temperature, 77%. (g) NaOH, H_2O, reflux, 50%.

cloalkylation which employs both of these possibilities and which creates the novel and highly reactive 3-(phenylsulfonyl)isoxazoline 2-oxide. As an equivalent of a diastereo- and enantioselective hydroxy–alkoxycarbonylation and hydroxycyanation, such systems become useful asymmetric building blocks for the synthesis of the important antiviral carbanucleosides.[7-9]

Initial studies explored the reaction of lithium [(phenylsulfonyl)methylene]nitronate (**1**)[10] with *cis*-1,4-diacetoxycyclopent-2-ene (**2a**) in the presence of 1–5 mol % of Pd(0) catalyst **5** and triphenylphosphine (TPP), which gave a single alkylation product identified as the isoxazoline 2-oxide **6a** on the basis of its spectral data and subsequent chemistry. For example, de-

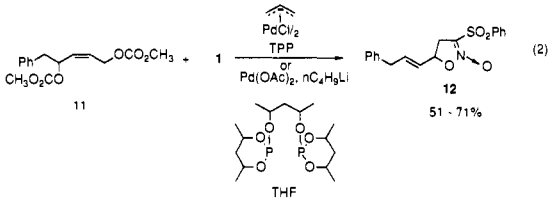


oxygenation with $SnCl_2{\cdot}2H_2O$ (CH_3CN, room temperature) gave a 94% isolated yield of the isoxazoline **7a**.[11] As a pseudoacyl sulfone, nucleophilic substitution of the sulfone occurred readily (91% yield) as illustrated by its solvolysis in basic methanol (K_2CO_3, CH_3OH, 50 °C) to the methoxy analogue **8a**. Reduction of the sulfone with $Mo(CO)_6$[13] in moist acetonitrile at reflux gave the (*Z*)-hydroxy nitrile **9a** (94% yield).[14] Reduction of the methoxyisoxazoline **8a** to the (*Z*)-hydroxy ester **10a** with $Mo(CO)_6$ required the presence of 3 equiv of boric acid and methanol to avoid amide formation (84% yield).



Reaction of the six-membered-ring analogue **4b** required refluxing THF, all other conditions being the same, to give a 92% yield of the isoxazoline 2-oxide **6b**. In a series of experiments completely analogous to that reported for the five-membered ring, the derivatives **7b** (89%), **8b** (86%), **9b** (94%), and **10b** (77%) were also synthesized.

Extrapolation to an acyclic unsymmetrical difunctional substrate **11** tested the chemoselectivity of the ionization.[15] A single regioisomeric isoxazoline 2-oxide **12** was isolated as a crystalline (mp 116–8 °C) solid. The chemoselectivity exhibited requires selective ionization of the sterically more accessible primary carbonate of **11**.



A key feature of this strategy to these intriguing heterocyclic building blocks is the prospect for asymmetric induction with the

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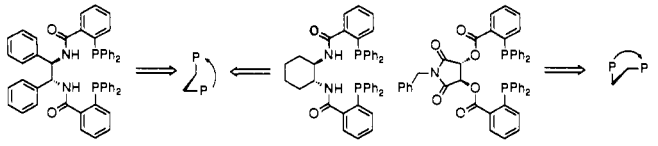
meso 2-ene-1,4-diol substrates **2–4** (n = 1 or 2). Using our modular asymmetric ligands **13–15**[1] (Pd:P = 1:2,4), **3a** or **4a** gave the isoxazoline 2-oxide in 95% ee (from **4a**, 94% yield), 96% ee (from **3a**, 94% yield, or **4a**, 93% yield), and 64% ee (from **4a**, 86% yield), respectively. As observed previously, the diamide ligands



13 **14** **15**

invariably give higher ee's than diester ligands. Assessment of the ee and assignment of the absolute configuration were performed by conversion of the hydroxy nitrile **9a** to the (*S*)-*O*-methylmandelates,[16] which establishes the absolute configuration of the cycloadduct to be as depicted in **6a** from the reactions with ligands **13** and **14** and its mirror image from the reaction with ligand **15**. In agreement with our model, the counterclockwise oriented binding posts of **13** and **14** initiated preferential ionization of the *pro-S* leaving group, whereas the clockwise oriented binding posts initiated preferential ionization of the *pro-R* leaving group.

In contrast to enzymatic reactions of these types of substrates which do not readily extrapolate from the five- to six-membered-ring systems,[17] the cycloalkylation of **2b** with ligand **14**, initially at 0 °C then at reflux, gave a 68% isolated yield of **6b** in addition to 23% of the initial C-alkylated but uncyclized product. The latter can be cyclized to the former by re-exposure to Pd(0) catalysts. Analysis of both products using the NMR (*S*)-*O*-methylmandelate method revealed that they had >97% ee!

This regio-, diastereo-, and enantioselective cycloalkylation served as a convenient entry into the important carbanucleosides as illustrated in Scheme I. Dicarbonate **16**, $[\alpha]_D$ −153.9° (*c* 3.75, $CHCl_3$), available in 60% overall yield and >95% ee from **3a**, proved to be a pivotal intermediate. For example, Pd-catalyzed condensation of dicarbonate **16** with adenine to give **17** provided entry to aristeromycin,[8] whereas similar reaction with 2-amino-6-chloropurine to give **18** ultimately led to carbovir,[9] an excellent candidate for development as a potential antiretroviral agent for the treatment of AIDS.[18]

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our programs. We thank the UCSF Mass Spectrometry Facility, sponsored by the NIH Division of Research Resources, for mass spectra.

