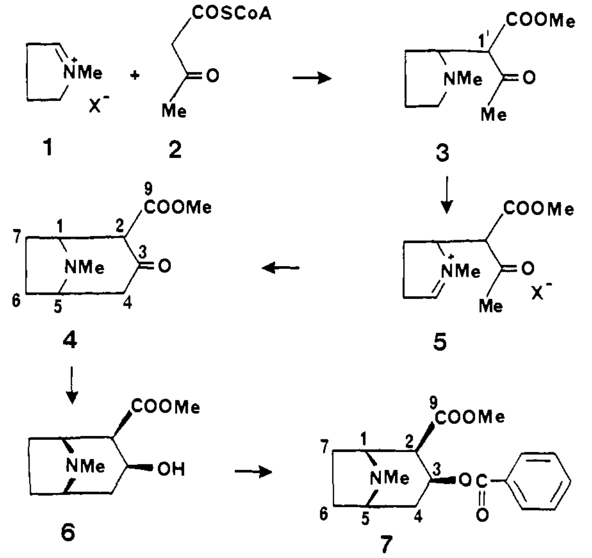
Scheme I. Hypothetical Terminal Steps in the Biosynthesis of Cocaine



presence of sodium hydride yielded [9-^{13}C,^{14}C,*O-methyl*-^{3}H]-2-carbomethoxy-3-tropinone.[8,9] Carbon-13 was introduced into this potential precursor in the hope that its incorporation into cocaine could be established by ^{13}C NMR spectroscopy. A solution of the labeled **4** (0.4 mmol, ^{14}C activity 1.89 × 10^8 dpm/mmol, $^{3}H/^{14}C = 0.29$) in water (40 mL) that contained Tween 80 (0.2 mL) was administered to seven *E. coca* plants (3–10 years old) by painting the solution on the leaves. One week later the leaves (fresh wt 285 g) were harvested and extracted to yield cocaine as previously described,[2] except that the ultimate extraction of cocaine from silica gel TLC plates was carried out with CH_2Cl_2 instead of a mixture of methanol and ethyl acetate (to avoid any exchange of the *O*-methyl group of cocaine with the solvent). The incorporation of radioactivity into the cocaine (387 mg, ^{14}C activity 1.68 × 10^5 dpm/mmol, $^{3}H/^{14}C = 0.27$, absolute incorporation (^{14}C) 0.45%, specific incorporation (^{14}C) 0.09%) was good.[10] However, the specific incorporation was not high enough to detect the presence of excess ^{13}C in the carbomethoxy group of cocaine by ^{13}C NMR spectroscopy. The high retention of tritium strongly suggested that **4** was incorporated intact into cocaine without any hydrolysis of the methyl ester. This was confirmed by chemical degradations of the labeled cocaine which have been previously described.[2,3] The *O*-methyl group of cocaine was found to contain 96% of the tritium, and the C-9 carbonyl group contained 98% of the ^{14}C.

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Note Added in Proof. Radioactive cocaine was also isolated from a second crop of leaves which were harvested (September 12, 1983) 11 weeks after the initial administration of labeled **4**. It had much lower ^{14}C activity (7.77 × 10^3 dpm/mmol) but still retained most of the tritium ($^{3}H/^{14}C = 0.20$).

Registry No. 3-Tropinone, 532-24-1; dimethyl carbonate, 616-38-6; 2-carbomethoxy-3-tropinone, 36127-17-0; cocaine, 50-36-2; barium [^{13}C]carbonate, 51956-33-3; silver nitrate, 7761-88-8; silver [^{13}C]-carbonate, 85323-65-5; [^{3}H]methyl iodide, 72165-55-0; [*carbonyl*-^{13}C,-*O-methyl*-^{3}H]dimethyl carbonate, 87351-10-8.

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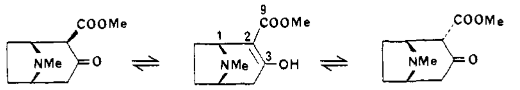
(6) Reaction of barium [^{13}C,^{14}C]carbonate (91% ^{13}C) with aqueous silver nitrate yielded silver [^{13}C,^{14}C]carbonate,[7] which on shaking with an ether solution of [^{3}H]methyl iodide at room temperature yielded [*carbonyl*-^{13}C,^{14}C,*O-methyl*-^{3}H]dimethyl carbonate. The C═O absorption of this ^{13}C-enriched material showed an isotope shift from 1750 to 1710 cm^{-1} in its IR spectrum.

