

Figure 1. Catalytic acetylations in the presence of complexes III, V, and VI of alcohols **1c** or **3** (5 mmol, 0.5 M in CDCl_3) at 33 °C: Δ **1c** + AcIm + III, 100:100:1; \circ **1c** + AcIm + V, 100:100:1; \square **3** + AcIm + Et_3N + V, 100:100:1:1; \blacksquare **3** + AcIm + Et_3N + VI, 100:100:1:1. For all experiments, controls have been made with the same AcIm in the absence of Pt(II) complex and have shown no acetylation.

lowing yields of acetates **2**, after 21 h at 23 °C: **2a**, 63%, **2c**, 75%; **2e**, 53%, and **2f**, 19.5%. The relative reactivities of the alcohols **1** toward this acetylation are similar to those observed with Pt(II). Acetylation of alcohol **1a** in the presence of complex III is faster than that of alcohol **1b** (expt 2, 3): $k_2:k_3 = 15$, this is in agreement with the relative basicities of the two pyridinic alcohols, but not with their coordination abilities.⁹ Furthermore, acetylation of phenyl-3-propanol **3** by complex III is much more efficient in the presence of Et_3N than *s*-collidine (expt 10, 11).¹¹

Owing to the trans effect of bound ethylene promoting ligand exchanges between AcIm , ImH , alcohol **1**, and acetate **2** (Scheme 1), one could expect the acetylation reactions to be catalytic in Pt. Accordingly the reaction between alcohol **1c**, AcIm (both 0.5 M in CDCl_3), and complex III, 100:100:1, gives acetate **2c** in 80% yield (**2c**:Pt = 80:1) after 30 h at 33 °C. The reaction is accompanied by an expected side reaction slowing down the acetylation (Figure 1A) and consuming the Pt complex by substitution of the ethylene ligand¹² to finally give a precipitate of impure $[\text{Pt}(\text{ImH})_4]^{2+} 2\text{Cl}^-$.¹⁴

The complex $\text{trans-}[\text{PtCl}_2(\text{n-Bu}_3\text{P})(\text{AcIm})]$ (V) can be used to achieve the stoichiometric acetylation of alcohol **3** in the presence of Et_3N without displacement of the activating phosphine ligand (expt 12); however, this acetylation is slower than that with complex III (expt 11). The acetylation of the pyridinic alcohol **1c** is also slower with complex V than with complex III (expt 13, 4). The phosphine complex V can be used for catalytic acetylation of alcohol **3** in the presence of Et_3N , the reaction between **3**, AcIm (both 0.5 M in CDCl_3), complex V, and Et_3N , 100:100:1:1, gives a 92% yield of acetate (acetate:Pt = 92:1) after 30 h at 33 °C (Figure 1A). At the end of the catalytic acetylation one can isolate a new complex $[\text{Pt}(\text{n-Bu}_3\text{P})(\text{ImH})_3]^{2+} 2\text{Cl}^-$ (VI).¹⁶ That complex VI could become the actual catalyst of the reaction with complex V is shown by the fact that further addition of the reactants to a solution of isolated VI leads to the acetylation of alcohol **3** and this catalytic acetylation is indeed faster than that initially observed with complex V itself (Figure 1B).

Further work is in progress to find better superacid catalysts¹⁷ and design a bifunctional catalyst¹⁸ complex bearing the general base in a suitable position on the activating ligand.

