128.52 (2 CH, a), 129.69 (2 CH, a), 133.21 (C, a), 136.86 (C, a), 139.29 (C, a), 151.06 (C of NC=N); mass spectrum, m/e 340 (M^+), 325, 236, 185, 104. Anal. Calcd for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46. Found: C, 78.01; H, 5.87; N, 16.51.

Reaction of Sulfur Dioxide and Ketene Imine 3a. Liquid sulfur dioxide (ca. 5 mL) was added to a freshly prepared solution (THF, 80 mL) of ketene imine **3a** (0.59 g, 3.17 mmol) at -40 °C. After warmup at room temperature and evaporation of the excess of sulfur dioxide, the residue was chromatographed (SiO_2, ethyl ether), yielding 0.50 g (1.106 mmol, 70%) of **bis[(*N*-mesitylcarbamoyl)cyclopropyl] sulfoxide (8)**: mp 225-226 °C (from methanol); IR (CCl_4, C_2Cl_4, CS_2) 3200-3100 (NH), 1670-1640 (*CO*NH), 1540-1515, 1470-1440, 1080 and 1070 (SO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33-1.60 (br, 8 H, 4 CH_2), 2.02-2.10 (br, 12 H, 4 CH_3), 2.27 (s, 6 H, 2 CH_3), 6.8-6.9 (br, 4 H, a), 8.4-8.53 (2 H of NH); ^{13}C NMR ($CDCl_3$) δ 11.39 (2 CH_2), 12.95 (2 CH_2), 18.32 (4 CH_3), 20.87 (2 CH_3), 40.22 (2 C), 129.00 (4 CH), 130.71 (2 C), 134.60 (4 C), 137.00 (2 C), 166.47 (2 C of CONH); mass spectrum, m/e 452 (M^+), 437, 250, 202. Anal. Calcd for $C_{26}H_{32}N_2O_3S$: C, 68.99; H, 7.13; N, 6.19; S, 7.08. Found: C, 68.46; H, 7.19; N, 6.10; S, 7.01.

The sulfoxide **8** (0.25 g, 0.553 mmol) was reacted with *m*-chloroperbenzoic acid (85%) (0.112 g, 0.553 mmol) at room temperature for 24 h. Removal of the solvent and chromatography on a preparative plate (SiO_2, 4:1 *n*-pentane-ethyl acetate) yielded 0.25 g of the corresponding **bis[(*N*-mesitylcarbamoyl)cyclopropyl]sulfone (9)**: mp 190-192 °C (from ethyl ether); IR (CCl_4, C_2Cl_4, CS_2) 3300-3100 (NH), 1680-1650, 1470-1450, 1380, 1330, 1122 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.73-1.87 (br, 4 H, 2 CH_2), 1.86-2.00 (br, 4 H, 2 CH_2), 2.17-2.27 (br, 12 H, 4 CH_3), 2.27-2.40 (br, 6 H, 2 CH_3), 6.87-7.00 (br, 4 H, a), 8.60-8.73 (br, 2 H of NH); mass spectrum, m/e 468 (M^+), 334.

Reaction of Phenyl Isocyanate (10) and Ketene Imine 3a. Keteneimine **3a** (0.663 g, 3.58 mmol) was reacted with **10** (1.096 g, 9.20 mmol) in THF (100 mL) at room temperature for 24 h. After evaporation of the solvent and of the excess of **10** in vacuo, chromatographic workup of the residue (SiO_2, 10:1 *n*-pentane-ethyl acetate) gave the following.

(a) 4-(Mesitylimino)-5-phenyl-5-azaspiro[2.3]hexan-6-one (11): 0.44 g (1.445 mmol, 40%); oil; IR (CCl_4, C_2Cl_4, CS_2) 3080-2930, 1735 (N-C=O), 1715 (N-C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8-1.0 (m, 2 H), 1.22- 1.40 (m, 2 H), 2.15 (s, 6 H, 2 CH_3), 2.25 (s, 3 H, 1 CH_3), 6.73-6.80 (br, 2 H, a), 7.03-7.53 (m, 3 H, a), 8.0-8.23 (m, 2 H, a); ^{13}C NMR ($CDCl_3$) δ 10.30 (2 CH_2), 18.25 (2 CH_3), 20.71 (CH_3), 39.37 (C_3), 118.85 (2 CH), 125.32 (CH), 127.38 (2 C), 128.47 (2 CH), 129.02 (2 CH), 132.96 (C), 136.44 (C), 140.98 (C), 154.06 (C of NC=N), 170.9 (C of NC=O); mass spectrum, m/e 304 (M^+), 185, 119. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 79.10; H, 6.66; N, 9.16.

