Journal of Organometallic Chemistry, 417 (1991) 313–325
Elsevier Sequoia S.A., Lausanne
JOM 21930REV

Review

Chemistry and Synthetic Utility of Metal Complexed Indoles

U.S. Gill[a], R.M. Moriarty[b], Y.Y. Ku[c] and I.R. Butler[d]

a. Medical Services Branch, Health and Welfare Canada, Ottawa, Ontario, Canada. K1A 0L3.
b. Chemistry Department, University of Illinois, Chicago, 60680 USA
c. Abbott Laboratories, North Chicago, Illinois, 60064-4000 USA
d. Chemistry Department, University College of North Wales, Bangor, Gwynedd, U.K. LL57 2UW.

(Received April 17th, 1991)

Contents

1.0 Introduction

Ring substituted indoles are prevalent among a wide variety of biologically active natural and synthetic products that include ergot alkaloids (1), Calabar bean alkaloids (2), marine indoles (3), synthetic β-blockers (4) and psilocin analogues (5). The goal of introduction of functional groups onto the aryl ring of an indole nucleus has continually been a challenge for organic chemists, since the commonly used methods for substituted indole synthesis involve multiple steps. The methodology for functionalization of the intact indole ring system is based upon the classical electrophilic aromatic substitution reaction (6a). Recently, organometallic methodology using transition-metal assisted synthetic approaches has been developed. For example, the olefination and alkylation of a 4-thallated indole derivative using palladium(II) as a catalyst has been achieved via a transmetallation-insertion-elimination process (6a-c). Other examples are palladium(0) catalyzed reactions of haloindoles, which proceed through an oxidative addition/insertion process to produce aryl alkylated indoles (7).

The use of π-arene complexes in organic synthesis has expanded rapidly in the past few years (8-12), and versatile methods for aryl-carbon bond formation have been developed (8-14). The reactions of such complexes are often characterized by a high degree of regio and stereoselectivity (15-23). For this reason such reactions have come to have increasing application in organic synthesis (24-30) and have been successfully incorporated in industrial processes (e.g. synthesis of Ibuprofen and Ketoprofen) (31).

Recently, we reported (32) that the co-ordination of the aryl ring of an indole substrate to a ligand bound ruthenium metal markedly alters its reactivity. In such a complex, all six carbons of the aryl ring are bound to the metal, and the metal moiety acts as a powerful, electron-withdrawing substituent. Various effects on indole substrate reactivity of metal co-ordination have been established (Fig. 1).

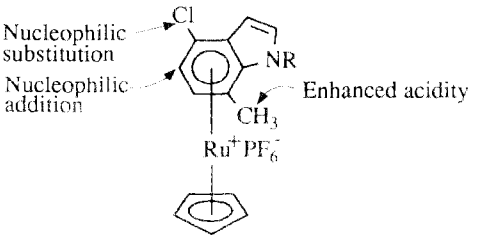


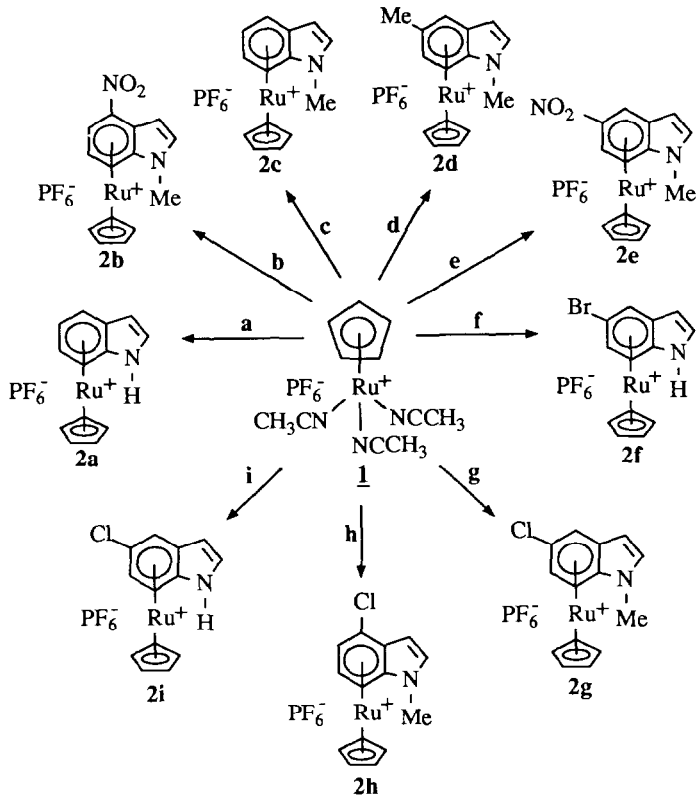
Figure 1. Effects on Aryl ring reactivity of $CpRu^{+}$(II) coordination

