units are quite different from those of polythioethers containing repeating ethylene sulfide units. The CO–CC torsional unit is energetically most stable in the anti conformation,[6,18] and the OC–CO unit favors gauche torsion angles;[7,19] both of these preferences are opposite to those manifested by the analogous sulfur-containing torsional units. Because of the gauche preference of the OC–CO unit, in its most stable conformations this unit will juxtapose its two oxygen atoms in a manner that is conducive to simultaneous interaction with a single metal cation. In contrast, the anti disposition preferred by SC–CS bonds in ethylene sulfide oligomers is not conducive to metal ion chelation. Incorporation of SCH_2CH_2S subunits into potential metal binding agents will be productive only if the ligand backbone somehow enforces a gauche juxtaposition of the two sulfurs, even in the absence of bound metal ions.[20]

Conclusion. The crystal structures we have reported, in conjunction with prior evidence in the literature, support the notion that macrocyclization of ethylene sulfide oligomers is not an optimal approach to the preorganizational enhancement of transition metal chelation by polythioethers. We are currently exploring alternative strategies that prearrange thioether sulfur atoms for metal ion complexation.

Acknowledgment. We thank Dr. Charles Campana of Nicolet Instrument Corp. for assistance in obtaining the crystallographic data. We also thank Thomas Stein and Caryn Lang for technical assistance. We are grateful for a Fellowship from the Graduate School of the University of Wisconsin—Madison (J.M.D.) and for support from the Searle Scholars Program (S.H.G.) and an American Cancer Society Junior Faculty Research Award (S. H.G.).

Registry No. 1, 125568-50-5; **2**, 125568-51-6; bis(2-mercaptoethyl) sulfide, 3570-55-6; α-chloro-*p*-xylene, 104-82-5; 1,8-dichloro-3,6-dithiooctane, 3563-36-8; 1,2-ethanedithiol, 540-63-6; 1-bromo-2-chloroethane, 107-04-0; *p*-methylbenzyl mercaptan, 4498-99-1.

Supplementary Material Available: Crystallographic details including tables of atomic coordinates and thermal parameters and packing diagrams of **1** and **2** (5 pages); listing of observed and calculated structure factors for **1** and **2** (10 pages). Ordering information is given on any current masthead page.

---

(18) Vögtle, F.; Weber, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 753.

(19) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.

(20) The ligand conformation observed crystallographically in tridentate transition-metal complexes of trithio-9-crown-3 is nearly the same as the conformation observed for the pure macrocycle in the solid state, and Cooper has noted that this lack of ligand reorganization upon coordination can be correlated qualitatively with complex stability. The conformational constraint associated with the nine-membered ring forces all SC–CS bonds to adopt gauche torsion angles in this trithioether. See: (a) Reference 1. (b) Rawle, S. C.; Sewell, T. J.; Cooper, S. R. *Inorg. Chem.* **1987**, *26*, 3769. (c) Glass, R. S.; Wilson, G. S.; Setzer, W. N. *J. Am. Chem. Soc.* **1980**, *102*, 5068.

Palladium-Catalyzed Alkylations in Aqueous Media

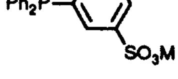
Albert L. Casalnuovo* and Joseph C. Calabrese

Contribution No. 5169 from the Central Research and Development Department,
E.I. du Pont de Nemours and Company, Experimental Station,
Wilmington, Delaware 19880-0328. *Received May 19, 1989*

Abstract: The efficient, catalytic alkylation of biomolecules and other organic substrates in aqueous media has been demonstrated. The water-soluble Pd(0) complex $Pd(PPh_2(m\text{-}C_6H_4SO_3M))_3$ (**2**: M = Na^+, K^+) was isolated and characterized by single-crystal X-ray diffraction. The relevant crystal data for this complex are as follows (M = K^+): $a = 12.618$ (1) Å, $b = 19.532$ (2) Å, $c = 24.423$ (3) Å, $\alpha = 100.65$ (1)°, $\beta = 94.37$ (1)°, $\gamma = 99.10$ (1)°; $P\bar{1}$, $T = -70$ °C, $d_c = 1.514$ g/cm³, $\mu = 7.74$ cm⁻¹; 14423 reflections; $R = 0.054$, $R_w = 0.053$. Crystalline, air-sensitive **2** catalyzed alkylation reactions in a variety of single-phase aqueous solvent systems. Hydrophobic or hydrophilic aryl and heteroaromatic halides underwent coupling reactions with aryl or vinyl boronic acids, alkynes, an alkene, and a dialkyl phosphite. Examples of the alkylation of biomolecules in aqueous media included the coupling of alkynes with unprotected iodonucleotides, iodonucleoside, and an iodoamino acid. This approach provided an alternative, convergent synthesis of T-505, part of a family of chain-terminating nucleotide reagents used in DNA sequencing and labeling.

The development of transition-metal reagents for use in aqueous solvent systems offers advantages for a wide variety of chemical processes ranging from large-scale industrial processes to fine organic synthesis.[1,2] The use of water-soluble reagents for large-scale chemical manufacture can simplify catalyst–product separation and is also attractive because of the economy and safety of using water as a solvent. Our interest in this area was spurred by the notion that water-compatible transition-metal reagents may allow the chemical modification of the molecules of life in their natural environment without the use of hydrophobic protecting groups.

We have initially focused on palladium-catalyzed alkylation and cross-coupling reactions using the known sulfonated phosphine $PPh_2(m\text{-}C_6H_5SO_3M)$ (**1**: M = Na^+, K^+)[3] to enhance the hydrophilicity of the catalyst. Despite both the broad synthetic utility of these alkylation reactions and the recent development of



1

---

(1) Reviews: (a) Kuntz, E. G. *CHEMTECH* **1987**, Sept., 570. (b) Sinou, D. *Bull. Soc. Chim. Fr.* **1986**, 480.

(2) (a) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 7542. (b) Borowski, A. F.; Cole-Hamilton, J. D.; Wilkinson, G. *Nouv. J. Chim.* **1978**, *2*, 137. (c) Okano, T.; Moriyama, Y.; Konishi, H.; Kiji, J. *Chem. Lett.* **1986**, 1463. (d) Kiji, J.; Okano, T.; Nishiumi, W.; Konishi, H. *Chem. Lett.* **1988**, 957. (e) Bahrmann, H.; Bach, H. *Phosphorous and Sulfur* **1987**, *30*, 611. Kuntz, E. U.S. Patent 4,248,802, Rhone-Poulenc Ind., 1981. (g) Kuntz, E. U.S. Patent 4,142,060, Rhone-Poulenc Ind., 1979. (h) Kuntz, E. U.S. Patent 4,087,452, Rhone-Poulenc Ind., 1978. (i) Alper, H. *J. Organomet. Chem.* **1986**, *300*, 1. (j) Smith, R. T.; Ungar, R. K.; Sanderson, L. J.; Baird, M. C. *Organometallics* **1983**, *2*, 1138. (k) Nuzzo, R. G.; Haynie, S. L.; Wilson, M. E.; Whitesides, G. M. *J. Org. Chem.* **1981**, *46*, 2861. (l) Bumagin, N. A.; Nikitin, K. V.; Beteskaya, I. P. *J. Organomet. Chem.* **1988**, *358*, 563. (m) Amrani, Y.; Lecomte, L.; Sinou, D.; Bakos, J.; Toth, I.; Heil, B. *Organometallics* **1989**, *8*, 542. (n) Larpent, C.; Patin, H. *Appl. Organomet. Chem.* **1987**, *1*(*6*), 529.

(3) Ahrland, S.; Chatt. J.; Davies, N. R.; Williams, A. A. *J. Chem. Soc.* **1958**, 276.

water-based catalyst systems for a number of other important chemical reactions, including hydrogenation, hydroformylation, carbonylation, and methathesis polymerizations,[1,2] palladium-catalyzed alkylations in aqueous solvents with water-soluble catalysts remain largely unexplored.[4] A related point of interest in this study was the synthesis, characterization, and properties of a water-soluble Pd(0) catalyst. While the intermediacy of Pd(0) can be inferred from reports of other aqueous Pd-catalyzed reactions that use sulfonated phosphines,[2c,d] no published accounts of the isolation of Pd(0) complexes containing sulfonated phosphines have appeared. Here we report a simple preparation of such a complex and its use in the catalytic alkylation of biomolecules and other organic substrates in aqueous media.