(b) 4-(Mesitylimino)-1,2,3,4-tetrahydrospiro[2-quinolone-3,1′-cyclopropane] (12): 0.50 g (1.645 mmol, 45%); mp 226-230 °C (from CH_2Cl_2); IR (Nujol) 3350-3300 (NH), 1683, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84-1.91 (br, 6 H, 2 CH_3), 1.92-2.07 (br, 4 H), 2.24-2.31 (br, 3 H, 1 CH_3), 6.60-7.40 (m, 4 H, a), 6.80-6.90 (br, 2 H, a), 10.0-10.20 (br, 1 H of NH); ^{13}C NMR ($CDCl_3$) δ 17.84 (2 CH_3), 20.73 (1 CH_3), 26.57 (2 CH_2), 30.89 (C), 116.99 (CH), 122.89 (CH), 123.53 (2 C), 126.51 (CH), 129.02 (2 CH), 131.31 (C), 132.50 (CH), 138.73 (C), 145.75 (C), 157.56 (C), 173.21 (C of NC=O); mass spectrum, m/e 304 (M^+), 289, 275, 185. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found C, 78.51; H, 6.65; N, 9.24.

Compound **12** (0.35 g, 1.15 mmol) was dissolved in $CHCl_3$ (25 mL) and thermostated at 20 °C for 1 week. Evaporation of the solvent and chromatography on preparative plate (SiO_2, 1:1 CH_2Cl_2-ethyl acetate) afforded, in order, 0.07 g (0.23 mmol, 20%) of unreacted **12** and 0.21 g (0.69 mmol, 75%) of **4-(mesitylimino)-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline (13)**: mp >230 °C dec (slowly; from ethyl ether); IR (Nujol) 3400-3100 (NH), 1628, 1580, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14-2.20 (br, 6 H, 2 CH_3), 2.20-2.28 (br, 2 H), 2.30-2.36 (br, 3 H, 1 CH_3), 4.20-4.43 (t, 2 H, OCH_2), 6.30-6.50 (br, 1 H of NH), 6.89-6.98 (br, 2 H, a), 7.20-8.00 (m, 4 H, a); ^{13}C NMR ($CDCl_3$) δ 18.25 (2 CH_3), 20.96 (1 CH_3), 26.53 (1 CH_2), 68.65 (OCH_2), 97.67 (C), 117.28 (C), 119.65 (CH), 122.71 (CH), 128.02 (CH), 128.49 (2 CH), 129.02 (CH), 134.2 (C), 137.02 (2 C), 144.86 (C), 147.68 (C), 169.18 (C); mass spectrum, m/e 304 (M^+), 60. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 79.03; H, 6.56; N, 9.25.

Crystal Data of 6,6-Diphenyl-4-(mesitylimino)-5-thiaspiro[2.3]hexane (5): $C_{26}H_{25}NS$, M_r = 383.6, monoclinic, space group $P2_1/n$, a = 9.210 (4) Å, b = 12.716 (5) Å, c = 18.102 (7) Å, β = 99.52 (3)°; Z = 4, d_c = 1.22 g cm^{-3}, V = 2090 Å^3, Mo K radiation, λ = 0.7107 Å. Of 3340 independent reflections, 2517 having $I > 2.5\ \sigma(I)$ were considered observed. Structure determination by direct methods and refined anisotropically. (SHELX program.) The most relevant interatomic distances (standard deviations) (in Å) within the three- and four-membered rings are as follows: S_1-C_2 = 1.887 (3); S_1-C_4 = 1.780 (4); C_2-C_3 = 1.548 (5); C_3-C_4 = 1.472 (4); C_3-C_{17} = 1.499 (5); C_3-C_{18} = 1.512 (5); C_{17}-C_{18} = 1.484 (6); C_4-N_{19} = 1.254. The dihedral angle between the three-membered ring and the least-squares mean plane through the four-membered ring is 86.5°. Within the four-membered ring the dihedral angle between the two planes formed by C_2-S_1-C_4 and C_2-C_3-C_4 respectively, is 11.6°. See paragraph at the end of the paper about supplementary material.

