oxidation by the catalyst $[(H_2O)(bpy)_2RuORu(bpy)_2(OH_2)]^{4+}$.[18,19] In keeping with these observations, we have thus far been unable to demonstrate the direct 2 e^- oxidation of **1** to **2**.

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Supplementary Material Available: Table of atomic positional and thermal parameters for $2{\cdot}3(CH_3)_2CO{\cdot}2H_2O{\cdot}CH_3CN$ (6 pages). Ordering information is given on any current masthead page.

(18) Gilbert, J. A.; Eggleston, D. S.; Murphy, W. R., Jr.; Geselowitz, D. A.; Gersten, S. W.; Hodgson, D. J.; Meyer, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 3855.
(19) This catalyst system also might operate by forming a μ_4-peroxo-bridged dimer of the binuclear ruthenium centers in the crucial O–O oxidative coupling step.

Palladium-Mediated Coupling between Organic Disulfides and Nucleic Acid Constituents

Don Bergstrom,* Peter Beal, Adil Husain, Robert Lind, and Jeffrey Jenson

Department of Chemistry, University of North Dakota Grand Forks, North Dakota 58202

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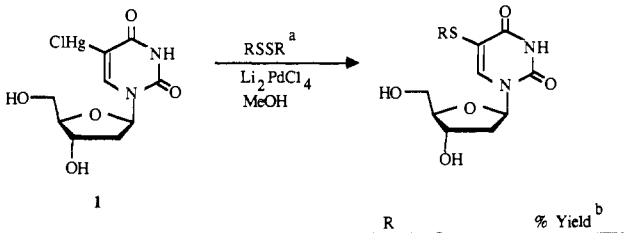
C-5 pyrimidine nucleosides and nucleotides have found notable applications as antiviral agents[1,2] and as constituents of modified nucleic acids useful as biochemical tools and diagnostic probes.[3-10] Pyrimidine dideoxyribonucleoside triphosphates modified at C-5 have recently found use in an automated rapid method for DNA sequencing.[11] In these applications C-5 serves as the site for attachment of linker arms to haptens, fluorophores,[12] metal ligands,[13] enzymes,[14] biotin,[3] or functional groups capable of facilitating the cleavage of complementary sequences. Among the unique advantages of C-5 as a site for attaching linker arms to nucleic acids are the lack of interference with binding of the modified sequence to complementary sequences and the flexibility to either modify a nucleic acid directly at the polynucleotide level, incorporate C-5 substituted nucleoside 5′-triphosphates enzymatically, or incorporate the modified nucleoside phosphoramidites in conventional automated synthesis.

We have previously described synthetic methodology for linking olefins at C-5 of pyrimidine nucleosides via palladium-mediated reactions of either mercurated or halogenated nucleosides.[15] The reaction has been extended to the modification of nucleoside 5′-triphosphates[16] and to nucleic acids.[17] A variation on this reaction allows linkage of terminal alkynes to suitably protected 5-iodopyrimidine nucleosides.[18] Both the alkene and alkyne versions of the palladium-mediated coupling reaction frequently give side products that may result from participation by solvent, lack of regioselectivity, or intramolecular participation by a nucleophilic group on the nucleoside.

We now wish to report the discovery of a novel reaction that may prove to be at least as versatile as the palladium-mediated coupling reactions of alkenes and alkynes. The only observed nucleoside containing side product is unmodified nucleoside. The reaction involves combining an organic disulfide with a methanol solution of lithium palladium chloride in which is suspended 5-(chloromercurio)-2′-deoxyuridine (**1**).[19] After stirring overnight at room temperature an insoluble palladium thiolate complex can be removed by filtration to yield a methanol solution of the product.

The disulfides shown in Scheme I were found to react with 5-(chloromercurio)-2′-deoxyuridine (**1**) to give 5-(alkylthio)- or 5-(arylthio)-2′-deoxyuridine (**2**).[20] Initially, when only 1 equiv of Pd(II) and 1 equiv of the mercurionucleoside was used the only disulfides to react were neutral ones (butyl and phenyl disulfides). Disulfides with polar functional groups did not react very well, if at all. These disulfides included 3,3′-dithiodipropionic acid, dimethyl 3,3′-dithiodipropionate, *N,N′*-bis(trifluoroacetyl)cystamine, and 2,2′-dithiodiethanol. When the amount of Pd(II) was doubled, all of the more polar disulfides gave good yields of product, with the exception of 2,2′-dithiodiethanol. Since the trifluoroacetyl-protecting group is easily removed from an amino group in concentrated ammonia, the *N,N′*-bis(trifluoroacetyl)-