In this review we will discuss the chemistry of cyclopentadienylruthenium complexes of indole substrates along with pertinent examples from chromium tricarbonyl complexes of indoles.

2.0 Synthetic Studies

The ready availability of $[CpRu(CH_3CN)_3]PF_6$, (**1**), (34) and the thermal lability of acetonitrile ligands prompted us to attempt the synthesis of indole (Cp)Ru(II) complexes (32) from complex **1** and an appropriate indole substrate (Scheme I).

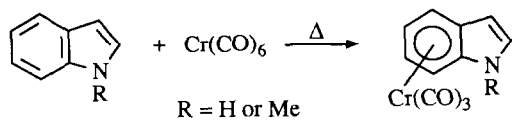
Scheme I



These thermally stable crystalline solid complexes are stable in air for long periods and can be stored at room temperature. The ^{1}H NMR resonances for the aryl ring protons are shifted upfield usually by about 0.4 to 0.6 ppm as compared to the corresponding free indole ligands. The proton decoupled ^{13}C NMR spectral data shows a sizable upfield shift for six ring carbon atoms complexed to the CpRu(II) unit.

Indole tricarbonylchromium complexes were first prepared as long ago as 1968 by E.O. Fischer et al. (33), but very little development in this area occurred until recently, when chromium complexes of indole and substituted indoles were studied by Semmelhack and others (30) for indole functionalization. These indole complexes are generally prepared from the thermal ligand exchange reaction between chromium hexacarbonyl, $Cr(CO)_6$, and an appropriate indole substrate (Scheme II). Synthesis of analogous salts of dicationic

Scheme II

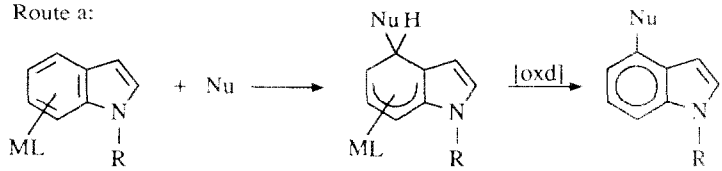


(η^6-indole)(η^5-C_5Me_5)M^{2+}(M=Rh, Ir or Co) complexes have also appeared in the literature (35), but their instability has precluded their use in organic synthesis.

3.0 Reactions with Nucleophiles

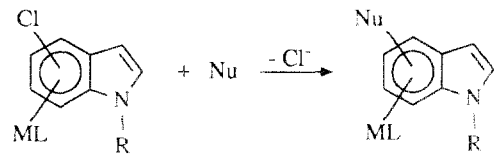
The synthetic potential of the nucleophilic attack upon metal complexed π-arenes has attracted considerable attention and has been reviewed (8-13, 30). However, the mechanistic aspects of this conceptually simple and fundamental organometallic reaction are not sufficiently addressed in the literature. Recently, we (32) and others (30) have explored the reactions of indole metal complexes with a variety of carbon, oxygen, sulphur, and nitrogen centered nucleophiles. In all the cases studied to date, attack by the nucleophile occurs exclusively at the complexed aryl ring. In general, two synthetic approaches have been employed: route a, addition/oxidation which provides an overall substitution by nucleophile for hydrogen (Section 3.1) and route b, direct displacement in which a halide or nitro group is replaced by various nucleophiles (Section 3.2).