Acknowledgment. We thank Giovanni Bragaglia and Paolo Bonetti, Ozzano E., for technical assistance.

Registry No. 3a, 98875-59-3; **5**, 98875-60-6; **6**, 98875-61-7; **8**, 98875-62-8; **9**, 98875-63-9; **10**, 103-71-9; **11**, 98875-64-0; **12**, 98900-98-2; **13**, 98875-65-1; *N*-mesitylcyclopropylformimidoyl chloride, 98875-66-2; thiobenzophenone, 1450-31-3; *N*-(dicyanomethylene)aniline, 19769-98-3; sulfur dioxide, 7446-09-5.

Supplementary Material Available: Full X-ray data for compound **5** (4 pages). Ordering information is given on any current masthead page.

Nickel-Catalyzed Markovnikov Addition of Hydrogen Cyanide to Olefins. Application to Nonsteroidal Antiinflammatories†

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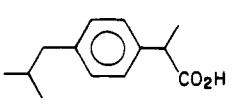
The two antiinflammatory drugs ibuprofen[1] (1) and



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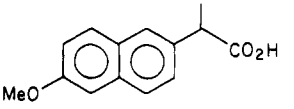
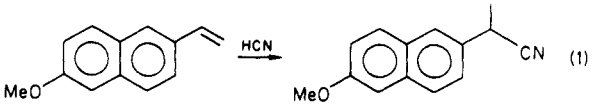


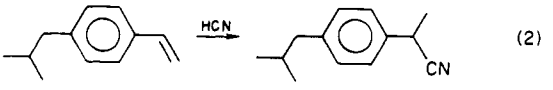
2

naproxen[2] (2) are members of the class of 2-arylpropionic acids toward which extensive synthesis research has been directed.[3] This reflects both the economic importance of these pharmaceuticals and the fact that none of the existing routes are fully satisfactory.[4]

An attractive approach to these compounds involves hydrocyanation of the corresponding vinylarenes (eq 1 and 2) followed by hydrolysis.



3 4 (1)



5 6 (2)

The anti-Markovnikov addition of HCN to butadiene is practiced on a large scale for the manufacture of adi-

† Contribution no. 3749.

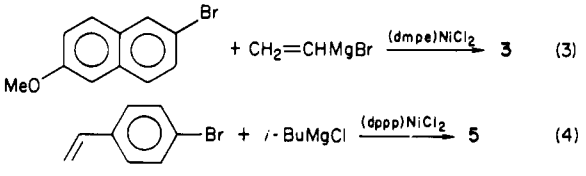
0022-3263/85/1950-5370$01.50/0

ponitrile (a nylon intermediate).[5] Our mechanistic studies of nickel-catalyzed olefin hydrocyanation[6] have allowed us to develop the Markovnikov addition of HCN to vinyl arenes as a new synthetic tool.[7]

Tetrakis(tri-*p*-tolyl phosphite)nickel(0) is an effective catalyst for the regiospecific hydrocyanation of **3** to **4** at temperatures greater than 50 °C. Lewis acid promoters generally used in monoene hydrocyanation are detrimental to selectivity, increasing the anti-Markovnikov addition product. Because the degradation of the nickel catalyst is second order in HCN concentration, the HCN is fed slowly as an HCN/N_2 gas mixture. This is easily accomplished by passing a controlled flow of nitrogen gas through liquid HCN maintained at 0 °C in an ice bath, through a P_2O_5 trap, and directly into the reaction vessel. The resulting vapor is approximately 35% HCN. In order to suppress competing oligomerization, it is also desirable to introduce **3** gradually during the course of the reaction. Using 5 mol % Ni catalyst, **4** was routinely prepared in 90–93% isolated yield. Comparable results were obtained with 2-vinylnaphthalene.