Registry No. **1**, 74738-03-7; **2a**, 54664-61-8; **2b**, 78776-45-1; **3a**, 4157-02-2; **3b**, 77300-23-3; **4a**, 143346-11-6; **4b**, 143346-18-3; **5**, 52522-40-4; **6a**, 143346-12-7; *ent*-**6a**, 143395-30-6; **6b**, 143346-19-4; **6b** open ring derivative, 143346-25-2; *end*-**6b**, 143395-31-7; **7a**, 143346-13-8; **7a** enantiomer, 143491-48-9; **7b**, 143346-20-7; **8a**, 143346-14-9; **8b**, 143346-21-8; **9a**, 143346-15-0; **9a** (*S*)-*o*-methyl mandelate ester, 143346-27-4; **9b**, 143346-22-9; **9b** (*S*)-*O*-methyl mandelate ester, 143346-26-3; **10a**, 143370-10-9; **10b**, 143346-23-0; **11**, 112655-09-1; **12**, 143346-16-1; **13**, 138517-62-1; **14**, 138517-61-0; **15**, 138517-64-3; **16a**, 143395-28-2; **16b**, 143346-24-1; **17**, 143346-17-2; **18**, 143395-29-3; aristeromycin, 19186-33-5; carbovir, 118353-05-2; tris(pentane-2,4-dioxy)diphosphine, 137939-55-0; allylpalladium chloride dimer, 12012-95-2; adenine, 73-24-5; 2-amino-6-chloropurine, 10310-21-1.

Supplementary Material Available: Experimental details for compounds **6a–10a**, **6b–10b**, **12**, **16a**, **16b**, **17**, and **18** (5 pages). Ordering information is given on any current masthead page.

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Kinetics of Methylation of a Cesium Enolate in THF. The Importance of the Free Enolate Ion in an Aggregated System[1]

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It is well-known that alkali metal enolates and related species are frequently aggregated in nonpolar solvents such as ethers and hydrocarbons.[2] Most of the recent research in this field has been directed toward the elucidation of the factors that influence the state of aggregation of lithiated species at equilibrium.[3] However, in the few kinetic studies that have been carried out,[4–6] it has usually been found that the reactive intermediate is present only in small or negligible concentrations relative to the predominant aggregate(s). Therefore, kinetic studies are an essential complement to equilibrium studies. Herein we present a preliminary report of our investigations of the cesium enolate of 1-(4-biphenylyl)-2-methyl-1-propanone[7] (*p*-phenylisobutyrophenone, PhIBP). This enolate was chosen because its spectrum (λ_{max} 380 nm, ϵ 2180 M^{-1} cm^{-1}) permits use of the double-indicator technique.

The equilibrium aggregation number of cesiated PhIBP (Cs-PhIBP) in tetrahydrofuran (THF) was determined by acidity studies of the type detailed previously[8] to be 2.17 ± 0.14 and 3.17 ± 0.15 at 25 and −20 °C, respectively, over a 10-fold concentration range (Figure 1).[9] The THF used in these experiments contained about 10^{-3} M water.[10] Note that the aggregation numbers are averages and therefore do not necessarily correspond directly to the species that are actually present; for example, the aggregation number 3.17 could equally arise from an essentially trimeric species or a mixture of dimers and tetramers.

Initial rate studies of the alkylation of Cs-PhIBP by methyl tosylate (MeOTs) were carried out at 25 and −20 °C in THF by following the decrease in the enolate absorbance to 5–10% reaction. The use of initial rates avoids potential complications from the possible formation of mixed aggregates[4b,e] (Cs-PhIBP/CsOTs). The data were fit by properly weighted least squares analysis[11] to the equation log (rate) = log (k) + x log [Cs-PhIBP] + y log [RX] where RX is the electrophile. In this equation x can be shown to be equal to $\bar{n}_k/\bar{n}$, where $\bar{n}$ is the equilibrium aggregation

(1) Carbon Acidity. 84.

(2) For reviews, see: (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624 and references therein. (c) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

(3) For leading references, see the following and the citations therein: (a) Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 794. (b) Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403.

(4) (a) Ellington, J. C.; Arnett, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 7778. (b) DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. (c) Arnett, E. M.; Maroldo, S. G.; Schriver, G. W.; Schilling, S. L.; Troughton, E. B. *J. Am. Chem. Soc.* **1985**, *107*, 2091. (d) Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078. (e) Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805. (f) Miller, J. A.; Zook, H. D. *J. Org. Chem.* **1977**, *42*, 2629. (g) Zook, H. D.; Rellahan, W. L. *J. Am. Chem. Soc.* **1957**, *79*, 881.

(5) In one instance, however, it was concluded that the predominant species is the true reactive intermediate: Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494.

(6) On the other hand, the aggregation and reactivity of simple alkyllithium compounds has been relatively well studied; see the citations in ref 2b and the following leading references: (a) Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715. (b) McGarrity, J. F.; Ogle, C. A.; Birch, Z.; Loosli, H. *J. Am. Chem. Soc.* **1985**, *107*, 1810.

(7) Long, L. M.; Henze, H. R. *J. Am. Chem. Soc.* **1941**, *63*, 1939.

(8) Kaufman, M. J.; Streitwieser, A. *J. Am. Chem. Soc.* **1987**, *109*, 6092.

(9) The errors are 1 standard deviation.

(10) The THF was distilled from sodium–benzophenone, degassed, stirred over sodium–potassium alloy until the characteristic blue color appeared, and vacuum transferred into a dried receiver. The water content was determined by the quenching of a strong base such as (diphenylmethyl)lithium.

(11) Wentworth, W. E. *J. Chem. Educ.* **1965**, *42*, 96.

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