The generality of the synthetic strategy developed was then tested with other sugars. The monosaccharides D-galactose, D-mannose, and D-fructose were all enzymatically acylated in pyridine in a regioselective manner (entries 5-7 in Table I): in the first two cases, by far the main products were the 6-*O*-acyl derivatives, while in fructose the two primary hydroxyl groups displayed comparable reactivities.[15] The methodology described in this work can be applied to efficient and selective enzymatic production of sugar monoesters to replace existing multistep chemical procedures.[1,2]

(15) The disaccharides sucrose, lactose, and maltose had very low reactivities in the porcine pancreatic lipase catalyzed transesterification with **1**, probably due to steric hindrances.

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Carbon-Hydrogen Bond Activation by Ruthenium for the Catalytic Synthesis of Indoles

William D. Jones*† and Walter P. Kosar

Department of Chemistry, University of Rochester Rochester, New York 14627

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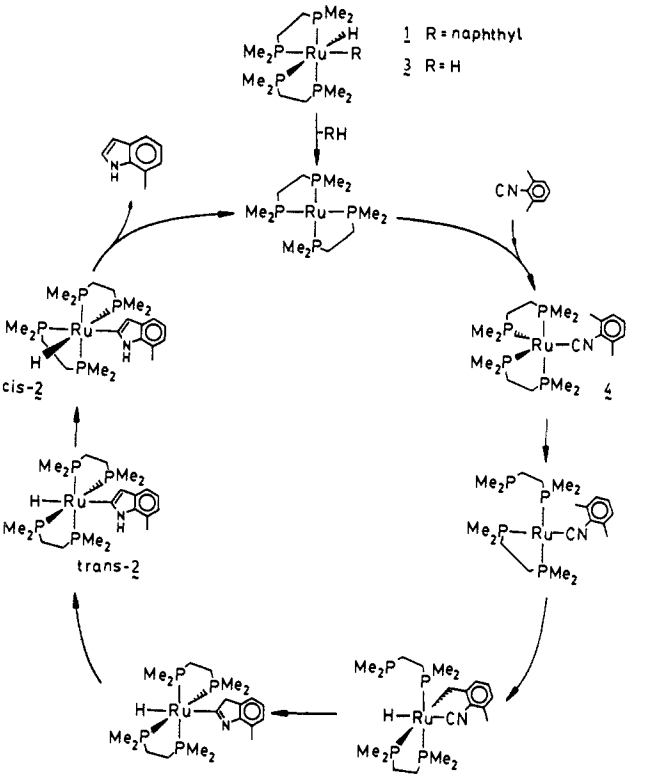
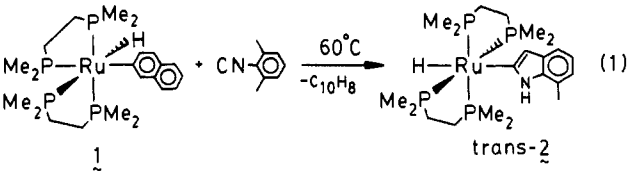
The intramolecular cyclometalation of sp^3 hybridized carbon-hydrogen bonds in ligand alkyl groups is well documented in transition-metal chemistry.[1] Recent studies have demonstrated the feasibility of intermolecular activation of sp^3 hybridized carbon-hydrogen bonds in free alkane molecules, which has stimulated a search for the functionalization of the C-H bond in a catalytic fashion.[2] We report here the activation of benzylic sp^3 hybridized C-H bonds and their catalytic conversion into an indole product using an isocyanide moiety to trap the activated species.

$Ru(DMPE)_2(naphthyl)H$ (**1**) was the first reported homogeneous metal complex to undergo reversible activation of arene and certain activated aliphatic C-H bonds.[3] We have found that thermolysis of **1** in C_6D_6 solution in the presence of 1 equiv of 2,6-xylyl isocyanide at 60 °C for 24 h results in the quantitative formation of naphthalene and a new species in which the ^1H NMR spectrum indicates a *trans*-$Ru(DMPE)_2HX$ configuration.[4] Only one of the xylyl methyl groups remains intact at δ 2.537 and the aromatic hydrogens of the isocyanide ligand appear as an asymmetric ABC pattern. A broad resonance is observed at δ 7.342

Scheme I

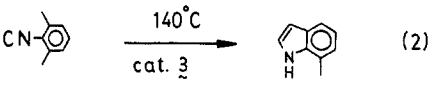


and an olefinic singlet is seen at δ 6.082. These data are consistent with the formation of a 2-substituted 7-methylindole ring and the formulation of the product as *trans*-$Ru(DMPE)_2$[2-(7-methylindole)]H (*trans*-**2**), isolated as yellow-orange crystals in 77% recrystallized yield (eq 1). Confirmation of the presence of an indole ring was obtained from an X-ray structural determination of *trans*-**2**.[5]



(1)

We have also discovered that thermolysis of 2,6-xylyl isocyanide in the presence of ~1 equiv of $Ru(DMPE)_2H_2$ (**3**) (140 °C, 24 H) in a sealed tube results in the catalytic conversion of the isocyanide into free 7-methylindole (eq 2). In one run, 10 mg



(2)

of **3** and 5 mg of 2,6-xylyl isocyanide (1:1.5 ratio) in 0.6 mL of C_6D_6 were heated for 25 h at 140 °C in a sealed tube. A ^1H NMR spectrum showed a 98% NMR yield of free 7-methylindole and no change in the quantity of **3**.

As little as 20 mol % of **3** is effective as a catalyst, although a competing metal-catalyzed dead-end side reaction is now observed. With low catalyst/isocyanide ratios, a competitive isocyanide dimerization to form a product in which the isocyanide inserts into the N-H bond of 7-methylindole in a 1,1 fashion is seen (eq 3). This dimer is apparently formed reversibly since continued heating at 140 °C ultimately results in the overall conversion of the 2,6-xylyl isocyanide into 7-methylindole in >90% yield.[6] Reaction of 50 mg of 2,6-xylyl isocyanide with 30 mg

† A.P. Sloan Fellow, 1984-1986. Camille and Henry Dreyfus Teacher Scholar, 1985-1987.

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(4) ^1H NMR of *trans*-**2** in C_6D_6: δ 7.342 (br s, 1 H); 7.650 (d, J = 8.5 Hz, 1 H); 7.211 (t, J = 7.2 Hz, 1 H); 6.897 (d, J = 7.3 Hz, 1 H); 6.082 (s, 1 H); 2.537 (s, 3 H); 1.450 (m, 4 H); 1.280 (m, 4 H); 1.230 (s, 12 H); 1.183 (s, 12 H); -12.742 (quint, J = 23.2 Hz, 1 H). Mass spectrum (75 eV): 532 (M^+), 531, 402 (M^+ - 130), 401 (M^+ - 131), 131 (M^+ - 401), 130 (M^+ - 402). IR (KBr): 1747, 1419, 1344, 1281, 941, 923, 887, 840, 788, 774, 738, 723, 700, 639 cm^{-1}. Anal. ($RuP_4NC_{21}H_{41}$): C, H, N.

(5) Thick yellow plates of *trans*-**2** crystallized in space group $Cmc2_1$ with Z = 4. Full-matrix anisotropic refinement converged at R_1 = 0.0302, R_2 = 0.0404. The indole lies in a crystallographic mirror plane with unique C_{indole}-Ru-P angles of 93.5° and 95.2°.

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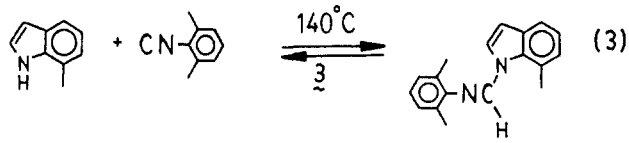

(3)

of **3** (5:1 ratio) in 0.6 mL of C_6D_6 (94 h, 140 °C, sealed tube) results in the formation of 7-methylindole in 70% isolated yield after sublimation (3.5 turnovers).

The mechanism of this cyclization was revealed in reactions under less severe conditions. Thermolysis of **3** in C_6D_6 under 534 mm of D_2 at 140 °C results in the slow formation of **3**-d_2 (84% exchange after 33 h). Irradiation of **3** for 2 h in the presence of 2,6-xylyl isocyanide at 25 °C produces ~25% yield of a new product formulated as $Ru(DMPE)_2(CN\text{-}2,6\text{-}C_6H_3Me_2)$ (**4**), on the basis of the similarity of the ^1H NMR spectral data to that of other $Ru(DMPE)_2L$ (L = CNPh, $CNCH_2CMe_3$, CO, PMe_3) complexes.[7,8] Upon standing at 25 °C, a C_6D_6 solution of **4** produces *trans*-**2** quantitatively (by ^1H NMR) after several days. Furthermore, heating a benzene solution of *trans*-**2** in a sealed tube under 540 mm of H_2 to 100 °C induces isomerization to *cis*-**2**.[9] Raising the temperature to 140 °C results in the rapid production of free 7-methylindole and **3** (95% complete in 2 h).

A proposed mechanism for this reaction is shown in Scheme I involving coordination of isocyanide to $[Ru(DMPE)_2]$ and dissociation of one end of a DMPE ligand followed by benzylic methyl group oxidative addition to generate a six-membered metallocycle ring.[10] The isocyanide insertion into the Ru–CH_2 bond is driven by the closure of the DMPE chelate to give stereospecifically the trans isomer. Tautomerism of the methylene hydrogen to the nitrogen generates the observed product *trans*-**2**. Isomerization from trans to cis occurs prior to reductive elimination, with the latter being the highest barrier in the catalytic cycle.

Several novel conclusions arise as a consequence of the proposed mechanism. First, while the intermediate in which the C–H bond undergoes oxidative addition to the metal might appear to be rather strained due to the anticipated linearity of the Ru–C–N–C linkage, the intramolecular oxidative addition still occurs. A resonance structure involving strong π-back-bonding with the Ru(0) center would manifest itself in both the reduction of the isocyanide stretching frequency and bending of the C–N–C bond. Another interesting feature of this system is that *C–H activation occurs even in the presence of an excess of the trapping ligand* (CNR), the reaction occurring due to the formation of a second vacant coordination site on ruthenium. Finally, this new route to indoles (most similar to the Madelung synthesis[11a] or the lithiation procedure of Ito and Saegusa[11b]) offers advantages over the traditional routes in that neutral conditions and lower temperatures are employed.[11c] Further extensions of this cyclization to include other indoles and heterocycles are under investigation.

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Supplementary Material Available: Description of the structural solution and an ORTEP plot of *trans*-**2**, tables of crystallographic data collection parameters, fractional atomic coordinates, anisotropic thermal parameters, and bond distances and angles (7 pages); table of calculated and observed structure factors (20 pages). Ordering information is given on any current masthead page.

(6) 7-methylindole and 2,6-xylyl isocyanide do not react at 140 °C in the absence of **3**. In the presence of **3**, the amount of dimer increases (up to 35% of the reaction mixture) and then decreases as isocyanide is converted into indole. ^1H NMR of dimer (C_6D_6): δ 8.550 (s, 1 H), 8.369 (d, J = 3.6 H, 1 H), 7.387 (d, J = 7.8 Hz, 1 H), 7.00 (m, 4 H), 6.817 (d, J = 7.2 Hz, 1 H), 6.510 (d, J = 4.1 Hz, 1 H), 2.152 (s, 6 H), 1.966 (s, 3 H). ^{13}C NMR ($CDCl_3$, attached proton test polarization shown in parentheses where observed): δ 18.61 (-), 21.81 (-), 108.28 (-), 119.83 (-), 121.18 (+), 122.14 (-), 123.75 (-), 123.93 (-), 127.15 (-), 128.29 (-), 128.66 (+), 131.34 (+), 134.34 (n.o.), 145.62 (-), 147.79 (n.o.). IR (C_6H_6): 1647 cm^{-1}. Mass spectrum (75 eV): 262 (M^+), 131, 130.

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(8) ^1H NMR of **4** in C_6D_6: δ 6.993 (d, J = 7.4 Hz, 2 H); 6.856 (t, J = 7.5 Hz, 1 H); 2.672 (s, 6 H); 1.300 (br s, 24 H). IR (KBr): $\nu_{C\equiv N}$ = 2048 cm^{-1}.

(9) ^1H NMR of *cis*-**2** in C_6D_6: δ 8.074 (br s, 1 H); 7.204 (t, J = 7.4 Hz, 1 H); 6.908 (d, J = 7.1 Hz, 1 H); 7.686 (d, J = 7.6 Hz, 1 H); 6.314 (s, 1 H); 2.491 (s, 3 H); 1.427 (d, J = 6.1 Hz, 3 H); 1.210 (d, J = 7.2 Hz, 3 H); 1.124 (d, J = 6.4 Hz, 3 H); 1.059 (d, J = 6.0 Hz, 3 H); 0.960 (d, J = 8.7 Hz, 3 H); 0.934 (d, J = 9.1 Hz, 3 H); 0.895 (d, J = 5.3 Hz, 3 H); 0.852 (d, J = 5.6 Hz, 3 H); 0.8–1.5 (m, ~8 H (broad resonance under DMPE doublets); -8.955 (dq, J = 83.6, 24.4 Hz, 1 H).

(10) $Ru(\eta^2\text{-DMPE})(\eta^1\text{-DMPE})(CNPh)_2$ forms from the reaction of $Ru(\eta^2\text{-DMPE})_2(CNPh)$ with CNPh. See ref 7b.

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The Sonochemical Hot Spot

Kenneth S. Suslick,* David A. Hammerton, and Raymond E. Cline, Jr.

School of Chemical Sciences
University of Illinois at Urbana—Champaign
Urbana, Illinois 61801
Received April 7, 1986

The chemical effects of ultrasound have been studied for over 50 years.[1,2] In site of this, our understanding of the reaction conditions created by ultrasonic irradiation of liquids is extremely limited. It is well accepted[2,3] that sonochemistry results from acoustic cavitation: the creation, expansion, and implosive collapse of bubbles in ultrasonically irradiated liquids.[4] We have used the sonochemical ligand substitution rates of volatile metal carbonyls to establish the site of sonochemical reactions.[5] We find that there are two regions of sonochemical reactivity: one corresponding to the gas phase within the collapsing cavity and the second to a thin liquid layer immediately surrounding the collapsing cavity. Furthermore, we are now able to determine experimentally the effective temperature in each reaction zone, through the use of comparative rate thermometry. The gas- and liquid-phase reaction zones have effective temperatures of 5200 and 1900 K, respectively.

In order to probe the nature of the sonochemical hot spot, we wished to determine the first-order rate coefficients of sonochemical ligand substitution as a function of metal carbonyl vapor pressure. However, the efficacy of cavitational collapse and the temperatures so generated are strongly dependent on the vapor pressure of the solvent system.[6] Therefore, sonolyses at various ambient temperatures were done in solutions of two *n*-alkanes which had been mixed in the proper proportion to keep the total system vapor pressure constant (at 5.0 torr).[7] Alkane solutions of metal carbonyls (0.01 M) were irradiated with a collimated

* Author to whom correspondence should be addressed.

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