Hydrocyanation of styrene or substituted styrenes such as **5** under similar conditions is less efficient because of extensive oligomerization even in the presence of radical inhibitors. The addition of a limited amount of Lewis acid such as zinc chloride helps overcome this problem by increasing the rate of hydrocyanation compared to oligomerization. For example, hydrocyanation of **5** (5 mol % Ni, 2 mol % $ZnCl_2$, 88 °C) afforded **6** in 65–70% yield along with 8–10% of the isomeric 3-arylpropionitrile. The isomeric nitriles are readily separated by flash chromatography.

This new reaction provides a very simple route for the synthesis of a series of homologous 2-arylpropionic acids. The requisite vinylarene starting materials are readily prepared from commercially available aryl bromides using the nickel-catalyzed cross-coupling chemistry of Komada[8] (eq 3 and 4). The product nitriles are readily hydrolyzed to the corresponding acids ($NaOH/H_2O$/ethylene glycol, 125 °C). The entire procedure is amenable to preparation of multigram quantities of material for biological testing.



Experimental Section

Hydrogen cyanide was obtained in small cylinders from Fumico, Inc. (Amarillo, TX).

Caution! Hydrogen cyanide (HCN) is very volatile and highly toxic and should be used only in a well-ventilated fume hood or drybox. Distilled HCN is prone to very exothermic oligomerization when heated and should be kept at 0 °C or lower at all times. The commercially available samples contain strong acidic inhibitors. Sensible precautions include not working alone and having available proper first aid equipment. Excess HCN may be disposed of by burning or by adding to aqueous sodium hypochlorite (which converts it to the cyanate). Liquid HCN dispensed from the cylinder should be slowly sparged with nitrogen for about 30 min to remove gaseous sulfur oxides (from the inhibitor) before using.[9]

Tetrakis(tri-*p*-tolyl phosphite)nickel(0)[10] and [bis(dimethylphosphino)ethane]nickel(II) chloride[11] were prepared by literature procedures. Other materials were commercial samples used as received. Flash chromatography was carried out following the procedure of Still.[12] Proton NMR spectra were recorded on a Nicolet NT360 WB spectrometer in $CDCl_3$ with respect to internal tetramethylsilane. Couplings (J) are in hertz.

2-Methoxy-6-vinylnaphthalene (3). To a solution of 2-bromo-6-methoxynaphthalene (9.48 g, 40 mmol) and [bis(dimethylphosphino)ethane]nickel(II) chloride (0.10 g, 0.36 mmol) in tetrahydrofuran (THF) (100 mL) was added dropwise 1.0 M vinylmagnesium bromide in THF (50 mL, 50 mmol). The mixture was stirred at room temperature overnight and then quenched in half-saturated NH_4Cl. Extraction with ether and removal of solvent afforded the crude product which was crystallized from hot heptane to afford needles of **3** (6.35 g, 86%) mp 91–93 °C. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.45; H, 6.49; ^1H NMR δ 3.92 (s, 3 H), 5.27 (d, J = 11, 1 H), 5.82 (d, J = 17, 1 H), 6.85 (dd, J = 11, 17, 1 H); 7.11–7.14 (m, 2 H), 7.61–7.71 (m, 4 H).

***p*-Isobutylstyrene (5).** To a solution of *p*-bromostyrene (9.15 g, 50 mmol) and [bis(diphenylphosphino)propane]nickel(II) chloride (0.15 g, 0.29 mmol) in ether (150 mL) was added dropwise 2.38 M isobutylmagnesium chloride in ether (25 mL, 60 mmol). The mixture was heated under reflux overnight and was then quenched with half-saturated NH_4Cl. Extraction with ether and removal of solvent afforded the crude product which was purified by flash chromatography (hexane eluant, R_f 0.50) to afford **5** (6.11 g, 76%) as a colorless liquid. Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 90.05; H, 10.03. ^1H NMR δ 0.87 (d, J = 7, 6 H), 1.81 (m, 1 H), 2.41 (d, J = 7, 2 H), 5.12 (dd, J = 1, 11, 1 H), 5.66 (dd, J = 1, 18, 1 H), 6.64 (dd, J = 11, 18, 1 H), (7.03 (d, J = 8, 2 H), 7.26 (d, J = 8, 2 H).

2-(6-Methoxynaphth-2-yl)propionitrile (4). Tetrakis(tri-*p*-tolyl phosphite)nickel(0) (1.00 g, 0.68 mmol), tri-*p*-tolyl phosphite (0.30 mL, 1.0 mmol) in toluene (15 mL) are heated to 88 °C under nitrogen. 2-Methoxy-6-vinylnaphthalene **3** (2.88 g, 15.6 mmol) and ionol (0.1 g, inhibitor) in toluene (15 mL) are fed to the catalyst mixture by syringe pump; 3 mL is added initially and the remainder fed at 4 mL/h. HCN/N_2 gas is introduced to the reaction mixture at 3 mL/min just above the liquid level. Addition of vinylarene is complete in 3.5 h, and HCN addition is stopped after 5.5 h. Flash chromatography of the reaction mixture (hexane/ethyl acetate, 75:25, R_f 0.39) results in the isolation of **4** (3.10 g, 15.0 mmol, 93% yield) as a white crystaline solid, mp 72–74 °C. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.71; H, 6.11; N, 6.23. ^1H NMR δ 1.71 (d, J = 7, 3 H), 3.92 (s, 3 H), 4.03 (q, J = 7, 1 H), 7.1–7.2 (m, 2 H), 7.38 (dd, J = 8, 2, 1 H), 7.71–7.77 (m, 3 H).

(1) Nicholson, J. S.; Adams, S. S. U.S. Patent 3 228 831, 1966, Boots Pure Drug Co. Ltd, England. Shen, T. Y. *Angew Chem., Int. Ed. Engl.* **1972**, *11*, 460–472.

(2) Harrison, I. T. U.S. Patent 3 658 858, 1972, Syntex Corp., Panama. Harrison, I. T.; Lewis, B.; Nelson, O.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203–205.

(3) A recent online literature search identified 208 references describing synthetic routes to **1** and 133 for **2**.

(4) Typically, laboratory synthesis of arylpropionic acids has been accomplished by the Darzen's reaction and conversion of the resultant α,β-epoxy ester to the desired acid by a multistep process. Recent alternative procedures utilizing a 1,2-aryl shift are still considerably more complicated than the procedure described herein. For a review, see: Giordana, C.; Castaldi, G.; Uggeri, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 413–419.

(5) *Chem. Eng. News* **1971**, *49*, 30. Parshall, G. W., "Homogeneous Catalysis"; Wiley-Interscience: New York, 1980.

(6) McKinney, R. J.; Nugent, W. A. to be published. For a comprehensive review of all published studies on the mechanism of homogeneous nickel-catalyzed olefin hydrocyanation, see: Tolman, C. A.; McKinney, R. J.; Seidel, W. C.; Druliner, J. D.; Stevens, W. R. *Adv. Catal.*, in press.

(7) For early efforts to effect Markovnikov hydrocyanation of styrene under cobalt catalysis, see: Arthur, P., Jr.; England, D. C.; Pratt, B. C.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 5364–5367. See also: Fallon, J. D.; Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P. *J. Chem. Soc., Chem. Commun.* **1985**, 4–5.

(8) Tamao, K.; Sumitani, K.; Kiso, Y., Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull Chem. Soc. Jpn.* **1976**, *49*, 1958–1969.

(9) For additional details, see: "Prudent Practices for Handling Hazardous Chemicals in Laboratories"; National Academy Press: Washington, DC, 1981; pp 45–47.

(10) Ittel, S. D. *Inorg. Synth.* **1977**, *17*, 118–120.

(11) Booth, G.; Chatt, J. *J. Chem. Soc.* **1965**, 3238–3241.

(12) Still, W. C. *J. Org. Chem.* **1978**, *43*, 2923–2925.