(7) Tsuyuki, T.; Simamura, O. *J. Org. Chem.* **1958**, *23*, 1079. This reference describes the preparation of [*carbonyl*-^{14}C]diethyl carbonate from barium [^{14}C]carbonate and ethyl iodide.

(8) Carroll, F. I.; Coleman, M. L.; Lewin, A. H. *J. Org. Chem.* **1982**, *47*, 13.

(9) The properties of 2-carbomethoxy-3-tropinone have been extensively investigated (Findlay, S. P. *J. Org. Chem.* **1957**, *22*, 13), and it was concluded that this compound exists as an equilibrium mixture of its enol (4ii) and the



4i 4ii 4iii

two keto forms with the carbomethoxy group in the axial (4i) or equatorial (4iii) position. The presence of these three tautomeric forms has been confirmed by ^{13}C NMR spectroscopy, the composition of the mixture being dependent on the solvent. In $CDCl_3$ the intense resonance due to C-9 in the ^{13}C-enriched material appears as three signals (relative intensity) at 171.4 (53.0), 169.3 (32.7), and 169.1 (14.4) ppm. The signal that appears at 102.0 ppm in the unenriched material is assigned to C-2 of the enol isomer 4ii and appears as a triplet ($^{1}J_{2,9} = 74.1$ Hz), due to a one-bond coupling with the enriched C-9.

(10) The previous best absolute incorporations[2,3] of DL-[5-^{14}C]ornithine [1-^{14}C]acetate and DL-[4-^{3}H]phenylalanine into cocaine were 0.039, 0.031, and 0.35%, respectively.

Intramolecular Nitrene C–H Insertions Mediated by Transition-Metal Complexes as Nitrogen Analogues of Cytochrome P-450 Reactions

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We have recently reported[1] that ((tosylimido)iodo)benzene (the tosylimide analogue of iodosobenzene) performs tosylamidation of cyclohexane under catalysis by Fe(III) or Mn(III) tetraphenylporphyrin chloride (TPPCl). The reaction is closely analogous to the hydroxylations by iodosobenzene with metal porphyrin catalysis extensively studied as models for oxidations by the cytochrome P-450 class of enzymes, which contain iron porphyrin.[2-6] Our nitrogen analogue is of special interest, as we pointed out,[1] because the additional valence of nitrogen makes it easy to impose selective geometric control on intramolecular versions of the process. We now wish to describe our study of the first example of such an intramolecular nitrogen functionalization of a saturated carbon.

2,5-Diisopropylbenzenesulfonamide (**1**)[7] was converted to the corresponding (imidoiodo)benzene derivative (**2**) by reaction with phenyliodine diacetate and KOH/MeOH, as in previous preparations of this class of compounds.[1,8] The off-white solid **2**, obtained in 89% yield, decomposed explosively at 100–110 °C and

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(1) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400. Subsequently there has been a report of alkane tosylamidation with ferrous chloride/chloroamine-T, which apparently proceeds by initial radical chlorination: Barton, D. H. R.; Hay-Motherwell, R. S.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 445. Recently aziridines have been synthesized stoichiometrically from alkenes with a nitridomanganese(V) porphyrin complex: Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073.

(2) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. Groves, J. T.; Kruper, W. J.; Haushalter, R. C. *Ibid.* **1980**, *102*, 6375.

(3) Chang, C. K.; Kuo M.-S. *J. Am. Chem. Soc.* **1979**, *101*, 3413. Chang, C. K.; Ebina, F. *J. Chem. Soc., Chem. Commun.* **1981**, 778.

(4) Smegal, J. A.; Schardt, B. C.; Hill, C. L. *J. Am. Chem. Soc.* **1983**, *105*, 3510. Smegal, J. A.; Hill, C. L. *Ibid.* 3515.

(5) Mansuy, D.; Bartoli, J.-F.; Momenteau, M. *Tetrahedron Lett.* **1982**, *23*, 2781.

(6) For use of tertiary amine oxides as oxidants instead of iodosobenzene, see: Nee, M. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6123.