Route a:



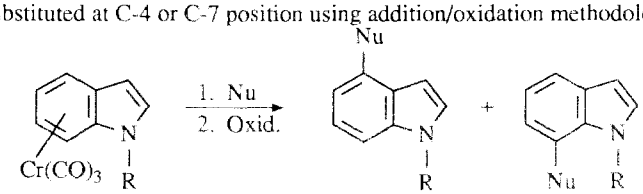
ML = $Cr(CO)_3$ or $CpRu^+(II)$

Route b:

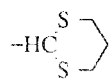


3.1 Addition/Oxidation

Semmelhack's group (30) has shown that chromium tricarbonyl complexed indoles could be substituted at C-4 or C-7 position using addition/oxidation methodology. They have



(eq 1)

Nu = CMe_2CN; CH_2CN; CMe_2CO_2-*t*-Bu; $CH_2CH{=}CHSiMe_3$; CHMeCN; 

observed a strong preference for addition at the C-4 position with minor amounts of addition products at the C-7 position (eq 1). Ketone enolates failed to add (< 20%), while ester enolates, cyano-stabilized carbanions, and 2-lithio-1,3-dithiane gave good results. However, the anion derived from 1,3-dithiane is reported to add preferentially at the C-7 position as compared to normal C-4 attack. The results of addition at the C-7 position in the case of the N-methyl-3-alkylindole chromium tricarbonyl complex have been explained in terms of steric and electronic effects, but this can be made to revert to C-4 by using bulky N-protecting group such as diphenyl-*t*-butylsilane.

3.2 Direct substitution

Direct nucleophilic aromatic substitution upon aryl halides is not commonly used in organic synthesis because of the necessity of introducing and then removing an activating group (NO_2 or CF_3). However, the activating metal moeity can be easily attached to an aryl ring of a halo or nitroarene in an η^6-fashion and then removed after chemical reaction, making (formal) substitution for halide or nitro group not only possible but often extremely facile. The most celebrated halogen arene complexes so far utilized for synthetic purposes are of $Cr(CO)_3$(8-10), CpFe (11-12), and CpRu (13).

We have aimed at both the synthesis of intermediates for natural products and effecting the controlled functionalization of the aryl ring of chloro and nitro indoles using their temporary complexation to a CpRu unit.

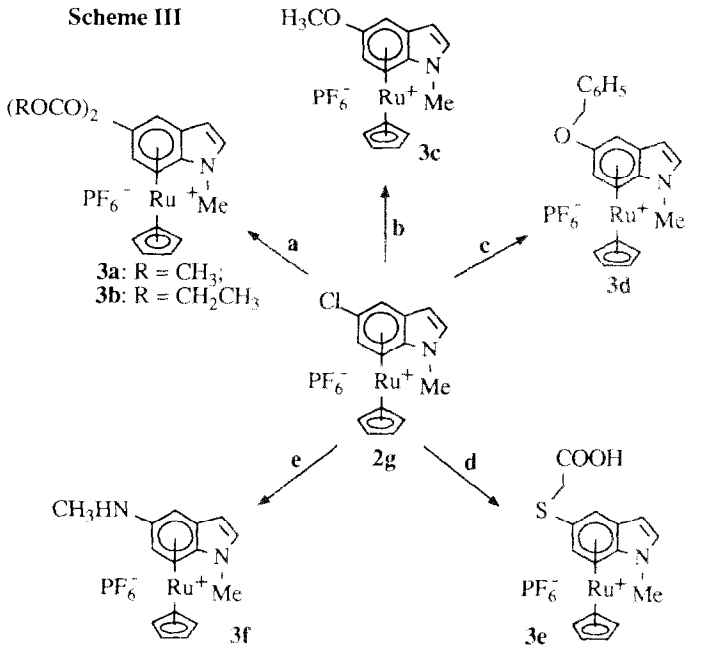
3.2.1 Chloroindoles

The method described in Scheme I (Section 2.0) allowed us to synthesize CpRu complexes of 4- and 5-chloroindoles. Despite their stability, they are highly reactive towards nucleophiles (Scheme III) (32). For example, the 5-chloro-N-methylindole (CpRu) complex reacts with dimethyl malonate anion to give a quantitative yield of complex **3a** (Scheme III, eq a).This selectivity probably reflects the ready reversibility of the initial coupling reaction i.e. formation of complex **4** followed by the irreversible loss of chloride.
The facility of these nucleophilic substitution reactions is ascribable to the special electron withdrawing ability of the CpRu unit. The extension of these aromatic substitution reactions with other carbon centered nucleophiles is planned.