2-(4-Isobutylphenyl)propionitrile (6). Tetrakis(tri-*p*-tolyl phosphite)nickel(0) (1.50 g, 1.0 mmol) and tri-*p*-tolyl phosphite (0.30 mL, 1.0 mmol) are dissolved in toluene (30 mL). Zinc chloride (0.06 g, 0.5 mmol) is dissolved in propionitrile (0.5 mL) and then added to the catalyst mixture which is then heated to 88 °C under nitrogen. *p*-Isobutylstyrene **5** (3.45 g, 21.5 mmol) is added by syringe pump; 0.30 g is added initially and the remainder added at 1.33 mL/h. HCN/N_2 is fed at 3 mL/min for 3 h and then 1 mL/min for 3 h. Flash chromatography of the reaction mixture (hexane/ethyl acetate, 90:10, R_f 0.32) results in the isolation of **6** (2.66 g, 14.2 mmol, 68% yield) as a colorless liquid. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.31; H, 8.95; H, 7.47. ^1H NMR δ 0.90 (d, J = 7, 6 H); 1.61 (d, J = 7, 3 H), 1.76–1.94 (m, 1 H), 2.47 (d, J = 7, 2 H), 3.86 (q, J = 7, 1 H), 7.14 (d, J = 8, 2 H), 7.25 (d, J = 8, 2 H).

(±)-Naproxen (2). To a stirred mixture of **4** (5.0 g, 23.7 mmol), potassium hydroxide (50 g), and water (30 mL) was added ethylene glycol (70 mL). When the initial exotherm subsided, the mixture was heated in a 125 °C oil bath for 24 h. The mixture was neutralized by slow addition of concentrated hydrochloric acid (100 mL) at 0 °C. The mixture was extracted with ether (3 × 100 mL) and the combined organics were extracted with H_2O (25 mL). Removal of solvent afforded a crude product which was recrystallized from hot toluene to afford **2** (4.62 g, 85%), mp 154–155.5 °C. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.12; H, 6.30. ^1H NMR δ 1.58 (d, J = 7, 3 H), 3.87 (q, J = 7, 1 H), 3.91 (s, 3 H), 7.09–7.15 (m, 2 H), 7.41 (dd, J = 8, 2, 1 H), 7.66–7.73 (m, 3 H).

Ibuprofen (1). In similar manner, we obtained, after recrystallization from heptane with cooling to −25 °C, **1** (4.50 g, 82%), mp 74 °C. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.69. ^1H NMR δ 0.89 (d, J = 7, 6 H), 1.50 (d, J = 7, 3 H), 1.76–1.86 (m, 1 H), 2.44 (d, J = 7, 2 H), 3.70 (q, J = 7, 1 H), 7.09 (d, J = 8, 2 H), 7.21 (d, J = 8, 2 H).

Registry No. (±)-**1**, 58560-75-1; (±)-**2**, 26159-31-9; **3**, 63444-51-9; (±)-**4**, 99148-33-1; **5**, 63444-56-4; (±)-**6**, 99148-34-2; (dmpe)$NiCl_2$, 14726-53-5; CH_2=CHBr, 593-60-2; *p*-BrC_6H_4CH=CH_2, 2039-82-9; (dppp)$NiCl_2$, 15629-92-2; *i*-BuCl, 513-36-0; $((p\text{-}H_3CC_6H_4O)_3P)_4Ni$, 36700-08-0; $(p\text{-}H_3CC_6H_4O)_3P$, 620-42-8; HCN, 74-90-8; $ZnCl_2$, 7646-85-7; 2-bromo-6-methoxynapthalene, 5111-65-9.

Reaction of 5,6-Benzobicyclo[2.2.1]hepta-2,5-diene with Thallium(III) Nitrate

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Thallium(III) nitrate (TTN) is known to be a useful and extremely versatile reagent in organic synthesis, particularly for ring contraction of cyclic alkenes,[2] which are often rapidly converted into the corresponding cyclocarboxaldehyde product. For instance, cyclohexene can be converted to cyclopentanecarboxaldehyde in 85% yield when treated with TTN in methanol followed by acid hydrolysis of the intermediate dimethyl acetal.[3] This rearrangement reaction has been postulated to proceed via the organothallium cation **1** and has been applied to both cycloheptene and cyclobutene systems,[3,4] giving good yields of ring-contracted products. Thus we were surprised to discover that use of this reaction on a bicyclic system produced not ring contraction, but oxidative nitration. In particular, reaction of 5,6-benzobicyclo[2.2.1]hepta-2,5-diene (benzonorbornadiene), **2**, with TTN in methanol did not give rise to the ring-contracted product **3** but afforded good yields of the nitrate ester derivatives **8** and **9**. The stereochemical analysis of these products and the mechanism of their formation are discussed below.