Experimental Section

General Methods. All reactions were carried out under a nitrogen atmosphere by using either Schlenk techniques or a Vacuum Atmospheres drybox. Organic solvents were distilled and degassed before use. HPLC grade water (EM Science) was degassed and used without distillation. 5-Iododideoxyuridine 5′-triphosphate was prepared from 5-iododideoxyuridine with use of a previously described method.[5] Other iodonucleotides and 3-iodotyrosine were obtained from the Sigma Chemical Co. The dye **4** was prepared as described elsewhere with propargylamine to displace the NHS ester.[6] Phenylboronic acid, propargylamine, phenylacetylene, ethyl acrylate, diethyl phosphite, 4-bromopyridine hydrochloride, and aromatic bromides and iodides were purchased from the Aldrich Chemical Co. and used without further purification. (*E*)-β-Phenylethenylboronic acid[7] and $PPh_2(m\text{-}C_6H_4SO_3M)$[3] were prepared according to published procedures. 4-Tolylboronic acid was prepared from 4-tolyllithium and triisopropoxyborane by using a published procedure.[8] IR, ^1H NMR, $^{13}C\{^1H\}$ NMR, and $^{31}P\{^1H\}$ NMR spectra were recorded on Perkin-Elmer 983G, QE 300, and Nicolet 300 spectrometers. GC analyses were obtained on a Hewlett Packard 5890 gas chromatograph with a high-performance cross-linked methyl silicone megabore column. HPLC analyses were obtained with use of a reverse-phase Vydak C18 column.

$Pd(PPh_2)(m\text{-}C_6H_4SO_3M)\cdot(H_2O)_4$ (2: $M = Na^+, K^+$). To an aqueous solution of 0.10 M Na_2PdCl_4 (2.42 mL, 0.242 mmol) was added a solution of **1** (0.314 g, 0.863 mmol) in 5 mL of ethanol. The resulting yellow solution was stirred for 5 min and then activated Zn dust was added (0.090 g, 1.38 mmol). The suspension was stirred for 1 h, filtered over Celite, and washed with ethanol. The yellow filtrate was concentrated in vacuo and layered with *t*-BuOH. Complex **1** was obtained as air-sensitive yellow crystals after 2–3 days: yield 0.285 g (94%). Yields typically varied from 85 to 94%. The potassium salt of **2** was synthesized in a similar fashion in high yield from K_2PdCl_4 and the potassium salt of **1**. ^1H (CD_3OD): 7.0–7.15 (m, 15 H), 7.15–7.28 (m, 18 H), 7.35, (t, br, 8.6 Hz, 3 H), 7.69 (m, 6 H). $^{31}P\{^1H\}$ (CD_3OD): 24.6 (s). Crystals of **2** ($M = Na^+$) contain from 3 to 5 equiv of H_2O/Pd after drying in vacuo based upon elemental analysis and Karl Fischer titration. Anal. Calcd for $C_{54}H_{42}Na_3O_9P_3PdS_3\cdot 3H_2O$: C, 51.74; H, 3.86; P, 7.41; Pd, 8.49. Found: C, 51.72; H, 3.89; P, 7.30, Pd, 8.82.

Sodium Borohydride Reduction of Pd(II) in the Presence of 1. Reduction by sodium borohydride gave a noncrystalline Pd(0) complex(es) of lower purity and a formulation closer to PdL_4 (suggested by elemental analysis and ^{31}P NMR). Aqueous solutions of this material were effective at catalyzing the alkylation reactions. In a typical procedure 4–5 equiv of **1** were added to a 0.1 M solution of Na_2PdCl_4 in water. A solution of $NaBH_4$ (2.2 equiv) in water was added dropwise to the stirring solution, during which time H_2 evolved. Water was removed in vacuo and the thoroughly dry residue was taken up in THF and filtered. The bright yellow filtrate was concentrated to dryness and the yellow solid collected. ^{31}P (CD_3OD): 13.3 (s, br; in THF-d_8, 20.9 (s, br, int. = 2.6), −6.6 (s, int = 1). Anal. Calcd for $PdC_{72}H_{56}P_4S_4O_{12}Na_4$: C, 55.30; H, 3.61; P, 7.92; S, 8.20; Na, 5.88. Found: C, 54.96; H, 3.91; P, 6.76; S, 8.24; Na, 7.82.

$p\text{-}CH_3C_6H_4C_6H_5$. To a solution of phenylboronic acid (0.122 g, 1 mmol) and 4-iodotoluene (0.218 g, 1.0 mmol) in 5 mL of acetonitrile was added a solution of **2** (0.120 g, 0.1 mmol) and Na_2CO_3 (0.212 g, 2 mmol) in 5 mL of water. The reaction mixture was heated under N_2 at 80 °C for 7 h. The reaction mixture was then extracted twice with benzene and the benzene extract analyzed by GC with an internal standard. The yield of biaryl was 70% by GC. A 7% yield of biphenyl was also detected. The biaryl was identified by high-resolution GC/MS. A sample of the biaryl was also isolated by extraction of the reaction mixture with Et_2O, drying over Na_2SO_4, filtration, and then concentration in vacuo. The residue was dissolved in hexane and passed through a small pad of silica gel with hexane as eluent. Removal of the solvent in vacuo gave an authentic sample of the biaryl. ^1H ($CDCl_3$): 2.23 (s, 3 H, CH_3), 7.09 (d, 7.4 Hz, 2 H, ArH), 7.16 (m, 1 H, ArH), 7.26 (t, 7.0 Hz, 2 H, ArH), 7.33 (d, 8.0 Hz, 2 H, ArH), 7.42 (m, 2 H, ArH). $^{13}C\{^1H\}$ ($CDCl_3$): 21.1 (s, CH_3), 126.94 (s), 126.97 (s), 128.66 (s), 128.70 (s), 129.4 (s), 136.9 (s, C_1), 138.4 (s, $C_{1',4}$), 141.2 (s, $C_{1',4}$). Mp = 45–47 °C (lit.[9] mp 44–47 °C). High-resolution GC/MS M^+ 168.0955; calcd 168.0939. Elemental composition = $C_{13}H_{12}$.

$4\text{-}CH_3C_6H_4\text{-}4'\text{-}C_5H_4N$. To a slurry of $4\text{-}BrC_5H_4N\cdot HCl$ (1.116g, 5.75 mmol) and *p*-tolylboronic acid (0.629 g, 4.63 mmol) in 10 mL of water was added 13 mL of 1 M Na_2CO_3, 5 mL of benzene, and a solution of the catalyst (0.88 mmol) in 8 mL of MeOH. The reaction was heated at 80 °C under N_2 for 6.5 h. After being cooled to room temperature, the reaction mixture was extracted with benzene and the benzene extract concentrated to dryness in vacuo. The residue was extracted with Et_2O, filtered, and concentrated to dryness in vacuo. The crude biaryl so obtained (0.928 g) was purified by flash chromatography on silica gel with ethyl acetate/petroleum ether/methanol (50/50/1). The pure biaryl was obtained as a white solid. Yield 0.771 g (98%). ^1H (THF-d_8): 2.37 (s, 3 H, CH_3), 7.28 (d, 8.0 Hz, 2 H, ArH), 7.53 (m, 2 H, ArH), 7.61 (d, 8.1 Hz, 2 H, ArH), 8.55 (d, 6.0 Hz, 2 H, ArH). ^1H NMR in agreement with literature.[10] Mp = 88–90 °C (lit.[11] mp 88–89 °C). Conversion to methyl benzoate via $KMnO_4$ and $MeOH/H^+$ ($M^+ = 213$).

$4\text{-}CH_3C_6H_4\text{-}4'\text{-}C_6H_4CH_2CO_2H$. To a slurry of $4\text{-}BrC_6H_4CH_2CO_2H$ (0.258 g, 1.2 mmol), *p*-tolylboronic acid (0.136 g, 1.0 mmol), and the catalyst (0.15 mmol) in 5 mL of water was added 2 mL of a 1 M solution of Na_2CO_3. The reaction mixture was heated at 80 °C for 10 h under N_2, cooled to room temperature, acidified with 10% HCl and extracted with Et_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness in vacuo. Extraction of the residue with Et_2O, followed by filtration and solvent evaporation, gave 0.216 g of crude product. The product was purified by flash chromatography on silica gel with $CH_2Cl_2/MeOH$ ($95/5 \rightarrow 90/10$). Yield 0.160 g of a white solid (71%). ^1H (CD_2Cl_2): 2.39 (s, 3 H, CH_3), 3.72 (s, 2 H, CH_2), 7.26 (d, 8.0 Hz, 2 H, ArH), 7.35 (d, 8.0 Hz, 2 H, ArH), 7.50 (d, 8.0 Hz, 2 H, ArH), 7.57 (d, 8.0 Hz, 2 H, ArH). IR (Nujol) $\nu_{C=O} = 1719, 1694\ cm^{-1}$. Mp = 180–184 °C (lit.[12] mp 178–180 °C).