Several non-carbon nucleophiles have also been combined with the 5-chloroindole complex (Scheme III). Interestingly, even an aqueous solution (40%) of methylamine reacted with the 5-chloroindole complex in THF at room temperature to give the desired 5-substitution product (Scheme III, eq e). In a further adaptation of the S_NAr methodology, we have also observed reaction of the disodium salt of mercaptoacetic acid with the 5-chloroindole complex (Scheme III, eq d).

The above results clearly indicate the feasibility of using the CpRu ligand as an auxiliary unit for introducing carbon, oxygen, nitrogen and sulphur nucleophiles at the C-5 position of indole. The potential synthetic application of this methodology is further demonstrated by functionalization of the C-4 position of the indole (Scheme IV). Since most biologically active indole alkaloids have functional units at the C-4 position of indole, selective functionalization at this position seems even more rewarding to our group. For example, the stabilized enolate anions generated from the reaction between dimethyl or diethyl malonate and NaH in THF at 0°C displaced the chlorine atom from the ruthenium complex of 4-chloro-N-methylindole (Scheme IV, eq a) giving the substitution product **5a** or **5b** respectively, having the carbon functionality at the C-4 position of indole.

Scheme III



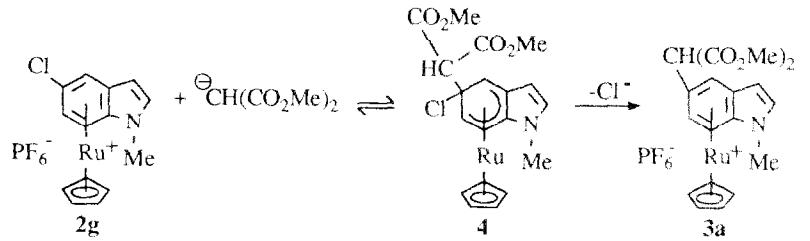
a $H_2C(CO_2R)_2$ (2 eq), NaH (2 eq), THF, 40-50°C, 10 h; H_3O^+, NH_4PF_6

b NaOH (20 eq), CH_3OH, 50°C, 14 h; H_3O^+, NH_4PF_6

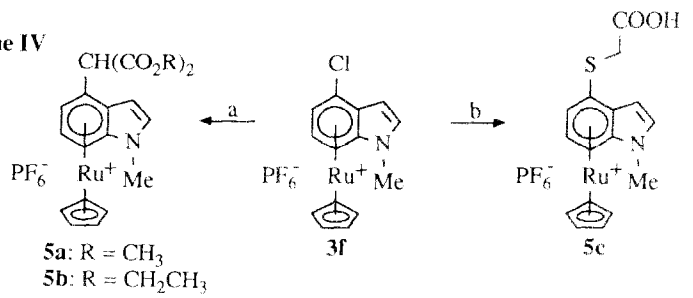
c $HOCH_2C_6H_5$ (4 eq), THF, 40-50°C, 10 h; H_3O^+, NH_4PF_6

d $HSCH_2CO_2H$ (10 eq), NaH (10 eq), THF, RT, 36 h; H_3O^+, NH_4PF_6

e H_2NCH_3 (400 eq), CH_2Cl_2, RT, 2 days; H_3O^+, NH_4PF_6.