Table I. ^1H NMR Parameters for 8 and 9

	δ_H ($CDCl_3$)		
	8	**9**	
1-H	3.93	3.84	
2-H	4.95	3.46	
3-exo-H	2.27	2.07	
3-endo-H	2.15	1.83	
4-H	3.60	3.44	
7-syn-H	4.91	4.75	
OCH_3		3.29	
	J_{HH}/Hz		
	8	**9**	dihedral angle/deg[a]
$^2J_{3\text{-endo},3\text{-exo}}$	13.5	12.7	
$^3J_{2\text{-endo},3\text{-endo}}$	7.2	7.1	2
$^3J_{2\text{-endo},3\text{-exo}}$	3.2	3.1	121
$^3J_{3\text{-exo},4}$	3.6	3.7	42
$^4J_{3\text{-endo},7\text{-syn}}$	0.97	1.3	

[a] Determined from X-ray crystallographic data; estimated standard deviations 1–2°.

Compound **2** was allowed to react with TTN in methanol followed by treatment with 2 N sulfuric acid. The reaction products were chromatographed on a silica gel column and the racemic nitrate esters **8** and **9** obtained as homogeneous bands.

The ^1H NMR spectrum (Table I) of **8** had four resonance patterns in the aliphatic region. At highest field was the AB portion of an ABX pattern centered at 2.21 ppm and integrating for two protons. Two signals at 3.93 and 3.60 ppm each integrated for one proton. The fourth aliphatic signal integrated for two hydrogens and was centered at 4.93 ppm.

The location of the two ONO_2 groups was immediately evident from the gross features of the ^1H NMR spectrum. The existence of an ABX pattern with a large coupling to the X proton can only be accommodated by three hydrogens located on carbons 2 and 3. The absence of another AB pattern potentially attributable to the hydrogens on C-7 immediately locates the remaining ONO_2 group. Analysis of the ABX pattern resulted in a J(AB) of 13.5 Hz and chemical shifts of 2.15 and 2.27 ppm for the C3 hydrogens. The lowest field resonances are readily assigned to the 2- and 7-hydrogens because of the strongly

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(1) McKillop, A.; Hunt, J. D.; Taylor, E. C.; Keinzle, F. *Tetrahedron Lett.* **1970**, *5275*. Byrd, J. E.; Cassar, L.; Eaton, P. E.; Halpen, J. *J. Chem. Soc. D* **1971** 40. Corey, E. J.; Ravindranath, T. *Tetrahedron Lett.* **1971**, *4753*. McKillop, A.; Taylor, E. C. *Chem. Br.* **1973**, *9*, 4. McKillope, A.; Hunt, J. D.; Taylor, E. C.; Keinzle, F.; Bigham, E. *J. Am. Chem. Soc.* **1973**, *95*, 3635. McKillop, A.; Taylor, E. C.; *Endeavour* **1976**, *35*, 88. Taylor, E. C.; Chiang, C.-S.; McKillop, A. *Tetrahedron Lett.* **1977**, 1927. Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548. Taylor, E. C.; Conley, R. A.; Johnson, D. K.; McKillop, A.; Ford, M. E. *J. Org. Chem.* **1980**, *45*, 3433. Crouse, D. J.; Wheeler, M. M.; Goemann, M.; Tobin, P. S.; Basu, S. K.; Wheeler, D. M. S. *J. Org. Chem.* **1981**, *46*, 1814. Varma, R. S.; Varma, M. *Monatsch. Chem.* **1982**, *113*, 1469. Bajwa, B. S.; Bhat, S. V.; Reden, J.; de Souza, N. J.; Fehlhaber, H. W. *Synth. Commun.* **1983**, *13*, 649.

(2) Ovelette, R. J. In "Oxidation in Organic Chemistry"; Trahanovsky, Ed., Academic Press: New York, 1973; Part B, Chapter III, pp 135–175.

(3) McKillop, A.; Swann, B. P.; Taylor, E. C. *Tetrahedron* **1970**, *26*, 4031.

(4) Byrd, J. E.; Cassar, L.; Eaton, P. E.; Halpern, J. *J. Chem. Soc. D* **1971**, 40.

0022-3263/85/1950-5372$01.50/0