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- A 5-mL CDCl_3 stock solution of 0.8 M AcIm (solvent initially passed through an alumina column) is prepared from 440 mg of pure (sublimed) AcIm (4 mmol) and 420 μL of 1,1,2,2-tetrachloroethane as internal standard (4 mmol); a 5-mL CDCl_3 stock solution of complex **1c**, 0.2 M, is prepared from 459 mg of the Pt complex (1 mmol) and 105 μL of tetrachloroethane (1 mmol). In a typical experiment 125 μL of the AcIm solution are added to 500 μL of the Pt complex solution in an NMR tube, both reactants being 0.16 M.
- Very recently the esterification of alcohols with 1-acylimidazoles, assisted by *N*-bromosuccinimide has been reported: T. Katsuki, *Bull. Chem. Soc. Jpn.*, **49**, 2019 (1976).
- Catalysis of the reactions between AcIm and nucleophilic reagents is well documented: D. G. Oakenfull, K. Salvesen, and W. P. Jencks, *J. Am. Chem. Soc.*, **93**, 188 (1971).
- Ortho methyl groups are known to slow down the exchange of a pyridinic ligand,¹⁰ and at 23 °C the first equilibrium of Scheme 1 corresponds to 93.5% and ca. 99% of III, respectively, for **1a** and **1b**.
- J. C. Chottard, D. Mansuy, and J. F. Bartoli, *J. Organomet. Chem.*, **65**, C19 (1974).
- However, Et_3N gives coalescence of the NMR signals of bound ethylene, and ligand substitution^{12,13} slowly leads to precipitation of one or several new complexes, therefore one then does not know the exact nature of the Pt active complex (vide infra).
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- ¹H NMR shows that V + ImH , 1:1, gives an equilibrium with 73% ImH bound to Pt(II) at 32 °C.
- Mp 188–189 °C, Anal ($\text{C}_{27}\text{Cl}_2\text{H}_{39}\text{N}_6\text{PPt}$) C, Cl, H, N, P, and correct spectral properties. VI has been independently synthesized from $[\text{Pt}_2(\text{n-Bu}_3\text{P})_2\text{Cl}_4]$.
- For instance, the stoichiometric acetylation of **1c** by $\text{cis-}[\text{Pt}(\text{n-Bu}_3\text{P})_2\text{Cl}(\text{AcIm})]^+ \text{ClO}_4^-$ is faster than that with III ($10^5 k = 20 \pm 2 \text{ M}^{-1} \text{ s}^{-1}$ at 23 °C) up to 45% yield, but suffers a side reaction under investigation.
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An Efficient Synthesis of Indole

Sir:

Carbanions, which are stabilized by an isocyano group,¹ have proved to be valuable organic reagents for nucleophilic introduction of masked α -aminoalkyl groups in organic syntheses.² Reactions of α -metalated alkyl isocyanides with certain electrophilic reagents have also permitted an efficient synthesis of various heterocycles.² Herein, we wish to report a new and versatile synthesis of indole derivatives based on selective ortholithiation of the alkyl group in *o*-alkylphenyl isocyanides and subsequent intramolecular ring closure.

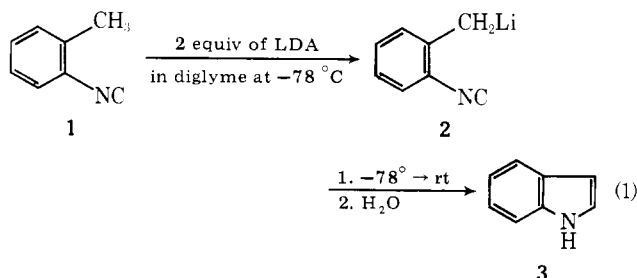
Lithiation³ at the methyl group of *o*-tolyl isocyanide (**1**) was successfully performed by treatment of **1** with 2 equiv of lithium diisopropylamide (LDA)⁴ in diglyme at -78 °C. The red colored carbanion, which was prepared by adding dropwise 176 mg (1.5 mmol) of **1** to LDA (3.0 mmol) in diglyme (4 ml) at -78 °C and then stirring for 30 min at the same temperature, was quenched with D_2O to yield *o*-tolyl isocyanide (>95% yield) with 93% deuterium incorporation at the methyl group. On the other hand, a similar treatment of **1** (1.5 mmol) with LDA (1.5 mmol) was followed by deuterolysis to regenerate

Table I. Alkylations of *o*-Tolyl Isocyanide

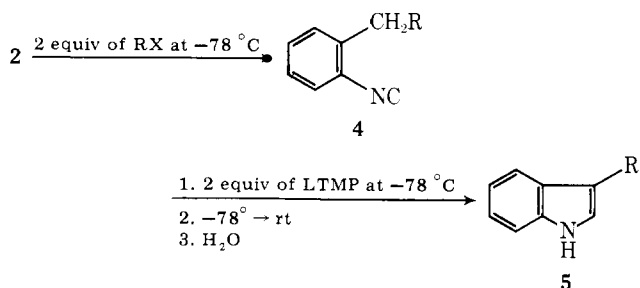
Alkyl halide (R-X)	<i>o</i> -Alkylphenyl isocyanide (4) ^a (%)
CH ₃ I	95
<i>n</i> -C ₄ H ₉ Br	83
<i>i</i> -C ₄ H ₉ Br	78
<i>i</i> -C ₃ H ₇ I	89
CH ₂ =CHCH ₂ Br	82
CH ₃ OCOCI	69