Scheme I



1

	R	% Yield [b]
2a	$-(CH_2)_3CH_3$	73
2b	$-C_6H_5$	55
2c	$-CH_2CH_2CO_2CH_3$	46
2d	$-CH_2CH_2NHCCF_3$ (O)	51

[a] All reactions were run overnight at room temperature with 2 mmol 5-HgCldU, 4 mmol Li_2PdCl_4, and 5 mmol RSSR in 40 mL of methanol solvent. [b] Yield of product after purification by silica gel chromatography eluting with 90% chloroform/10% ethanol.

(1) De Clercq, E.; Walker, R. T. *Pharmacol. Ther.* **1984**, *26*, 1.
(2) Bergstrom, D. E.; Ruth, J. L.; Reddy, P. A.; De Clercq, E. *J. Med. Chem.* **1984**, *27*, 279.
(3) Brigati, D. J.; Myerson, D.; Leary, J. J.; Spalholz, B.; Travis, S. Z.; Fong, C. K. Y.; Hsiung, G. D.; Ward, D. C. *Virology* **1983**, *126*, 32.
(4) Leary, J. J.; Brigati, D. J.; Ward, D. C. *Proc. Natl. Acac. Sci. USA.* **1983**, *80*, 4045.
(5) Manuelidis, L.; Langer-Safer, P. R.; Ward, D. C. *J. Cell Biol.* **1982**, *95*, 619.
(6) Smith, G. H.; Doherty, P. J.; Stead, R. B.; Gorman, C. M.; Graham, D. E.; Howard, B. H. *Anal. Biochem.* **1986**, *156*, 17.
(7) Hutchison, N. J.; Langer-Safer, P. R.; Ward, D. C.; Hamkalo, B. A. *J. Cell. Biol.* **1982**, *95*, 609.
(8) Binder, M. S.; Tourmente, S.; Roth, J.; Renaud; Gehring, W. J. *J. Cell Biol.* **1986**, *102*, 1646.
(9) Welcher, A. A.; Torres, A. R.; Ward, D. C. *Nucl. Acids Res.* **1986**, *14*, 10027.
(10) Melton, D. A.; Krief, P. A.; Rebagliati, M. R.; Maniatis, T.; Zinn, K.; Green, M. R. *Nucl. Acids Res.* **1984**, *12*, 7035.
(11) 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.
(12) Haralambidis, J.; Chai, M.; Tregear, G. W. *Nucleic Acids Res.* **1987**, *15*, 4857.
(13) Dreyer, G. B.; Dervan, P. B. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 968.
(14) Jablonski, E.; Moomaw, E. W.; Tullis, R. H.; Ruth, J. L. *Nucleic Acids Res.* **1986**, *14*, 6115.
(15) (a) Bergstrom, D. E.; Ruth, J. L. *J. Org. Chem.* **1978**, *43*, 2870. (b) Bergstrom, D. E.; Warwick, P.; Ruth, J. L. *J. Org. Chem.* **1981**, *46*, 1432. (c) Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem. Soc.* **1978**, *100*, 2870. (d) Bergstrom, D. E.; Ruth, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 1587.
(16) Langer, P. R.; Waldrop, A. A.; Ward, D. C. *Proc. Natl. Sci. U.S.A.* **1981**, *78*, 6633.
(17) Bigge, C. F.; Lizotte, K.; Panek, J. S.; Mertes, M. P. *J. Carbohydr., Nucleosides, Nucleotides* **1981**, *8*, 295.
(18) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854.
(19) Bergstrom, D. E.; Ruth, J. L. *J. Carbohydr. Nucleosides, Nucleotides* **1977**, *4*, 257.
(20) All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy, high resolution FAB mass spectrometry, and ultraviolet spectroscopy.

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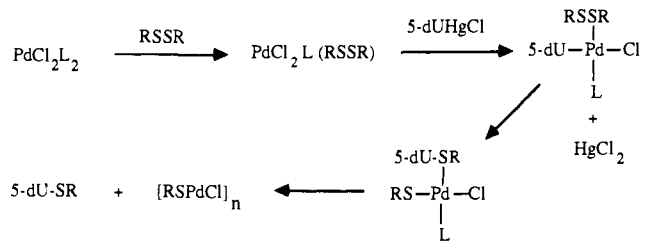
Scheme II



cystamine reaction provides useful entry to C-5 linker arms terminating by a primary amino group. An attempt to link a thiol group on the end of a five-atom chain by the reaction of 1,2-dithiane with 5-(chloromercurio)-2′-deoxyuridine and Li_2PdCl_4 in methanol gave essentially no coupled product. This result may be a function of competing reactions between disulfide and Pd(II). In the absence of 5-(chloromercurio)-2′-deoxyuridine there is a relatively rapid reaction between Pd(II) and organic disulfides, including 1,2-dithiane, to give unidentified yellow-orange complexes.

Preliminary studies with 5-chloromercuriocytidine show that it couples as well to disulfides. However, mercurated 2′-deoxyuridine 5′-monophosphate gave very little C-5 substituted product with *n*-butyl disulfide. The primary product following H_2S workup was primarily 2′-deoxyuridine 5′-monophosphate.

Other synthetic sequences[21-23] have been described for generating thioether linkages at C-5 but none appear to offer the simplicity and apparent versatility of the current reaction.

The disulfide coupling reaction appears to represent an example of an unexplored area of organopalladium chemistry. Although it was recently established that aryl sulfides can be synthesized via either organonickel or organopalladium intermediates, these reactions proceed under quite different conditions (strongly basic and elevated temperatures) involving oxidative addition of transition-metal complexes to aryl halides and thiolate anions.[24-27]

Mechanistic studies up to this point have been rather limited, but it is possible to propose a rational mechanism on the basis of literature precedence and on the basis of a number of relatively simple observations and experiments. It was established at the outset that Pd(II) is an absolute requirement. No reaction occurs in its absence. Consequently there is no direct exchange reaction with the disulfide similar to that observed between halogens and arylmercury compounds (leading to aryl halides), nor is the coupling reaction observed when Pd(0) [as $Ph_3P)_4Pd$] is used in place of Pd(II). The disulfide was also an absolute requirement; reactions attempted with thiol in place of disulfide gave immediate precipitation of a metal complex, and no sulfide product could be found. Unlike the reaction among 5-(chloromercurio)-2′-deoxyuridine, Li_2PdCl_4, and olefins, which results in the reduction of Pd(II) to Pd(0), no Pd(0) formation is observed in the disulfide reaction. At least three known distinct steps are likely to be involved in the overall reaction. First, Pd(II) is known to form complexes with disulfides which are relatively unstable and apparently break down in the presence of nucleophilic solvents to give μ[2] bridging thiolate complexes.[28] Second, palladium must undergo a metal–metal exchange reaction with the 5-(chloromercurio)-2′-deoxyuridine to generate a complex in which palladium is covalently linked at C-5. Finally there must be a step in which the disulfide is cleaved with generation of the C-5 sulfur link and bonding of a thiolate ligand to palladium. This formal process is shown schematically in Scheme II. The actual structures of the intermediates and details of the timing of these events will require further study.

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Supplementary Material Available: Experimental data consisting of reagents and methods and a general procedure for coupling 5-(chloromercurio)-2′-deoxyuridine to disulfide and tables of ^1H and ^{13}C NMR data (4 pages). Ordering information is given on any current masthead page.

(21) Dinan, F. J.; Bardos, T. J. *J. Med. Chem.* **1980**, *23*, 569.
(22) (a) Rupp, W. D.; Prusoff, W. H. *Biochem. Biophys. Res. Commun.* **1965**, *18*, 158. (b) Smith, K. C.; Aplin, R. T. *Biochemistry* **1966**, *5*, 2125.
(23) Hayakawa, H.; Tanaka, H.; Obi, K.; Itoh, M.; Miyasaka, T. *Tetrahedron Lett.* **1987**, *28*, 87.
(24) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, 13.
(25) Murahashi, S.; Yamamura, K.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408.
(26) Chrisau, H. J.; Chabaud, B.; Chene, A.; Christol, H. *Synthesis* **1981**, 892.
(27) Foa, M.; Santi, R.; Garavaglia, F. *J. Organomet. Chem.* **1981**, *206*, C29.
(28) Boschi, T.; Crociani, B.; Toniolo, L.; Belluco, U. *Inorg. Chem.* **1970**, *9*, 532.