Scheme IV

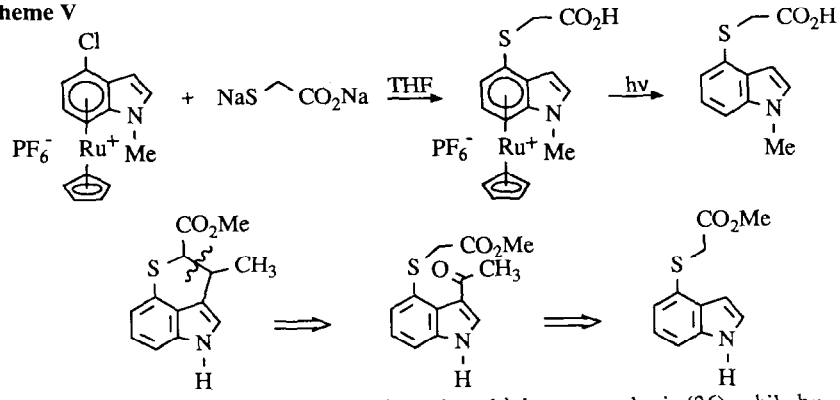


a $H_2C(CO_2R)_2$ (2 eq), NaH (2 eq), THF, 40-50°C, 10 h; H_3O^+, NH_4PF_6

b $HSCH_2CO_2H$ (10 eq), NaH (10 eq), THF, RT, 36 h; H_3O^+, NH_4PF_6.

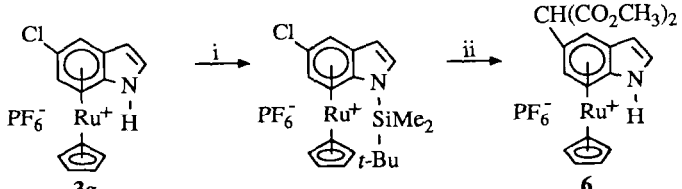
The significance of our methodology is finally emphasized by the fact that the reaction of the complex **3f** and the disodium salt of mercaptoacetic acid gave the 4-(N-methylindolyl)thioacetic acid complex **5c** (Scheme IV, eq b) from which the free indole ligand (i.e. 4-sulfur substituted indole) can be disengaged from the metal complex. Similarly, a 4-sulfur substituted indole is the key intermediate in the total synthesis of the antibiotic alkaloid, *chuengxingmycin* (Scheme V).

Scheme V



It was prepared by Prof. Kozikowski's group through multiple step synthesis (36), while by using our organometallic methodology this kind of intermediate can be easily prepared in three steps (Scheme V).

Scheme VI



i: NaH / TH F / *t*-BuSiMe$_2$Cl
ii: NaH / THF / $CH_2(CO_2CH_3)_2$; HCl / H_2O

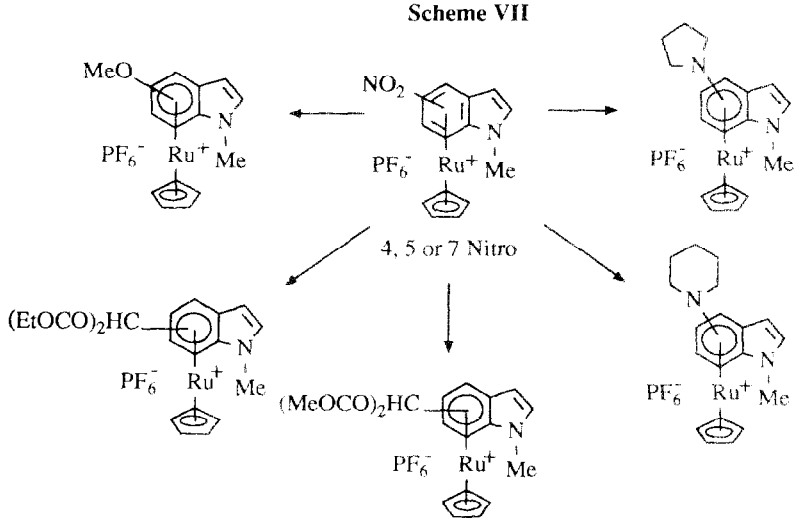
For simplicity, we have focused our efforts on the ruthenium complexes of N-methylindole derivatives, in order to overcome the problem of competing nucleophilic attack at the nitrogen protecting group. Besides using methyl as the N-protecting group, the t-butyldimethylsilyl group was also tested. It was found that it is an excellent N-protecting group for the nucleophilic substitution reaction using a carbon nucleophile and was conveniently removed during the HCl aqueous workup (Scheme VI, **6**)