^a Products **4** were isolated by distillation in vacuo and identified by elementary analysis, IR, and NMR spectral data.

o-tolyl isocyanide (>95% yield) with 50% deuterium incorporation at the methyl group. The selective lithiation of **1** was solvent dependent. Use of monoglyme, instead of diglyme, gave *o*-lithiomethylphenyl isocyanide (**2**), but in somewhat decreased yield. When **1** was treated with LDA in ether or THF, **2** was generated in a low yield, being accompanied substantially by an addition of LDA to the isocyano carbon of **1**, which resulted in the formation of *N,N*-diisopropyl-*N'*-(*o*-tolyl)formamide, after hydrolysis.



The *o*-lithiomethylphenyl isocyanide (**2**) in diglyme at -78°C thus obtained was allowed to warm up to room temperature to produce, after H₂O workup, indole (**3**) in an almost quantitative yield. Moreover, the *o*-lithiomethylphenyl isocyanide (**2**) at -78°C can be elaborated with electrophiles such as alkyl halides and epoxides to give ortho-substituted phenyl isocyanides, from which 3-substituted indoles can be derived. Reactions of *o*-lithiomethylphenyl isocyanide (**2**) with alkyl halides are illustrated as follows. For example, 411 mg (3 mmol) of *n*-butyl bromide was added dropwise to **2** (1.5 mmol) in diglyme (4 mL) at -78°C , which was prepared according to the above procedure, and then the mixture was stirred for 30 min to furnish *o*-pentylphenyl isocyanide in 83% yield. Additional alkylations of **2** are summarized in Table I.



o-Alkylphenyl isocyanides (**4**) obtained were cyclized to 3-substituted indoles (**5**) in fairly good yields via the ortholithiation of the alkyl group in **4** according to the procedure employed for the preparation of indole (**3**) from *o*-tolyl isocyanide (**1**), except that lithium 2,2,6,6-tetramethylpiperidide (LTMP) was used in place of LDA.⁵ The results are summarized in Table II.

Reaction of *o*-lithiomethylphenyl isocyanide (**2**) with alkylene oxides provides a convenient synthetic route to tryptophol derivatives. When **2** (1.5 mmol), generated by the above procedure, was reacted with 216 mg (3.0 mmol) of 1-butene

Table II. Preparation of 3-Alkylindoles

R in 4	Lithium amide	5 (%) ^a
H	LDA	100 ^b
CH ₃	LTMP	95 ^b
<i>n</i> -C ₄ H ₉	LTMP	85 ^c
<i>i</i> -C ₄ H ₉	LTMP	78 ^c
CO ₂ CH ₃	Cu ₂ O	86 ^d

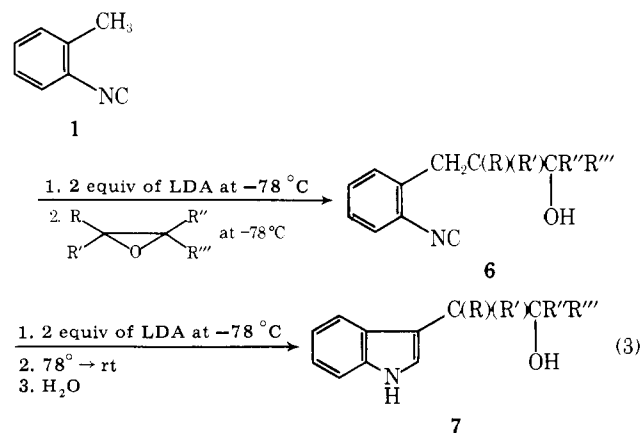
^a Products **5** were isolated by distillation in vacuo. ^b Indole and skatole were identified by comparison with authentic samples. ^c 3-*n*-Butylindole and 3-isobutylindole were identified by comparison with authentic samples prepared independently.⁶ ^d *o*-Carbomethoxymethylphenyl isocyanide was heated at 55°C for 6 h with a catalytic amount of Cu₂O in benzene to produce 3-carbomethoxyindole in 86% yield.⁷

Table III. One-flask Synthesis of Tryptophol Derivatives

Alkylene oxide	Tryptophol derivative (7) (%) ^a
R = R' = H; R'' = R''' = CH ₃	68 ^{b,c}
R = R' = R'' = H; R''' = C ₂ H ₅	61 ^{b,c}
R = R' = R'' = H; R''' = CH ₃	65 ^{b,c}
R = R' = H; R'' = R''' = -(CH ₂) ₄ -	42 ^{c,d}