$4\text{-}CH_3C_6H_4\text{-}4'\text{-}C_6H_4SO_3Na$. A solution of *p*-tolylboronic acid (0.136 g, 1 mmol) in 5 mL of ethanol was added to a solution of $4\text{-}BrC_6H_4SO_3Na$ (0.323 g, 1.25 mmol), Na_2CO_3 (0.212 g, 2 mmol), and the catalyst (0.06 mmol) in 5 mL of water. The reaction mixture was heated at 80 °C under N_2 for 7 h, cooled to room temperature, and filtered. The solids were washed with water, benzene, and ether giving the analytically pure biaryl as a white solid. The filtrate from the initial filtration was concentrated in vacuo and filtered again to give a second crop of the biaryl. Yield 0.210 g (78%). ^1H (CD_3OD): 2.37 (s, 3 H, CH_3), 7.27 (d, 7.9 Hz, 2 H, ArH), 7.54 (d, 8.2 Hz, 2 H, ArH), 7.67 (m, 2 H, ArH), 7.85 (m, 2 H, ArH). $^{13}C\{^1H\}$ (CD_3OD/D_2O): 21.1 (s, CH_3), 127.4 (s), 127.5 (s), 127.9 (s), 130.5 (s), 138.4 (s), 138.9 (s), 144.2 (s), 144.6 (s). Anal. Calcd for $C_{13}H_{11}NaO_3S$: C, 57.77; H, 4.10. Found: C, 57.67; H, 4.10.

5-((*E*)-β-Phenylethenyl)-2′-deoxyuridine. To a mixture of 5-iodo-2′-deoxyuridine (0.177 g, 0.5 mmol), Na_2CO_3 (0.138 g, 1.3 mmol), and the catalyst (0.05 mmol) in 5 mL of water was added (*E*)-β-phenylethenylboronic acid (0.096 g, 0.65 mmol) in 2 mL of methanol. The reaction mixture was heated at 80 °C for 3 h under a N_2 atmosphere, cooled to room temperature, and concentrated to dryness in vacuo. The remaining residue was washed with benzene. The benzene-insoluble solids were analyzed by ^1H NMR in CD_3OD with an internal standard

---

[4] Arylsulfinic acids have been coupled to biaryls with Pd(II) in aqueous solvent: (a) Garves, K. *J. Org. Chem.* **1970**, *35*, 3273. The Pd(II) catalyzed coupling of 5-mercuriuridines with styrenes in aqueous media has been reported: (b) Bigge, C. F.; Kalaritis, P.; Deck, J. R.; Mertes, M. P. *J. Am. Chem. Soc.* **1980**, *102*, 2033. (c) Langer, P. R.; Waldrop, A. A.; Ward, D. C. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 6633. (d) Ruth, J. L.; Bergstrom, D. E. *J. Org. Chem.* **1978**, *43*, 2870. (e) The $Pd(OAc)_2$ catalyzed coupling of aryl iodides with acrylic acid in aqueous media was reported during the preparation of this manuscript. Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem.* **1989**, *371*, 397.

[5] Ruth, J. L.; Cheng, Y. C. *Mol. Pharmacol.* **1981**, *20*, 415.

[6] Hobbs, F. W.; Cocuzza, A. J. Eu. Patent Appl. 251786, Du Pont Co., 1988.

[7] Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249.

[8] Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.

[9] Aldrich Catalogue, 1988–1989, p 1216.

[10] Isikura, M.; Ohta, T.; Masanao, T. *Chem. Pharm. Bull.* **1985**, *33(II)*, 4755.

[11] Katritzky, A. R.; Bettrami, H.; Sammes, M. P. *J. Chem. Soc., Perkin Trans.* **1980**, *1*, 2480.

[12] Steen, R. V. Neth. Patent 6,511,845, 1966; *Merck. Chem. Abstr.* **1966**, 10532c.

(55% yield by ^{1}H NMR). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 90/10). The pale yellow solids obtained were washed with a small amount of methanol to give the nucleoside as a white solid. Purification of the solids obtained from the methanol filtrate by preparative plate chromatography (CH_2Cl_2/MeOH 90/10) gave a second batch of the nucleoside. Yield 0.078 g (47%). ^{1}H (CD_3OD/CD_2Cl_2): 2.30 (m, 2 H, $H_{2'}$), 3.76–3.90 (ABX), 3.3, 2.9, 12.0 Hz, 2 H, $H_{5'}$), 3.95 (m, 1 H, $H_{3'}$), 4.45 (m, $H_{4'}$), 6.32 (t, 6.5 Hz, 1 H, $H_{1'}$), 6.90 (d, 16.3 Hz), 1 H, H_β), 7.1–7.5 (m, 6 H, $H_\alpha + H_{a-d}$), 8.33 (s, 1 H, H_6). $^{13}C\{^1H\}$ (CD_3OD/CD_2Cl_2): 41.3 (s, $C_{2'}$), 62.2 (s, $C_{5'}$), 71.4 (s, $C_{3'}$), 86.5 (s, $C_{4'}$), 88.4 (s, $C_{1'}$), 113.1 (s, C_5), 120.6, (s, C_β), 126.9 (s, C_b), 128.0 (s, C_d), 129.1 (s, C_c), 130.0 (s, C_α), 137.9 (s, C_6), 138.5 (s, C_a). 151.2 (s, C_2), 164.2 (s, C_4). Anal. Calcd for $C_{17}H_{18}N_2O_5 \cdot CH_3OH$: C, 59.66: H, 6.12; N. 7.73. Found: C, 59.45; H, 6.06; N, 7.27. CH_3OH solvate also detected by ^{1}H NMR.

(4-Tolyl)phenylacetylene. To a solution of 4-iodotoluene (0.448 g, 2.06 mmol), phenylacetylene (0.230 g, 2.25 mmol), and NEt_3 (0.304 g, 3 mmol) in 8 mL of acetonitrile was added the catalyst (0.043 mmol) in 10 mL of water. A solution of CuI (0.010 g, 0.05 mmol) in 2 mL of acetonitrile was added and the reaction was stirred at ambient temperature for 5 h. The reaction mixture was concentrated in vacuo to remove acetonitrile and extracted with hexane. The hexane extracts were dried over Na_2SO_4, filtered, and concentrated to dryness in vacuo. The crude product was chromatographed on silica gel with hexane as the eluent. Yield 0.377 g (96%). ^{1}H ($CDCl_3$): 2.30 (s, 3 H, CH_3), 7.09 (d, 8.0 Hz, 2 H), 7.26 (m, 3 H), 7.36, (d, 8.1 Hz, 2 H), 7.46 (m, 2 H). $^{13}C\{^1H\}$: 21.5 (s, CH_3), 88.8 (s, $\equiv$C), 89.6 (s, $\equiv$C), 120.3 (s, $C_{4,1'}$), 123.6 (s, $C_{4,1'}$), 128.3 (s, $C_{3'}$), 129.1 (s, C_3), 131.5 (s, $C_{2',3}$ (overlap)), 138.3 (s, C_1). Mp = 71–72 °C (lit.[13] mp 70–71 °C). High resolution GC/MS M^+ = 192.0956. Calcd: 192.0939. Elemental formula $C_{15}H_{12}$.

5-(Propargyltrifluoroacetamido)-2′-deoxyuridine. To a mixture of iododeoxyuridine (0.354 g, 1 mmol), the catalyst (0.1 mmol), and uridine (0.244 g, internal standard) in 10 mL of water was added a solution of CuI (0.038 g, 0.2 mmol) in 6 mL of acetonitrile followed by the slow addition of a solution of NEt_3 (0.202 g, 2 mmol) and propargyltrifluoroacetamide (0.452 g, 3 mmol) in 4 mL of acetonitrile. The resulting brown reaction was stirred at room temperature and monitored hourly by HPLC. The product was identified by comparison to an authentic sample of the nucleoside[6,14] and the yield calculated by comparison to standard solutions of uridine, iododeoxyuridine, and the product nucleoside. With use of this procedure a yield of 96% was obtained after 3 h of stirring with complete consumption of iododeoxyuridine.

T-505 Chain Terminator. To a solution of 5-Iododideoxyuridine 5′-triphosphate (100 μmol) and the catalyst (22 μmol) in 3 mL of water was added a solution of the dye (125 μmol) and triethylamine (0.020 g, 200 μmol) in 3 mL of an acetonitrile/water mixture (2:1 v:v). To the resulting bright yellow solution was added dropwise a solution of CuI (0.010 g, 50 μmol) in 1 mL of acetonitrile. The solution was stirred for 2 h at 25 °C under N_2, the solvent removed in vacuo, and the remaining residue chromatographed (DEAE Sephadex A-25-120 ion exchange column, bead size 40–120 μm) with an aqueous solution of triethylammonium bicarbonate buffer (pH = 7.6, 0.1–1 M gradient). The product was collected by UV monitoring at 500 nm and then liophilized. Yield 50%. The identity of the product was confirmed by comparison to an authentic sample of T-505 and by bioassay as a chain-terminating reagent.[14]