3.2.2 Nitroindoles

In spite of the ready availability of nitroindoles, an efficient and general method to introduce alkyl sidechains bearing useful functional groups into these compounds via S_NAr substitution reactions remained unexplored. This deficiency is apparently due to lack of a direct

method for incorporation of activating metal moeties onto the aryl ring of these compounds. Our initial success with S_NAr reactions upon cyclopentadienylruthenium complexed chloroindoles motivated us to ponder more deeply the unique activating aspects of the CpRu unit and the potential reactivities of CpRu complexed nitroindoles. We sought to isolate stable salts of CpRu complexed nitroindoles for structural characterization and reactivity testing. These new nitroindole complexes were soon found to be readily obtained from the direct thermal ligand exchange reaction of tris acetonitrilecyclopentadienylruthenium(II) hexafluorophosphate, **1**, with the corresponding N-methyl 4-, 5- or 7-nitroindole substrates (Scheme VII). The CpRu complexes of 4-, 5- or 7-nitroindole seemed ideal substrates for

Scheme VII

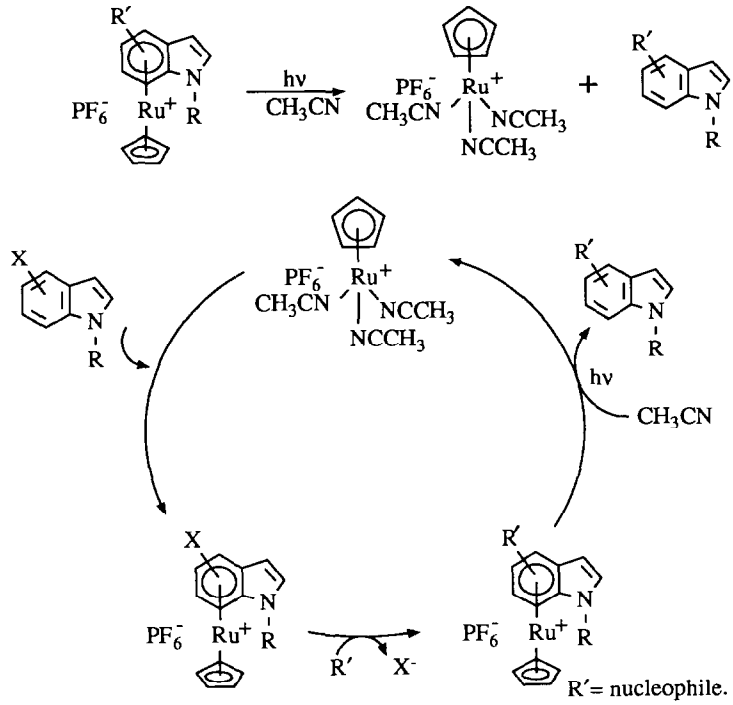


regiospecific functionalization of the aryl ring of these indoles via direct IPSO nucleophilic substitution of the nitro group (37). Indeed these new ruthenium complexes underwent smooth S_NAr substitution reactions with carbon and nitrogen, as well as oxygen nucleophiles (Scheme VII). These S_NAr substitution reactions proceeded under milder conditions than those observed with the chloroindole series. We have sought to develop general methods for regiospecific indole functionalization by examining the reactions of nitroindole complexes with appropriate nucleophiles. To date, we have found the combination of dimethyl or diethyl malonate anions generated from dimethyl or diethyl malonate in the presence of K_2CO_3 in THF with complexes to be most effective. The reactions of these anions proceeded rapidly at 40°C, giving good yields averaging about 80% of the corresponding substituted indole complexes. We tried several non-carbon centred nucleophiles for S_NAr substitution reactions upon nitroindole complexes. For example, amino nucleophiles, namely pyrrolidine and piperidine, have been used successfully for S_NAr reactions to yield the corresponding η^6-(4-, 5- or 7-N-pyrrolidino-N-methylindole) (η^5-CpRu) hexafluorophosphate and η^6-(N-piperidino-N-methylindole) (η^5-CpRu) hexafluorophosphates. The oxygen centred nucleophile (MeO^-) also yielded the corresponding methoxyindole complexes. Further diversification in the use of nucleophiles is in progress.