^a Isolated yields. ^b A negligible amount of isomeric tryptophol derivative, which may be formed by nucleophilic attack of **2** at the more substituted carbon of alkylene oxide, was accompanied, as judged by NMR analysis. ^c Products **7** were identified by comparison with authentic samples prepared independently.⁸ ^d Reaction of **2** with cyclohexene oxide was carried out by stirring the mixture at -78°C for 5 h followed by the addition of 2 equiv of LDA.

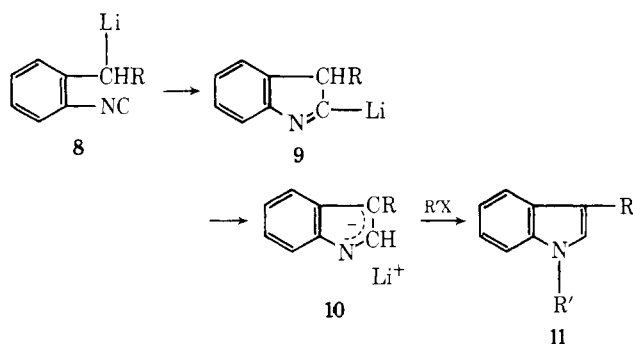
oxide at -78°C for 2 h, *o*-(γ -hydroxypropyl)phenyl isocyanide (**6**; R = R' = R'' = H, R''' = C₂H₅) was produced in 65% yield along with 3-(β -hydroxybutyl)indole (**7**; R = R' = R'' = H, R''' = C₂H₅) (18% yield) after H₂O workup. Unlike the case of transformation of *o*-tolyl isocyanide (**1**) to 3-alkylindole (**5**), it was not necessary to isolate the intermediate of *o*-(γ -hydroxyalkyl)phenyl isocyanide (**6**) in the tryptophol synthesis.



According to the following procedure, tryptophol derivatives were prepared in moderate yields from **1** and alkylene oxide in one flask. To the mixture of 1-butene oxide (3.0 mmol) and **2** (1.5 mmol) which had been stirred at -78°C for 2 h, LDA (3.0 mmol) in diglyme (2 mL) was added dropwise and then stirred for additional 2 h at the same temperature. The reaction mixture was allowed to warm up to room temperature and then worked up with H₂O to furnish 3-(β -hydroxybutyl)indole (**7**; R = R' = R'' = H, R''' = C₂H₅) in 61% isolated yield, which was identified by comparison with an authentic sample pre-

pared independently.⁸ Some one-flask syntheses of tryptophol derivatives are listed in Table III.

The present indole synthesis constitutes an interesting example of a "5-endo-digonal" ring closure as classified by Baldwin,⁹ in which the carbanion of **8** intramolecularly adds to the adjacent isocyano carbon, resulting in the formation of lithium derivative **9**. However, attempts to trap the lithium



derivative **9** with electrophiles, which could provide an entry to 2-substituted indole, were not successful. When **2** prepared in diglyme at $-78\text{ }^{\circ}\text{C}$ was allowed to warm up to $-25\text{ }^{\circ}\text{C}$, the characteristic red color of **2** gradually changed to brown. The brown solution at $-25\text{ }^{\circ}\text{C}$ was treated with alkyl halides and with alkylene oxides to afford 1-alkylindoles and 1-(β -hydroxyalkyl)indoles, respectively, in good yields (**11**: R = H, R' = $n\text{-C}_4\text{H}_9$, 82%; R = H, R' = $(\text{CH}_3)_3\text{Si}$, 87%; R = H; R' = $\text{CH}_3\text{CH}_2\text{CO}$, 79%; R = H, R' = $\text{C}_2\text{H}_5\text{CH}(\text{OH})\text{CH}_2$, 84%; R = H, R' = $(\text{CH}_3)_2\text{C}(\text{OH})\text{CH}_2$, 65%). The finding indicates that the lithium derivative **9** is rapidly converted to **10** even at $-25\text{ }^{\circ}\text{C}$. Consequently this procedure presents a convenient synthesis of 1-substituted indoles starting with *o*-tolyl isocyanide.