A Rhodium Complex That Combines Benzene Activation with Ethylene Insertion. Subsequent Carbonylation and Ketone Formation

Chanchal K. Ghosh and William A. G. Graham*

Department of Chemistry, University of Alberta Edmonton, Alberta, Canada T6G 2G2

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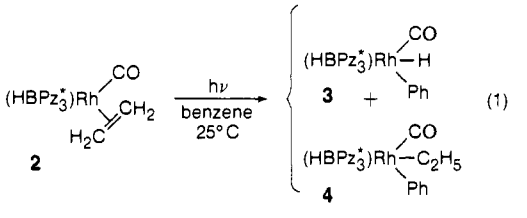
Following our recent report[1] of highly efficient photochemical carbon–hydrogen activation by dicarbonyl{tris(3,5-dimethylpyrazol-1-yl)borato}rhodium(I), $(HBPz^*_3)Rh(CO)_2$ (**1**), we have investigated the derivative $(HBPz^*_3)Rh(CO)(C_2H_4)$, **2**.[2] We now describe a remarkable photochemical reaction of **2** in which benzene activation and insertion of the ethylene ligand are combined to form an ethylphenylrhodium product.[4] We further report the carbonylation of this product and subsequent release of ethyl phenyl ketone.

Ultraviolet irradiation at 25 °C of a degassed benzene solution of **2** (3.6 mM) for 8 min resulted in its complete conversion to **3**[1] and **4**[5] in approximately equal yield (eq 1).[6] Separate ex-



(1) Ghosh, C. K.; Graham, W. A. G. *J. Am. Chem. Soc.* **1987**, *109*, 4726-4727.
(2) The new complex **2** was prepared by reaction of $KHBPz^*_3$ with $[(\mu\text{-Cl})Rh(CO)(C_2H_4)]_2$.[3] Data for **2**: IR (*n*-hexane) ν_{CO} 2013 cm^{-1}; ^1H NMR (CD_2Cl_2, −60 °C, 400 MHz) δ 5.90 (s, 2 H), 5.60 (s, 1 H), 3.15 (d, 2 H, J = 8.5 Hz), 2.33 (s, ~8 H), 2.32 (s, ~6 H), 2.20 (s, 3 H), 2.16 (s, 3 H); MS (16 eV, 90 °C), 456 (7%) M^+, 428 (100%) $[M - CO/C_2H_4]^+$, 400 (71%) $[M - CO - C_2H_4]^+$; Anal. ($C_{18}H_{26}BN_6ORh$) C, H, N.
(3) Powell, J.; Shaw, B. L. *J. Chem. Soc. A* **1968**, 211-212.
(4) In a paper which appeared as this manuscript was in preparation (McGhee, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 4246-4262) kinetic evidence was presented for an intermediate $[(\eta\text{-}C_5Me_5)Ir(\eta^2\text{-propene})]$ which oxidatively added benzene and was trapped by phosphine after insertion to produce $(\eta\text{-}C_5Me_5)Ir(PR_3)(Ph)(n\text{-propyl})$. In other related work, benzene activation followed by insertion of an isocyanide ligand into the resulting iron–phenyl bond were proposed as key steps in a catalytic cycle (Jones, W. D.; Foster, G. P.; Putinas, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5047-5048).
(5) Data for **4**: colorless crystals mp 175-178 °C; IR (*n*-hexane) ν_{CO} 2043 cm^{-1}; ^1H NMR (CD_2Cl_2, ambient, 200 MHz) δ 7.34 (d, 1 H), 7.13 (t, 1 H), 6.98 (t, 1 H), 6.79 (t, 1 H), 6.58 (d, 1 H), 5.90 (s, 1 H), 5.80 (s, 1 H), 5.79 (s, 1 H), 2.65 (m, 1 H), 2.49 (s, 3 H), 2.48 (s, 3 H), 2.46 (s, 3 H), 2.44 (s, 3 H), 2.20 (m, 1 H), 1.68 (s, 3 H), 1.58 (s, 3 H), 0.69 (t, 3 H, J = 7 Hz); MS (16 eV, 100 °C), 534 (32%) M^+, 505 (100%) $[M - C_2H_5]^+$, 477 (70%) $[M - C_2H_5 - CO]^+$, 428 (24%) $[M - C_2H_5 - C_6H_5]^+$, 400 (16%) $[M - C_2H_5 - C_6H_5 - CO]^+$. Anal. ($C_{24}H_{32}BN_6ORh$) C, H, N.

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