3.3 Decomplexation

The effective removal of the coordinated ruthenium is of vital importance to the utility of this procedure. This may be achieved photolytically in the presence of acetonitrile to give the free modified indole substrate and tris-acetonitrile(η-cyclopentadienyl)ruthenium(II) - hexafluorophosphate as indicated in the following equation and cycle (Scheme VIII).

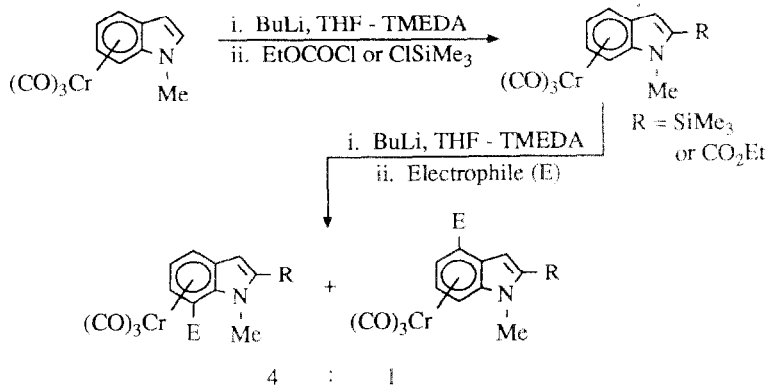
Scheme VIII



4.0 Ring lithiation

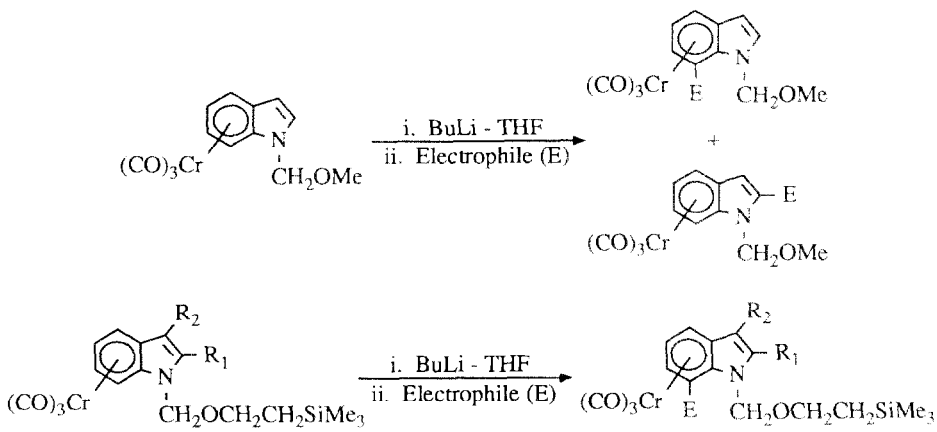
Recently, Widdowson's group (38) has shown that N-protected indoletricarbonyl chromium (0) complexes may also be functionalized at the C-4 or C-7 position of the indole nucleus via a lithiation/electrophilic quench sequence (Scheme IX).

Scheme IX



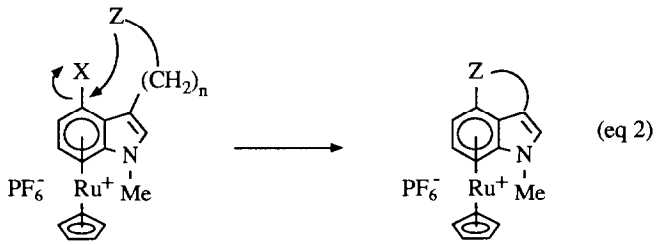
Series of Electrophiles: $ClCO_2Et$; MeI; PhCHO; CH_2=CHCHO; PhSCl; Me_2C=$CHCH_2Cl$

In order to carry out a regioselective lithiation/electrophilic quench sequence at the C-7 position they used methoxymethyl and 2-trimethylsilylethoxymethyl groups for N-protection as shown in the following equations:



5.0 Second generation of CpRu complexed indoles

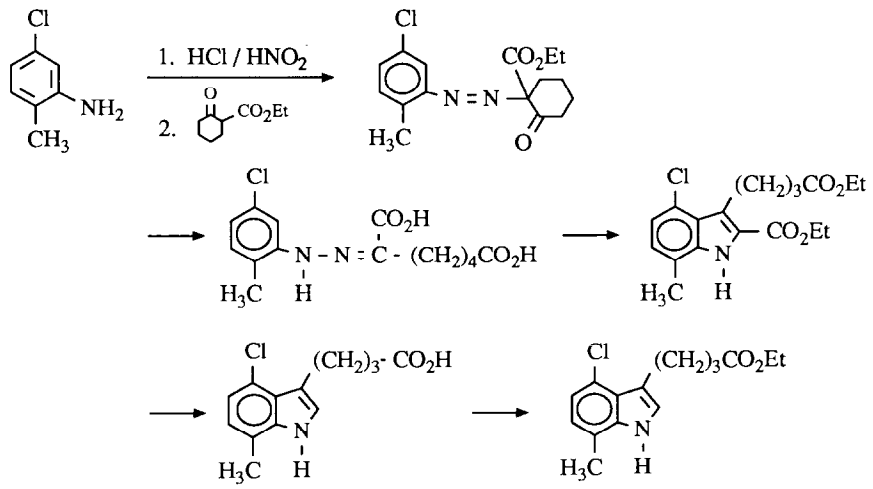
In addition to exploring a wide variety of nucleophilic coupling partners for chloro as well as nitroindole ruthenium complexes, we have been interested in studying the chemistry of a new class of indole ruthenium complexes (described in section 2.0) possessing a nucleophilic substituent at the C-3 position eq. 2, in order to further probe the utility of the CpRu unit in intramolecular cyclization reactions (39).



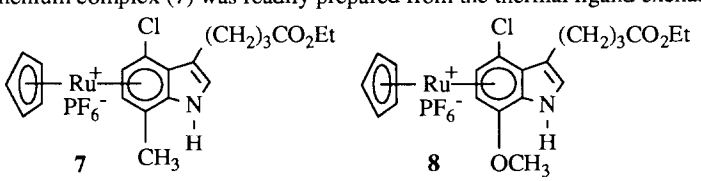
(eq 2)

We were first attracted to the synthesis of indole substrates bearing a nucleophilic centre in the side chain at the C-3 position. The synthetic strategies for the synthesis of such precursors are depicted in Scheme X.

Scheme X



The ester ruthenium complex (**7**) was readily prepared from the thermal ligand exchange



reaction between the corresponding free ester indole substrate and tris-acetonitrile cyclopentadienylruthenium hexafluorophosphate (**1**) according to the methodology described in section 2.0. Our preliminary attempts to effect the intramolecular cyclization reaction have been thwarted by the insufficient acidity of the ester methylene group and by the loss of the quite acidic proton alpha (i.e. CH_3 group) to the complexed ring to yield starting material after aqueous workup. We now have prepared complex (**8**) although the overall yield of this complex is much lower than that of the methyl analogue. The synthesis of corresponding nitro analogues of these complexes is in progress, as well as the chemistry of these new ruthenium complexes.

6.0 Conclusions

The reactions described above illustrate what can be achieved in the area of transition metal indole chemistry. Selection of new coupling partners for the indole transition metal complexes and second and third generation indole ruthenium complexes should result in significant new applications in the synthesis of both natural and synthetic products. Another emerging area of application for CpRu(II) unit and other electrophilic metal complexes, is their use to tag biomolecules in immunology (40).

6.0 References

1. Floss, H.G. Tetrahedron 1976, 32, 873.
2. Robinson, B. The Alkaloids; Manske, R.H.F.; Holmes, H.L., Eds.; Acad. NY 1967; Vol X, Chapter 5.
3. Christopherson, C. Marine Indoles in Marine Natural Products: Chemical and Biological Perspectives: Scheuer, P.J., Ed.; Academic Press, NY 1982, Vol V, pp 259-285.
4. Tsuda, Y.; Yoshimoto, K.; Nidlikawa, T. Chem. Pharm. Bull. 1981, 29, 3593.
5. Repke, D.B.; