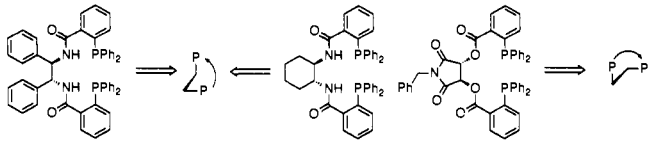
meso 2-ene-1,4-diol substrates **2–4** (n = 1 or 2). Using our modular asymmetric ligands **13–15**[1] (Pd:P = 1:2.4), **3a** or **4a** gave the isoxazoline 2-oxide in 95% ee (from **4a**, 94% yield), 96% ee (from **3a**, 94% yield, or **4a**, 93% yield), and 64% ee (from **4a**, 86% yield), respectively. 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]

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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.

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(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.

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(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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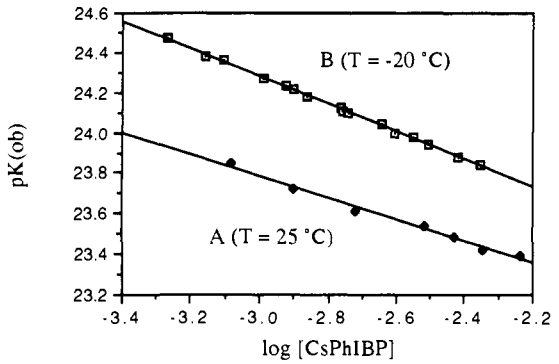

Figure 1. Dependence of the observed cesium ion pair acidity of PhIBP on the concentration of Cs-PhIBP. The slope of the plot is equal to $1/\bar{n} - 1$, where $\bar{n}$ is the average equilibrium aggregation number[8] of Cs-PhIBP. A: $T = 25$ °C, slope = -0.54 ± 0.03. B: $T = -20$ °C, slope = -0.69 ± 0.02.

Table I. Initial Rate Kinetics for the Reaction of Cs-PhIBP with MeOTs in THF[a]

T (°C)	log k	x[b]	y[c]	$\bar{n}_k$[d]
25.0[e]	-2.3 ± 0.3	0.23 ± 0.05	1.02 ± 0.07	0.50 ± 0.11
-20.0[f]	-4.0 ± 0.1	0.22 ± 0.02	1.16 ± 0.04	0.70 ± 0.07

[a] Errors are 1 standard deviation. [b] Kinetic order in Cs-PhIBP. [c] Kinetic order in MeOTs. [d] Kinetic aggregation number. See text. [e] Twelve points. [f] Eighteen points.

number and $\bar{n}_k$, the average "kinetic aggregation number", is the average aggregation number over those aggregates that react directly with the electrophile. The results are summarized in Table I. The fractional orders in Cs-PhIBP indicate that aggregates lower than those predominating at equilibrium are the actual reactive intermediates. A value of $\bar{n}_k = 0.5$ means that a dissociated species is the reactive entity; that is, at 25 °C we find that the reactive species is the free enolate ion, even though Cs-PhIBP is substantially aggregated![12] Since these ion pairs are more tightly bound than the monomeric indicator cesium salts, conductivity studies of the indicators[13] then indicate that the free enolate ion is present at no higher than about 5×10^{-6} M when the total enolate concentration is 2.5×10^{-3} M; therefore, the free enolate ion must be at least about 1000 times as reactive toward MeOTs as the predominating aggregate(s). At −20 °C the identity of the reactive intermediate(s) is somewhat ambiguous ($\bar{n}_k = 0.70$), but it is clear that the free enolate ion still plays an important role in the reaction.

Products of the reaction were analyzed by gas chromatography. The ratio of products resulting from alkylation at carbon to those resulting from alkylation at oxygen (the C/O ratio) is about 1.2, independent of the temperature and the extent of reaction. The insensitivity of the product distribution to the extent of conversion is evidence that the CsOTs does not affect $\bar{n}_k$; that is, the free enolate ion is the reactive intermediate throughout the reaction. That the C/O ratio is insensitive to the temperature is surprising, given that $\bar{n}_k = 0.70$ at −20 °C; that is, at this temperature, species other than the free enolate ion (monomeric ion pair or higher aggregates) apparently contribute significantly to the reactivity. However, it is possible to show that any mechanism that changes the free ion concentration ratio $[PhIBP^-]/[Cs^+]$ to a value greater than unity will cause an increase in the value of $\bar{n}_k$, even if the free enolate ion is the only reactive intermediate. For example, this effect would occur if CsOTs or Cs-PhIBP aggregates complexed a fraction of the free Cs^+.

Finally, in a preliminary experiment, the lithium enolate of PhIBP was treated with MeOTs in THF at 25 °C. The reaction was slow compared to the Cs-PhIBP reactions, and after about 10% reaction, the C/O ratio was about 0.4. This result establishes that the free enolate ion is not the dominant reactive intermediate in this case (compared to the C/O ratio obtained in the Cs-PhIBP reactions). Moreover, the lithium cation apparently diminishes the nucleophilicity of the carbon atom relative to the oxygen.

Acknowledgment. This research was supported in part by NIH Grant GM 33609.

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β-Sialyl Phosphite and Phosphoramidite: Synthesis and Application to the Chemoenzymatic Synthesis of CMP-Sialic Acid and Sialyl Oligosaccharides

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A major problem in oligosaccharide synthesis[1] is sialylation.[2] The tertially hindered anomeric center and the lack of an electron-demanding group adjacent to the anomeric center of sialic acid (NeuAc) make the sialylation reaction particularly difficult to execute in an elimination-free and stereocontrolled manner. The same problems are also encountered in the chemical synthesis of CMP-NeuAc. Here we report the synthesis of β-sialyl dibenzyl phosphite using dibenzyl *N,N*-diethylphosphoramidite[3] (DDP) and the application of the glycosyl phosphite[4] to the synthesis of α2,6- and α2,3-linked sialyl saccharides. We also report the chemical synthesis of a protected CMP-sialic acid for use in the study of enzymatic transfer of unnatural NeuAc.[5]

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