5-(Propargylamino)-2′-deoxycytidine 5′-Monophosphate. To a solution of 5-iodo-2′-deoxycytidine 5′-monophosphate (disodium salt·1.5H_2O, 0.050 g, 0.1 mmol) and the catalyst (0.020 mmol) in 2 mL of water was added a solution of propargylamine (0.055 g, 1 mmol) and NEt_3 (0.101 g, 1 mmol) in 1 mL of CH_3CN. A solution of CuI (0.006 g, 0.03 mmol) in 1 mL of CH_3CN was added dropwise to the stirring solution. The reaction mixture was stirred for 3 h at ambient temperature and then concentrated to dryness in vacuo. The residue was taken up in 0.1 M triethylammonium bicarbonate, filtered, and chromatographed as described for T-505 (monitored at 254 nm). The yield was determined from the ^{1}H NMR spectrum of the isolated material and an internal standard. ^{1}H (D_2O): 8.31 (s, 1 H, H_6), 6.06 (t, J = 5.9 Hz, 1 H, $H_{1'}$), 4.39 (q, 4.8 Hz, 1 $H_{4'}$), 3.80–4.01 (m, 3 H, $H_{3',5',5''}$), 3.87, (s, 2 H, H_α), 2.31 (d t, 13.9, 5.7 Hz, 1 H, $H_{2',2''}$), 2.15, (d t, 13.9, 6.1 Hz, 1 H, $H_{2',2''}$). ^{13}C (D_2O): 164.2 (s, $C_{4'}$), 155.5 (s, C_2), 146.3 (s, C_6), 90.7 (s, C_5), 86.4 (s, C_γ), 86.1 (s, $C_{1'}$), 85.7 (d, J_{P-C} = 9.1 Hz, $C_{4'}$), 77.6 (s, C_β), 69.4 (s, $C_{3'}$), 63.2 (d, 4.9 Hz, $C_{5'}$), 39.7 (s, $C_{2'}$), 29.5 (s, C_α). $^{31}P\{^1H\}$ (D_2O): 2.1 (s).

($HO_2CCH(NH_2)CH_2)(C_6H_3OC(CH_2NH_2)CH)$ (3). A stirring solution of 3-iodotyrosine (0.158 g, 0.51 mmol), propargylamine (0.055 g, 1 mmol), NEt_3 (0.101 g, 1 mmol), phenylalanine (0.050 g, internal standard), and the catalyst (0.07 mmol) in 5 mL of 60% aqueous acetonitrile was treated with a solution of CuI (0.019 g, 0.1 mmol) in 1 mL of acetonitrile at room temperature. The reaction was stirred overnight, filtered over Celite, and then analyzed by HPLC. A yield of 0.126 g (82%) was calculated from linear plots of the internal standard and purified product. Samples of the purified material were obtained by preparative HPLC. ^{1}H (D_2O): 3.20–3.45 (ABX, 5.6, 7.6, 14.6 Hz, 2 H, $ArCH_2$), 4.30 (d d, 5.8, 7.3 Hz, 1 H, H_α), 4.34 (s, 2 H, CH_2N), 6.92 (s, 1 H, H_3), 7.25 (d, 8.6 Hz, 1 H, H_6), 7.52 (d, 8.1 Hz, 1 H, H_7), 7.52 (s, 1 H, H_3). $^{13}C\{^1H\}$ (D_2O): 35.2 (s, $CH_2N/ArCH_2$), 35.9 (s, $CH_2N/ArCH_2$), 54.3 (s, C_α), 107.0 (s, C_3), 111.5 (s. C_7), 116.0 (s, C_5), 122.1 (s, C_4) 126.1 (s, C_6), 128.7 (s, C_9), 149.4 (s, C_2), 154.3 (s, C_8), 171.2 (s. CO_2). Anal. Calcd for $C_{12}H_{14}N_2O_3 \cdot 2HCl$: C, 46.92; H, 5.25; N, 9.12; O, 15.63. Found: C, 47.05; H, 5.20; N, 9.18; O, 15.39.

Diethyl (4-Methylphenyl)phosphonate. To a solution of 4-iodotoluene (0.448 g, 2.06 mmol), diethyl phosphite (0.378 g, 2.5 mmol), and NEt_3 (0.303 g, 3 mmol) in 5 mL of acetonitrile was added a solution of catalyst (0.2 mmol) in 10 mL of water. The reaction was stirred at ambient temperature and monitored by GC. After 1.5 h, complete consumption of 4-iodotoluene was observed along with the formation of a single product. The reaction mixture was extracted with benzene, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was extracted with Et_2O, filtered, and concentrated in vacuo. The resulting oil was dried under high vacuum. Yield 0.480 g. ^{1}H (C_6D_6): 1.02 (t, 7.0 Hz, 6 H, CH_3), 1.95 (s, 3 H, $ArCH_3$), 3.96 (m, 4 H, CH_2), 6.90 (d d, 4.0, 7.9 Hz, 2 H), 7.90 (d d, 8.0, 13.0 Hz, 2 H). $^{31}P\{1H\}$ (C_6D_6): 19.3 (s). $^{13}C\{^1H\}$ ($CDCl_3$): 16.1 (d, 6.1 Hz, CH_3), 21.4 (s, $ArCH_3$), 61.8 (d, 5.0 Hz, CH_2), 125.1 (d, 190 Hz, C_1), 129.0 (d, 15.2 Hz), 131.6 (d, 10.1 Hz), 142.6 (s, C_4). GC/MS: M^+ = 228.05.

Ethyl 4-Methylcinnamate. To a solution of 4-iodotoluene (0.224 g, 1.0 mmol), ethyl acrylate (0.400 g, 4 mmol), and NEt_3 (0.202 g, 2 mmol) in 3 mL of acetonitrile was added a solution of the catalyst (0.1 mmol) in 3 mL of water. The reaction was heated for 12 h at 80 °C during which time a palladium mirror formed on the reaction flask. The reaction was analyzed by GC with allyl cinnamate as an internal standard. Yield: ethyl 4-methylcinnamate (63%), toluene (13%), and iodotoluene (7%). ^{1}H (C_6D_6): 1.00 (t, 7.3 Hz, 3 H, CH_3), 1.95 (s, 3 H, $ArCH_3$), 4.07 (q, 7.3 Hz, 2 H, CH_2), 6.42 (d, 14.7 Hz, 1 H, H_β), 6.78 (d, 7.0 Hz, 2 H, ArH), 7.03 (d, 7.0 Hz, 2 H, ArH), 7.81 (d, 14.7 Hz, 1 H, H_α). High-resolution GC/MS: M^+ = 190.0992, calcd: 190.0994. Elemental formula $C_{12}H_{14}O_2$.

X-ray Crystallography. A golden yellow irregular block with dimensions 0.52 × 0.59 × 0.68 mm obtained from *t*-BuOH/EtOH/H_2O was mounted in a glass capillary under Ar and placed on an ENRAF-NONIUS CAD4 diffractometer equipped with a Mo Kα source, graphite monochromator, and FTS gas-cooled low-temperature unit operating at −70 °C. The diffractometer routines indicated a triclinic cell with dimensions a = 12.618 (1) Å, b = 19.532 (2) Å, c = 24.423 (3) Å, α = 100.65 (1)°, β = 94.37 (1)°, γ = 99.10 (1)°, which were verified by partial rotation photographic projections along each of the three reciprocal axes. With $Z = 4$, the calculated density for $PdK_3S_3P_3O_{13}C_{54}H_{54}$ is 1.514 g/cm^3.

A total of 25643 data was collected over the range $1.7 \leq 2\theta \leq 52.0$ with the use of the ω-scan method with a scan width of 1.20–1.90° ω and scan speeds of 1.70–5.00 deg/min. The data were treated in the usual manner for Lorentz polarization as well as for a 27% decrease in intensity as indicated by two monitor reflections. The merged data (R-merge = 2.0%, 1780 duplicates) yielded 14423 unique reflections with $I \geq 3.0\sigma(I)$.

The solution was accomplished via an automated Patterson analysis that revealed two independent trianions, six potassium ions, and approximately eight water molecules in the asymmetric unit. The anions align in the lattice into layers with hydrophilic (ionic) and hydrophobic (aromatic) sides, with two layers sandwiching a cation layer containing potassium coordinated to the SO_3 and H_2O oxygen atoms. Due to the multiple oxygen sites available in this bilayer, two of the potassium ions are dispersed over five sites, while at least four of the waters appear scattered over five sites. In addition, one of the phenylsulfonate rings is librationally disordered about the P–C axis. The assignment of partially occupied potassium vs water oxygen atoms was based on the most reasonable expected donor/acceptor coordination geometry for each peak. A complete X-ray analysis of the sodium analogue[15a] is more severely

---

(13) Huggin, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 3002.

(14) (a) Hobbs, F. *J. Org. Chem.* **1989**, *54*, 3420. (b) Prober, J. M.; Trainor, G. L.: Dam, R. J.; Hobbs, F. W.; Robertson, C. W.; Zagursky, R. J.; Cocuzza, A. J.; Jensen, M. A.; Baumeister, K. *Science* **1987**, *238*, 336. (c) Trainor. G. L.: Jensen. M. A. *Nucl. Acids Res.* **1988**, *16*(*24*), 11846.

(15) (a) a = 12.630 (2) Å, b = 19.382 (5) Å, c = 24.420 (10) Å, α = 99.10 (3)°, β = 95.82 (2)°. γ = 99.31 (2)°, R = 15.8, R_w = 16.1, 8526 observed reflections. (b) Kisin, A. V.; Sergienko, V. S.; Stromnova. T. A. et al *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, *4*, 894. (c) Tolman, C. A.; Seidel, W. C.: Gerlach, D. H. *J. Am. Chem. Soc.* **1972**, *94*, 2669.

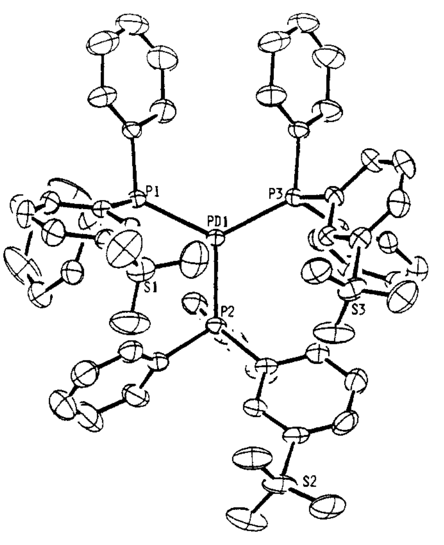


Figure 1. ORTEP drawing of **2** including aryl and sulfonic acid groups.

disordered and is not included here. However, it should be noted that palladium geometry is not substantially affected by the disorder, as the two trianions here plus the two observed in the sodium analogue have nearly identical coordination geometry. An ordered acentric model was not considered due to the size of the problem and the reasonable thermal parameters of most atoms in the centric case.

The coordinates and thermal parameters were refined via full-matrix least-squares analysis based on F, with scattering factors taken from *International Tables for Crystallography*, Vol IV, and included terms for the anomalous scattering of Pd, K, S, and P. All atoms except the two least occupied water oxygen atoms were refined with anisotropic thermal parameters. Carbon and hydrogen atoms were included as fixed atom contributors with C–H = 0.95 Å and $B_{iso} = 5.0$. Water hydrogens were omitted. Absorption effects were ignored due to the small absorption coefficient ($\mu = 7.74$) and the nearly isotropic shape of the crystal. Disordered atoms were modeled by first adjusting the occupancy factor for each atom until a reasonable isotropic temperature factor was obtained and then allowing coordinates and thermal parameters to refine with fixed assigned occupancy factors. The disordered SO_3 group was modeled as three 1/3 occupied sulfur atoms and seven oxygen sites. The refinement converged slowly due to the parameter coupling caused by the smearing. However, the final model converged with a maximum shift/error of 0.12 and a maximum correlation of 0.81 between two disordered sulfur peaks. The largest peak on the final difference map was 1.1 e/Å^3, 1.7 Å from a partially occupied water. The final refinement model used 1476 parameters, with $R = 0.054$ and $R_w = 0.053$ and the standard deviation of an observation of unit weight 1.85.

Atomic coordinate and equivalent isotropic thermal parameters are listed in Table I, and selected interatomic distances and intramolecular angles are listed in Table II. A complete table of atomic parameters, tables of distances and angles, and tables of observed and calculated structure factor amplitudes are given in the supplementary material.

Results and Discussion

I. Catalyst Preparation and Characterization. Treatment of a well-mixed aqueous ethanol solution containing Na_2PdCl_4 and the sulfonated phosphine $Ph_2P(m\text{-}C_6H_4SO_3M)$ (**1**: M = Na$^+$, K$^+$; 3.5 equiv) with an excess of Zn dust for 1 h gave a homogeneous, air-sensitive yellow solution of the trisubstituted complex **2**, $Pd(P(C_6H_5)_2(C_6H_4SO_3M))_3$, after filtration. The slow diffusion of *t*-BuOH into this solution afforded complex **2** as an analytically pure, air-sensitive, crystalline hydrate in yields ranging from 85 to 95%. The formulation of **2** as a trisubstituted complex was consistent with the analytical data ($^{31}P\{^1H\}$: 24.6 ppm (s)) and was subsequently verified by single-crystal X-ray diffraction analysis of the potassium salt. Attempts to synthesize a Pd(0) complex via $NaBH_4$ reduction gave a material of lower purity; however, aqueous solutions of this product were active catalysts for the coupling reactions (vide infra).

The solid-state structure of **2**, shown in Figures 1 and 2, consists of two crystallographically independent PdP_3 units with 4 H_2O/Pd included in the lattice. The overall coordination geometry about Pd is trigonal planar. Pd–P bond distances and angles, presented in Table II, are similar to those reported for $Pd(PPh_3)_3$.[15b] Evidence for bonding interactions between Pd and H_2O was not observed. The most interesting aspect of the structure is the way in which the hydrophobic and hydrophilic groups are accommodated within the lattice. When the unit cell is viewed along the x-axis, as shown in Figure 2, the alignment of sulfonate groups in a bilayer structure is apparent. Potassium ions and included water reside between separate sheets of the sulfonate moieties. To our knowledge, this is the first reported structure of a metal complex containing a sulfonated phosphine.

Variable-temperature $^{31}P\{^1H\}$ NMR analysis of **2** in CD_3OD showed no significant change in the sharp singlet resonance from −85 to 25 °C. The addition of excess ligand, **1**, to CD3OD solutions of **2** caused a large broadening and an upfield shift of the singlet resonance. Sharpening of this broad resonance was not observed as low as −90 °C. So, while phosphine exchange is rapid and presumably occurs via a PdP_4 complex, direct evidence for a PdP_4 species was not observed.[15c] In this regard we note that, unlike $Pd(PPh_3)_3$, the synthesis of complex **2** is not complicated by the competitive crystallization of a tetracoordinate complex. For example, attempts to synthesize a tetracoordinate complex with 4 equiv of **1** yielded complex **2** upon crystallization.

The physical and chemical properties of complex **2** complement the widely used catalyst $Pd(PPh_3)_4$. Pure **2** is soluble in water, lower alcohols, THF, and DMF and insoluble in most other dry, organic solvents. Aqueous solutions of **2** are stable for weeks when maintained under an inert atmosphere. And, as shown in Table III, complex **2** will efficiently catalyze a variety of alkylation reactions[16] in an aqueous medium (eq 1).

$$RX + R'Y \rightarrow RR' \qquad (1)$$

$$X = Br, I;\ Y = H, B(OR)_2;\ R = \text{aryl, heteroaromatic};$$
$$R' = \text{aryl, vinyl, alkynyl, } P(O)(OR)_2$$

II. Cross-Coupling Reactions. The use of aryl and vinyl boronic acids as substrates in these alkylation reactions attracted our initial attention because water has been used as part of a two-phase reaction medium where the catalyst and organic halide reside in the *organic phase*.[16c–e] Entries 1 to 5 of Table III illustrate the use of aqueous solutions of complex **2** as a catalyst for reactions of this type.

The reactions were carried out in a single, basic aqueous phase or in a two-phase, basic aqueous–organic medium and were generally complete within several hours at 80 °C. The water content of the aqueous medium ranged from 50% to 100%. Both hydrophilic and hydrophobic organic halides were utilized and yields of coupled product ranged from moderate to excellent. In most cases, reduction of the organic halide to RH was a minor pathway (≤10%). In principle it is possible to utilize the solubility characteristics of the catalyst to recover product and recycle the catalyst. With 4-bromopyridine (entry 2), it was possible to separate the coupled product and recycle the catalyst with a two-phase aqueous–organic system. A visual inspection suggested that some leaching of palladium species into the organic phase occurred; however, this was not investigated in detail.

The available data suggest that the relative distributions of the organic halide and catalyst between the aqueous and organic phases (in two-phase systems) can affect the product yield. For example, our use of a conventional $Pd(PPh_3)_4$ catalyst with the

---

[16] (a) Davies, S. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Baldwin, J. E., Ed.; Organic Chemistry Series; Pergamon: New York, 1982; Vol. 2, p 218. (b) Reactivity and Structure Concepts in Organic Chemistry. Tsuji, J. *Organic Synthesis with Palladium Compounds*; Hafner, K., Reese, C. W., Trost, B. M., Lehr, J., Schleyer, P., Zahradnik, R., Eds.; Springer-Verlag: New York, 1980; Vol. 10, p 137. (c) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11* (7), 513. (d) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1987**, *1*, 25. (e) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (f) Sonogashira, K.; Tohida, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (g) Edo, K.; Yamanaka, H.; Sakamoto, T. *Heterocycles* **1978**, *9*, 271. (h) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854. (i) Vincent, P.; Beaucourt, J. P.; Pichat, L. *Tetrahedron Lett.* **1981**, *22*, 945. (j) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Synthesis* **1981**, *1*, 56. (k) Xu, Y.; Zhang, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1606. (l) Petrakis, K. S.; Nagabhushan, T. L. *J. Am. Chem. Soc.* **1987**, *109*, 2831. (m) Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem. Soc.* **1978**, *100*, 8106.

Table I. Fractional Coordinates ($\times 10^3$) and Isotropic Thermal Parameters

atom	*x*	*y*	*z*	*B*(iso)
Pd(2)	8497.0 (3)	4852.5 (2)	1895.8 (2)	2.4 (1)′
K(1)	4583 (1)	537 (1)	4372 (1)	5.1 (1)′
K(2)	6195 (1)	2594 (1)	4575 (1)	3.7 (1)′
K(3)	8894 (1)	1824 (1)	5002 (1)	5.9 (1)′
K(4)	3827 (2)	3962 (1)	4883 (1)	7.6 (1)′
K(5)	2897 (3)	2097 (2)	5335 (2)	7.2 (1)′
K(6)	8245 (5)	4354 (3)	5096 (2)	11.6 (2)′
K(6′)	10599 (4)	278 (3)	5390 (3)	12.6 (3)′
K(7)	6407 (12)	6612 (10)	3584 (7)	10.9 (7)′
K(7″)	7863 (13)	8904 (9)	4044 (8)	10.8 (7)′
S(1)	3550 (1)	1932 (1)	3976 (1)	3.5 (1)′
S(2)	3960 (1)	−1473 (1)	4400 (1)	3.8 (1)′
S(3)	7194 (1)	686 (1)	3931 (1)	3.6 (1)′
S(4)	9242 (1)	3166 (1)	4212 (1)	5.6 (1)′
S(5)	5967 (2)	4389 (1)	4016 (1)	4.9 (1)′
S(6)	9278 (16)	7264 (17)	3701 (7)	7.1 (6)′
S(6′)	9030 (31)	7502 (24)	3663 (10)	14.5 (15)′
S(6″)	9727 (7)	6904 (5)	3822 (4)	5.5 (3)′
P(1)	2597 (1)	922 (1)	1727 (1)	2.2 (1)′
P(2)	3075 (1)	−738 (1)	2342 (1)	2.1 (1)′
P(3)	5521 (1)	252 (1)	1720 (1)	2.2 (1)′
P(4)	9316 (1)	3966 (1)	2145 (1)	2.7 (1)′
P(5)	6659 (1)	4742 (1)	1893 (1)	2.5 (1)′
P(6)	9603 (1)	5760 (1)	1633 (1)	2.6 (1)′
O(1W)	3029 (6)	578 (4)	5182 (4)	11.7 (3)′
O(2W)	7022 (5)	3431 (3)	5649 (3)	9.1 (3)′
O(3W)	10780 (5)	1270 (4)	4612 (3)	11.5 (3)′
O(4W)	1842 (4)	3300 (5)	5098 (3)	10.6 (3)′
O(5W)	4995 (10)	3712 (13)	5759 (5)	15.5 (10)′
O(6W)	2113 (8)	4341 (5)	4276 (4)	9.6 (4)′
O(7W)	8691 (7)	5151 (5)	4756 (6)	16.0 (5)′
O(8W)	8541 (7)	571 (5)	5511 (3)	13.0 (4)′
O(9W)	8867 (15)	5326 (11)	3566 (8)	7.7 (5)
O(10W)	1015 (16)	5802 (10)	4390 (9)	10.1 (5)
O(11)	3735 (4)	2618 (2)	4311 (2)	6.0 (2)′
O(12)	4539 (4)	1713 (3)	3829 (2)	5.5 (2)′
O(13)	2909 (4)	1401 (3)	4209 (2)	6.6 (2)′
O(21)	4791 (4)	−1762 (3)	4679 (2)	5.5 (2)′
O(22)	3953 (4)	−737 (2)	4653 (2)	5.1 (1)′
O(23)	2918 (4)	−1914 (2)	4349 (2)	5.4 (1)′
O(31)	8228 (4)	588 (2)	4183 (2)	5.3 (2)′
O(32)	6928 (3)	1350 (2)	4190 (2)	4.2 (1)′
O(33)	6330 (4)	95 (2)	3908 (2)	5.3 (1)′
O(41)	9963 (5)	2670 (5)	4197 (2)	11.6 (4)′
O(42)	9766 (5)	3908 (4)	4393 (2)	10.9 (3)′
O(43)	8385 (3)	2992 (2)	4540 (2)	4.6 (1)′
O(51)	5049 (5)	4714 (3)	4161 (2)	8.9 (3)′
O(52)	6021 (6)	3809 (3)	4287 (2)	8.2 (2)′
O(53)	6911 (6)	4920 (4)	4121 (2)	9.9 (3)′
O(61)	8296 (17)	7700 (11)	3350 (8)	9.1 (7)′
O(61′)	8391 (14)	6599 (14)	3672 (9)	6.9 (7)′
O(62)	9842 (18)	8087 (15)	3983 (9)	9.5 (9)′
O(62′)	10384 (14)	6808 (11)	4273 (5)	7.3 (6)′
O(63′)	9573 (23)	7580 (17)	3907 (22)	6.8 (10)′
O(64)	9714 (16)	7177 (14)	4188 (9)	6.7 (7)′
O(64′)	8833 (18)	6479 (31)	3729 (15)	15.1 (19)′
C(11)	2314 (4)	1504 (3)	2352 (2)	2.3 (1)′
C(11′)	1227 (4)	488 (3)	1421 (2)	2.8 (2)′
C(11″)	2942 (4)	1511 (3)	1238 (2)	2.7 (2)′
C(12)	3004 (4)	1571 (3)	2848 (2)	2.4 (1)′
C(12′)	793 (6)	502 (5)	888 (3)	7.6 (3)′
C(12″)	3374 (5)	1226 (4)	766 (3)	4.1 (2)′
C(13)	2780 (4)	1955 (3)	3348 (2)	2.6 (1)′
C(13′)	−264 (7)	142 (7)	679 (3)	10.4 (4)′
C(13″)	3654 (6)	1617 (5)	366 (3)	5.4 (3)′
C(14)	1896 (5)	2295 (3)	3365 (2)	3.4 (2)′
C(14′)	−843 (6)	−258 (5)	1007 (4)	7.4 (3)′
C(14″)	3539 (5)	2317 (4)	453 (3)	5.1 (2)′
C(15)	1233 (4)	2248 (3)	2885 (3)	3.5 (2)′
C(15′)	−437 (5)	−264 (3)	1525 (3)	4.3 (2)′
C(15″)	3140 (6)	2616 (4)	925 (3)	5.2 (2)′
C(16)	1428 (4)	1848 (3)	2381 (2)	3.0 (2)′
C(16′)	578 (4)	125 (3)	1738 (3)	3.8 (2)′
C(16″)	2831 (5)	2211 (3)	1317 (2)	3.7 (2)′
C(21)	3889 (4)	−1119 (3)	2826 (2)	2.2 (1)′
C(21′)	2665 (4)	−1465 (3)	1741 (2)	2.6 (1)′
C(21″)	1825 (4)	−721 (3)	2678 (2)	2.6 (1)′
C(22)	3608 (4)	−1206 (3)	3349 (2)	2.5 (1)′
C(22′)	2134 (4)	−1311 (3)	1264 (2)	3.0 (2)′
C(22″)	938 (5)	−1252 (3)	2546 (3)	3.9 (2)′
C(23)	4299 (4)	−1454 (3)	3706 (2)	2.9 (2)′
C(23′)	1825 (5)	−1824 (4)	787 (2)	3.9 (2)′
C(23″)	−19 (5)	−1156 (5)	2772 (3)	5.7 (3)′
C(24)	5237 (5)	−1633 (3)	3542 (3)	4.1 (2)′
C(24′)	2035 (5)	−2486 (4)	760 (3)	3.9 (2)′
C(24″)	−92 (6)	−544 (5)	3130 (4)	6.2 (3)′
C(25)	5531 (5)	−1545 (3)	3030 (3)	3.8 (2)′
C(25′)	2571 (5)	−2656 (3)	1217 (3)	4.0 (2)′
C(25″)	787 (6)	−29 (4)	3278 (3)	4.9 (2)′
C(26)	4867 (4)	−1286 (3)	2673 (2)	3.1 (2)′
C(26′)	2890 (5)	−2147 (3)	1708 (2)	3.2 (2)′
C(26″)	1732 (5)	−103 (3)	3053 (2)	3.5 (2)′
C(31)	6665 (4)	595 (3)	2266 (2)	2.3 (1)′
C(31′)	5779 (4)	−641 (3)	1444 (2)	2.3 (1)′
C(31″)	5970 (4)	740 (3)	1185 (2)	2.5 (1)′
C(32)	6516 (4)	542 (3)	2816 (2)	2.4 (1)′
C(32′)	4999 (4)	−1097 (3)	1062 (2)	2.8 (2)′
C(32″)	5930 (5)	1458 (3)	1285 (2)	3.6 (2)′
C(33)	7384 (4)	738 (3)	3234 (2)	2.8 (2)′
C(33′)	5111 (5)	−1803 (3)	882 (2)	3.4 (2)′
C(33″)	6296 (6)	1872 (3)	909 (3)	4.5 (2)′
C(34)	8399 (4)	981 (3)	3097 (2)	3.4 (2)′
C(34′)	5984 (5)	−2047 (3)	1074 (3)	3.4 (2)′
C(34″)	6682 (5)	1566 (4)	428 (3)	4.9 (2)′
C(35)	8549 (4)	1036 (3)	2557 (3)	3.8 (2)′
C(35′)	6772 (4)	−1597 (3)	1452 (3)	3.6 (2)′
C(35″)	6687 (6)	865 (4)	316 (3)	5.4 (3)′
C(36)	7693 (4)	844 (3)	2140 (2)	3.0 (2)′
C(36′)	6676 (4)	−902 (3)	1640 (2)	2.8 (2)′
C(36″)	6344 (5)	444 (3)	691 (2)	4.1 (2)′
C(41)	8712 (4)	3435 (3)	2624 (2)	2.6 (1)′
C(41′)	10705 (4)	4237 (3)	2481 (2)	2.7 (2)′
C(41″)	9468 (4)	3289 (3)	1546 (2)	3.2 (2)′
C(42)	9167 (4)	3483 (3)	3167 (2)	3.3 (2)′
C(42′)	11522 (4)	3857 (3)	2362 (3)	3.8 (2)′
C(42″)	9386 (5)	2576 (3)	1548 (3)	3.9 (2)′
C(43)	8645 (4)	3077 (3)	3515 (2)	3.2 (2)′
C(43′)	12560 (5)	4109 (5)	2630 (3)	5.6 (3)′
C(43″)	9594 (5)	2115 (4)	1080 (3)	5.0 (2)′
C(44)	7700 (4)	2619 (3)	3329 (2)	3.3 (2)′
C(44′)	12786 (5)	4733 (4)	3005 (3)	5.2 (2)′
C(44″)	9890 (6)	2340 (5)	613 (3)	5.4 (3)′
C(45)	7233 (4)	2565 (3)	2791 (3)	3.4 (2)′
C(45′)	11990 (6)	5107 (4)	3112 (3)	4.8 (2)′
C(45″)	9970 (6)	3043 (5)	601 (3)	5.6 (3)′
C(46)	7728 (4)	2978 (3)	2444 (2)	3.0 (2)′
C(46′)	10964 (5)	4873 (3)	2858 (3)	3.8 (2)′
C(46″)	9742 (5)	3517 (4)	1059 (3)	4.3 (2)′
C(51)	5984 (4)	4180 (3)	2337 (3)	2.9 (2)′
C(51′)	6099 (4)	4330 (3)	1173 (2)	2.7 (1)′
C(51″)	5952 (4)	5500 (3)	2033 (2)	3.0 (2)′
C(52)	6204 (5)	4425 (3)	2918 (3)	3.4 (2)′
C(52′)	5261 (5)	4532 (3)	876 (3)	4.2 (2)′
C(52″)	6490 (5)	6154 (3)	2001 (3)	3.8 (2)′
C(53)	5755 (5)	4044 (3)	3290 (3)	3.7 (2)′
C(53′)	4994 (5)	4247 (4)	305 (3)	4.8 (2)′
C(53″)	5961 (7)	6735 (3)	2085 (4)	5.9 (3)′
C(54)	5078 (5)	3400 (3)	3088 (3)	3.7 (2)′
C(54′)	5514 (6)	3757 (4)	28 (3)	4.6 (2)′
C(54″)	4913 (7)	6655 (4)	2227 (4)	6.4 (3)′
C(55)	4862 (4)	3148 (3)	2524 (3)	3.9 (2)′
C(55′)	6322 (5)	3533 (3)	315 (3)	4.6 (2)′
C(55″)	4387 (5)	6014 (4)	2266 (4)	5.8 (3)′
C(56)	5304 (4)	3536 (3)	2140 (2)	3.1 (2)′
C(56′)	6624 (5)	3822 (3)	880 (3)	3.5 (2)′
C(56″)	4894 (5)	5430 (3)	2178 (3)	4.4 (2)′
C(61)	10331 (4)	6353 (3)	2268 (2)	3.2 (2)′
C(61′)	9081 (4)	6392 (3)	1263 (2)	2.4 (1)′
C(61″)	10680 (4)	5543 (3)	1201 (2)	2.9 (2)′
C(62)	9710 (6)	6537 (5)	2697 (3)	6.6 (3)′
C(62′)	9566 (4)	7104 (3)	1349 (2)	3.1 (2)′
C(62″)	11470 (4)	5204 (3)	1408 (3)	3.8 (2)′
C(63)	10184 (7)	6985 (6)	3193 (3)	8.6 (3)′
C(63′)	9190 (5)	7553 (3)	1035 (3)	3.7 (2)′
C(63″)	12262 (5)	5002 (4)	1073 (3)	4.7 (2)′
C(64)	11297 (7)	7232 (5)	3258 (3)	7.2 (3)′
C(64′)	8328 (5)	7306 (4)	640 (3)	3.9 (2)′
C(64″)	12280 (5)	5132 (4)	547 (3)	4.6 (2)′
C(65)	11884 (5)	7043 (4)	2850 (3)	5.2 (2)′
C(65′)	7837 (5)	6615 (3)	554 (3)	3.9 (2)′
C(65″)	11496 (5)	5448 (4)	337 (3)	4.3 (2)′
C(66)	11421 (4)	6606 (3)	2352 (3)	3.6 (2)′
C(66′)	8201 (4)	6161 (3)	865 (2)	3.4 (2)′
C(66″)	10707 (4)	5659 (3)	660 (2)	3.2 (2)′

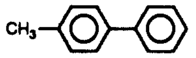
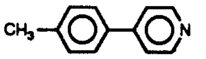
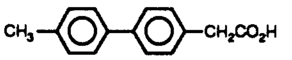
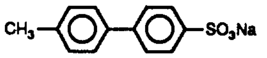
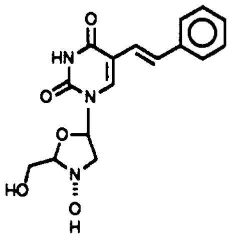
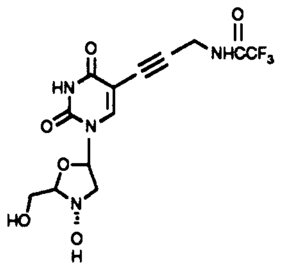
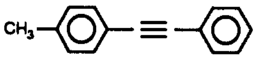
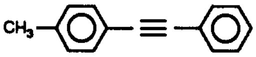
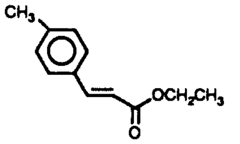
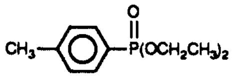
Table II. Selected Distances (Å) and Angles (deg) for the Solid-State Structure of **2**

Pd1–P1	2.311	P1–Pd1–P2	116.1
Pd1–P2	2.317	P1–Pd1–P3	126.0
Pd1–P3	2.298	P2–Pd1–P3	117.0
Pd2–P4	2.302	P4–Pd2–P5	118.3
Pd2–P5	2.295	P4–Pd2–P6	116.3
Pd2–P6	2.297	P5–Pd2–P6	125.4

highly lipophobic sodium *p*-bromobenzenesulfonate under standard two-phase conditions[16c] gave only a 36% isolated yield of the biaryl as compared to 78% for complex **2** (entry 4, single phase). Conversely, the use of complex **2** in a two-phase system (H_2O/C_6H_6) for the synthesis of 4-methylbiphenyl gave a markedly lower yield in comparison to the single-phase system (entry 1).

The Pd-catalyzed coupling of terminal acetylenes with organic halides is a widely used reaction in organic synthesis.[14a,b,16f–i] Notably, these reactions have been utilized for the chemical modification of biomolecules in *nonaqueous* media. Results of the alkylation of aryl and heteroaromatic halides by terminal alkynes catalyzed by complex **2** in aqueous media are displayed in entries 6 to 11. The reactions were generally conducted in 50% aqueous acetonitrile solutions at ambient temperature with a CuI promoter. Again, both hydrophilic and hydrophobic substrates were utilized with complete conversion of the organic iodide and yields ranging from 50 to 100%. In general, the catalyst loading was not optimized, though there are indications that the catalyst can be highly efficient. For example, in the case of 4-methyldiphenylacetylene, a reaction half-life of 15 min was obtained with use of as little as 0.1 mol% **2** at 30 °C (entry 12).