In comparison with the previous methods of indole synthesis,¹⁰ the synthesis of 1- and 3-substituted indoles in this study has some advantages: good yields of the products and simple manipulations as well as the ready availability of the starting *o*-tolyl isocyanide.¹¹

Work is in progress to investigate a full scope of the present indole synthesis.

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- It is noteworthy that 2,4-xylyl isocyanide was treated with 2 equiv of LDA in diglyme at $-78\text{ }^{\circ}\text{C}$ to produce 2-lithiomethyl-4-methylphenyl isocyanide selectively. This observation suggests that the lithiation at the ortho methyl group of **1** may be assisted by the neighboring isocyano function.
- LDA was prepared by adding dropwise 1 mol of diisopropylamine at $-78\text{ }^{\circ}\text{C}$ to 1 mol of *n*-butyllithium (1.8 M hexane solution).
- Cyclization of *o*-*n*-pentylphenyl isocyanide with LDA afforded only 30% of 3-*n*-butylindole along with *N,N*-diisopropyl-*N'*-(*o*-*n*-pentylphenyl)formamide (60%).
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Active Site Models of Horseradish Peroxidase Compound I and a Cytochrome P-450 Analogue: Electronic Structure and Electric Field Gradients

Sir:

Recent work has been reported with partially purified cytochrome P-450's in which the normal enzymatic pathway is by-passed and an active form produced by the addition of certain peroxides and peracids to the ferric state of the enzyme.¹ More recently, optical spectra have been obtained for an enzymatically active adduct of soluble P-450_{cam} and peracetic acid.² A strong resemblance is suggested between the enzymatically active species of cytochrome P-450 and compound I, an intermediate formed by the reaction of peroxides, peracids and other oxidants with ferric horseradish peroxidase.^{3,4}

Unlike the cytochrome P-450 analogue, compound I is stable enough to have been isolated and more fully characterized. One axial ligand appears to be an imidazole group⁵ while a single oxygen atom has been shown to be transferred to the iron by peracid and peroxide substrates.^{3,6} Magnetic susceptibility studies indicate a $S = 3/2$ state⁷ although no ESR has been detected.⁸ Mössbauer resonance spectra yield a quadrupole splitting of $\Delta E_Q = 1.20\text{ mm/s}$ and confirm the presence of unpaired spin.⁹ Numerous formal oxidation and spin states of the iron and its ligands have been suggested⁴ to account for the unpaired spins and two oxidizing equivalents above the ferric resting state known to be present¹⁰ in this formal $[\text{FeO}]^{3+}$ complex. They include: (Fe(V) $S = 3/2$) with a spin paired porphyrin ring;¹¹ (Fe(IV) $S = 1$) with a porphyrin radical,¹² and (Fe(III) $S = 3/2$ or $S = 1/2$) with the two oxidizing equivalents centered on a singlet or triplet porphyrin ring.^{8,12}

Electronic spectra seem most consistent with the presence of a π cation radical indicating that one of the three unpaired spins is delocalized on the porphyrin ring in an a_{2u} π orbital centered on the pyrrole nitrogens.^{4,13} These results imply that the (Fe(IV) $S = 1$, porphyrin $S = 1/2$) model for compound I is most reasonable. However, in spite of extensive experimental investigations, the ground state electronic structure of compound I and the distribution of the three unpaired electrons among the iron and its ligands have not been totally resolved.

As shown by previous studies,^{14,15} the use of iterative extended Hückel theory¹⁶ coupled with calculation of one electron properties can help determine the electronic configuration and spin distribution of transition metal complexes such as the active site of compound I. Given the possible similarity of compound I and the uncharacterized active species of cytochrome P-450, further comparisons can help lead to an understanding of the electronic structure of the oxygen atom which serves as an activated axial ligand for both systems. A model for the active site of compound I shown in Figure 1 was therefore formulated with axial imidazole and atomic oxygen ligands for input to an IEHT program previously parameterized

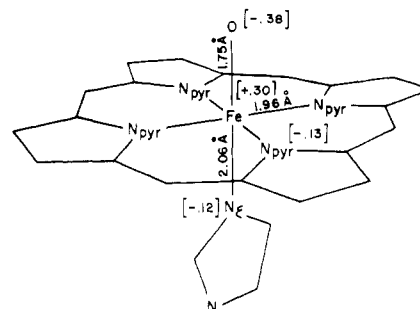


Figure 1. Geometry and calculated net atomic charges $[\pm q]$ for compound I.