(7) Newton, A. *J. Am. Chem. Soc.* **1943**, *65*, 2439.

(8) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.

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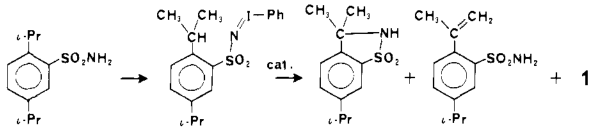
Table I. Catalyzed Reactions of the Imidoiodobenzene Derivative **2** in CH_3CN

	yields[a]		
catalyst	**3**	**4**	**1**
Fe^{III}(TPP)Cl	77%	1.4%	12%
Mn^{III}(TPP)Cl	16%	4.5%	34%
$[Fe^{III}(cyclam)Cl_2]Cl$[b]	42%	4.1%	36%
$FeCl_3$	16%	0.2%	23%
$Rh_2(OAc)_4$	86%	0.2%	5.2%

[a] Yields by HPLC, based on **2**. [b] Cyclam is 1,4,8,11-tetraazacyclotetradecane (ref 10).

showed a ^1H NMR spectrum (in Me_2SO) with methyl doublets at δ 0.92 and 1.21 and methines at δ 2.88 and 3.86, along with a complex aromatic multiplet. The spectrum changed as the sample decomposed. The compound decomposed slowly in air but was stable at −20 °C. It was rapidly reduced by aqueous $NaHSO_3$ to **1** and iodobenzene.

Although **2** was insoluble in most solvents, including CH_3CN and CH_2Cl_2, its reactions could be examined in suspension. In a typical procedure, 44 mg (0.1 mmol) of **2** and 3.5 mg (0.005 mmol) of Fe^{III}(TPP)Cl were stirred in 3 mL of pure degassed CH_3CN. The suspended **2** disappeared in 30 min; after an additional 30 min the solvent was evaporated, and products were analyzed by reverse-phase HPLC. The product mixture consisted of 85% of the insertion product **3** (mp 123.5–124.5 °C),[9] 1.5% of the unsaturated sulfonamide **4**,[9] and 13% of the original sulfonamide **1**. The total yield was 90.4%. Since **2** did not stand up to attempted purification, the missing 10% may partly reflect impure starting material. However, in Table I we list the yield for this and related reactions based on the weight of the starting material **2**; the yields listed are probably underestimates.



1 **2** **3** **4**

As Table I shows, Mn^{III}(TPP)Cl was a much inferior catalyst for the insertion reaction and led to a low total yield of the three analyzed products. Similarly, the Fe(III) complex of 1,4,8,11-tetraazacyclotetradecane[10] and $FeCl_3$ itself were inferior to Fe^{III}(TPP)Cl. However, $Rh_2(OAc)_4$[11] was an excellent catalyst, forming more insertion product **3** and less of the other products than any other catalyst examined. With the rhodium complex, 94% of the product mixture was **3**.

In the absence of any catalyst the starting material **2** was essentially undecomposed after 1 h suspended in CH_3CN and afforded 65% of **1** and only 1.4% of **3** and 0.3% of **4** after 22 h. However, **2** suspended in carefully purified CH_2Cl_2 decomposed completely in 1 h, affording 26% **3**, 4.5% **4**, and 24% **1**. The reactions with Fe^{III}(TPP)Cl or Mn^{III}(TPP)Cl were poorer in CH_2Cl_2, only 35% of the insertion product **3** forming with the Fe^{III}(TPP)Cl catalyst. CH_2Cl_2 has often been used as solvent in other P-450 model systems.[2-6] Poor yields of insertion product **3** were also obtained on thermolysis of **2** or thermolysis or photolysis of the corresponding sulfonyl azide.[12] Strikingly, our intramolecular insertion process is much better with an iron porphyrin than a manganese porphyrin catalyst, in contrast to previous model systems[1,2-5] but in analogy to the natural enzymatic system. Furthermore, in both CH_3CN and CH_2Cl_2 the manganese catalyst afforded proportionately more olefin product **4** compared with insertion product **3**. Thus the optimum for a clean reaction uses the imidoiodobenzene derivative **2** in CH_3CN with Fe^{III}(TPP)Cl or $Rh_2(OAc)_4$ as catalysts.