Table III. Reaction Conditions and Yields for Aqueous Alkylation Reactions Catalyzed by **2**[a]

RX	R'Y	RR'	solvent (v/v)	*t*, h	temp, °C	yield[b]
1. *p*-$IC_6H_4CH_3$[c]	$C_6H_5B(OH)_2$		H_2O/CH_3CN (50/50)	7	80	70[c,d]
2. 4-BrC_5H_4N[e]	*p*-$CH_3C_6H_5B(OH)_2$		$H_2O/CH_3OH/C_6H_6$ (70/15/15)	6.5	80	98[e]
3. *p*-$BrC_6H_4CH_2CO_2H$[e]	*p*-$CH_3C_6H_5B(OH)_2$		H_2O	10	80	71[e]
4. *p*-$BrC_6H_4SO_3Na$[e]	*p*-$CH_3C_6H_5B(OH)_2$		H_2O/EtOH (60/40)	7	80	78[e]
5. 5-iodo-2'-deoxyuridine[f]	(*E*)-$C_6H_5CH{=}CHB(OH)_2$		$H_2O/MeOH$ (70/30)	3	80	47[f]
6. 5-iodo-2'-deoxyuridine[g]	propargyltrifluoroacetamide		H_2O/CH_3CN (50/50)	4	25	95[h]
7. 5-iodo-2'-deoxycytidine 5'-monophosphate	$HC{\equiv}CCH_2NH_2$	5-(propargylamine)-2'-deoxycytidine 5'-monophosphate	H_2O/CH_3CN (50/50)	3	25	73
8. 5-iodo-2'-deoxycytidine 5'-monophosphate	$HC{\equiv}CCH_2NH_2$	5-(propargylamine)-2'-deoxycytidine 5'-monophosphate	H_2O/CH_3CN (96/4)	6	25	52
9. 5-iodo-2'-deoxyuridine 5'-triphosphate	**4**	T-505	H_2O/CH_3CN (50/50)	3	25	50
10. 3-iodotyrosine[g]	$HC{\equiv}CCH_2NH_2$	**3**	H_2O/CH_3CN (50/50)	12	25	82[h]
11. *p*-$IC_6H_4CH_3$[g]	$HC{\equiv}CC_6H_5$		H_2O/CH_3CN (50/50)	3	25	100
12. *p*-$IC_6H_4CH_3$[g]	$HC{\equiv}CC_6H_5$		H_2O/CH_3CN (10/90)	2	30	100[d]
13. *p*-$IC_6H_4CH_3$[i]	ethyl acrylate		H_2O/CH_3CN (50/50)	12	80	65[d,j]
14. *p*-$IC_6H_4CH_3$[k]	$HP(O)(OCH_2CH_3)_2$		H_2O/CH_3CN (50/50)	2	25	100

[a] 0.1 mol % **2**, entry 12; 5 mol %, 4; 10 mol %, 1, 5, 6, 10, 11, 13, 14: 15 mol %, 2, 3: 20 mol %, 7–9. [b] Isolated yields based on RX unless otherwise noted. [c] 1 equiv RX, 1 equiv RY. 2 equiv Na_2CO_3; RH 10%, RR 7%. [d] G.C. yield. [e] 1.25 equiv RX, 1 equiv RY, 2 equiv Na_2CO_3. Yield based on RY. [f] 1 equiv RX, 1.3 equiv RY. 2 equiv Na_2CO_3. 38% RH based on ^1H NMR. [g] 1 equiv RX, 1.25–3 equiv RY, 2 equiv NEt_3, CuI/**2** = 2/1. [h] HPLC yield. [i] 1 equiv RX. 4 equiv RY. 2 equiv NEt_3. [j] RH. 13%; RI, 7%. [k] 1 equiv RX, 2.5 equiv RY. 3 equiv NEt_3.

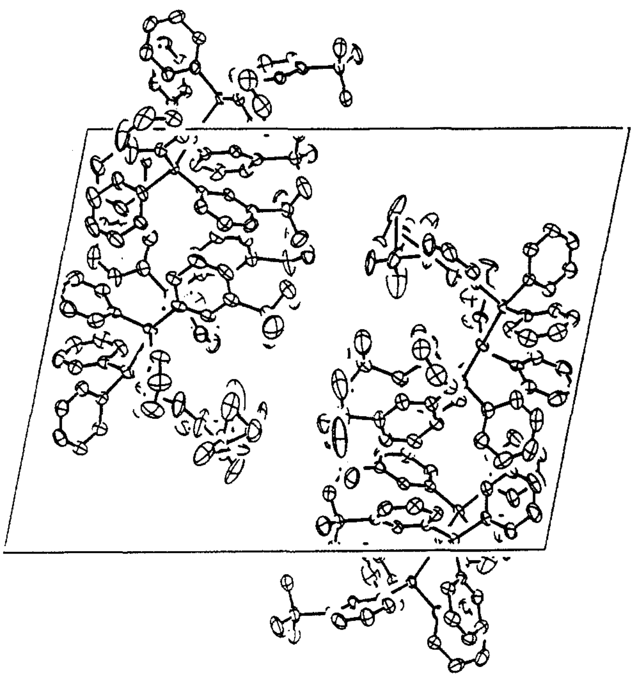
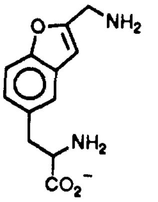


Figure 2. ORTEP drawing of **2** showing alignment of the sulfonate groups in the unit cell. The view is along the crystallographic *x*-axis. Water and K^+ have been omitted for clarity.

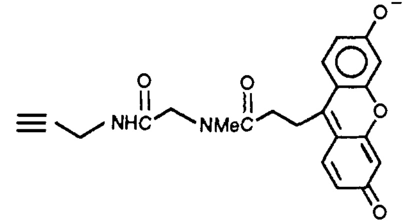
Unprotected nucleosides, nucleotides, and amino acids undergo coupling with acetylenes (entries 6–11). Iododeoxcytidine 5′-monophosphate and iododeoxyuridine were coupled to propargylamines in good to excellent yield (entries 6–8). 2-Iodotyrosine was coupled to propargylamine leading initially to the expected alkyne, which then cyclized in situ to give the benzofuran derivative **3**.[17] Conventional palladium catalysts were ineffective for this reaction in aqueous media.[18]



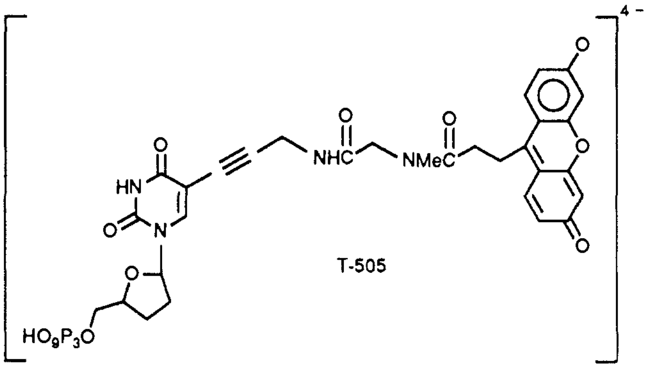
3

Other types of alkylation reactions are catalyzed by **2** in aqueous media. Examples include an aqueous version of the Heck reaction[16a,b] (entry 13) and the coupling of a dialkyl phosphite with an aromatic iodide to give an arylphosphonate (entry 14).[16j-l]

A demonstration of the synthetic versatility afforded by this technique is illustrated in an alternative synthesis of T-505, part of a family of chain-terminating nucleotide reagents used in automated DNA sequencing and labeling.[14] In the commercial syntheses of these reagents, the acetylene coupling reaction is carried out prior to the introduction of the hydrophilic triphosphate and fluorescein dye groups due to the insolubility of $Pd(PPh_3)_4$ in water. An alternative and equally convergent route is available with complex **2**. The C–C coupling reaction can be conducted in the final step in an aqueous medium with 5-iododideoxyuridine 5′-triphosphate and the unprotected fluorescein dye **4**. Synthesis by this route afforded T-505 in 50% isolated yield (entry 9).



4



In summary, the water-soluble Pd(0) catalyst Pd(PPh2(*m*-$C_6H_5SO_3M$))$_3$ (**2**) was synthesized and structurally characterized. Complex **2** efficiently catalyzed a variety of alkylation reactions in an aqueous medium. The catalyst was tolerant of a broad range of functional groups, including those present in unprotected nucleotides and an unprotected amino acid. The use of **2** increases the range of synthetic strategies available to the chemist by making C–C coupling reactions viable in aqueous media. Attempts to broaden the scope of these reactions are underway.

Acknowledgment. The author acknowledges W. Nugent for many helpful discussions and suggestions. Thanks are also extended to T. Fukunaga and B. Smart for project support, to F. Hobbs and G. Trainor for the synthesis of **4** and the iodonucleotide, to A. Vatvars, P. Korolkoff, and F. Kitson for analytical services, and T. Kline, E. Duvall, and W. Marshall for their excellent technical assistance.

Supplementary Material Available: Tables of atomic parameters and distances and angles for **2** and numbering scheme for alkylation products (13 pages); listing of observed and calculated structure factor amplitudes for **2** (37 pages). Ordering information is given on any current masthead page.

---

(17) (a) Arcadi, A.; Marinelli, F.; Cacchi, S. *Synthesis* **1986**, *9*, 749. (b) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. (c) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071.

(18) Catalysts included $Pd_2(dba)_3 \cdot CHCl_3$, $Pd(O_2CCF_3)_2$, $Pd(OAc)_2$, and Na_2PdCl_4.