As expected, converting our original intermolecular tosylamidation of cyclohexane with Fe^{III}(TPP)Cl or Mn^{III}(TPP)Cl catalysis[1] to an intramolecular directed metal–nitrene insertion reaction has greately improved its efficiency. It remains to be seen whether our reaction can be generalized to a "remote functionalization" reaction,[13] involving intramolecular or intracomplex reactions over larger distances. If so, this analogue of an enzymatic hydroxylation could prove to be a very useful synthetic reaction.

Acknowledgment. Support by the National Science Foundation and by an NIH training grant are gratefully acknowledged.

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(9) Characterized by NMR and mass spectroscopy.

(10) Chan, P.-K.; Poon, C.-K. *J. Chem. Soc., Dalton trans.* **1976**, 858.

(11) $Rh_2(OAc)_4$ has been used to elicit carbene reactivity from diazo compounds; for an example, see: Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. A. W. Schwabacher (unpublished work) has used it with phosphoryl azides to catalyze nitrene insertions.

(12) 2,5-Diisopropylbenzenesulfonyl azide was also inert to $Rh_2(OAc)_4$, Fe^{III}(TPP)Cl, and Mn^{III}(TPP)Cl in refluxing acetonitrile.

(13) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

Why Terminal Alkynes Cannot Be Metathesized. Preparation and Crystal Structure of a Deprotonated Tungstenacyclobutadiene Complex, $W(\eta^5\text{-}C_5H_5)[C_3(CMe_3)_2]Cl$[1a]

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During our ongoging studies aimed at determining the scope of metathesis of alkynes[2] by $W(CR)(OCMe_3)_3$,[3] we found that terminal alkynes could not be metathesized. We believe we now know why.

$W(\eta^5\text{-}C_5H_5)(CCMe_3)Cl_2$,[4] a molecule that will *not* metathesize alkynes, reacts with $Me_3CC{\equiv}CH$ in ether to give approximately equal amounts of two products in high yield. One is red, soluble in pentane, and analyzes as $WCp[C_3(CMe_3)_2]Cl$ (**1**, Cp = η^2-C_5H_5);[5a] the other is orange, soluble in dichloromethane (not pentane), and analyzes as $WCp[C_3H_2(CMe_3)_2]Cl_3$ (**2**).[5b] Addition of 2 equiv of HCl to **1** gives **2** essentially quantitatively. If triethylamine is present in the reaction between $WCp(CCMe_3)Cl_2$ and *tert*-butylacetylene only the red product is produced along with 1 equiv of NEt_3HCl (eq 1). We have not been able to convert **2** to **1** with triethylamine or $Ph_3P{=}CH_2$.

$$WCp(CCMe_3)Cl_2 + Me_3CC{\equiv}CH \xrightarrow{Et_3N} WCp[C_3(CMe_3)_2]Cl + NEt_3HCl \quad (1)$$

NMR and IR data suggest that **2** is a *tert*-butyl (*tert*-butylvinyl-substituted)methylene complex, i.e., $CpCl_3W{=}C(CMe_3)[trans\text{-}HC{=}CH(CMe_3)]$.[6] This proposal is strengthened

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(1) (a) Multiple Metal–Carbon Bonds. 34. (b) Massachusetts Institute of Technology. (c) State University of New York at Buffalo.

(2) (a) Wengrovius, J. H.; Sancho, J.; Schrock, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3932. (b) Sancho, J.; Schrock, R. R. *J. Mol. Catal.* **1982**, *15*, 75.

(3) (a) Schrock, R. R.; Listemann, M. L.; Sturgeoff, L. G. *J. Am. Chem. Soc.* **1982**, *104*, 4291. (b) Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645.

(4) Churchill, M. R.; Ziller, J. W.; McCullough, L.; Pedersen, S. F.; Schrock, R. R. *Organometallics* **1983**, *2*, 1046.

(5) (a) Anal. Calcd for $WC_{16}H_{23}Cl$: C, 44.21; H, 5.33; Cl, 8.16. Found: C, 44.56; H, 5.51; Cl, 8.10. (b) Anal. Calcd for $WC_{16}H_{25}Cl_3$: C, 37.86; H, 4.96; Cl, 20.95. Found: C, 38.23; H, 5.03; Cl, 20.88.

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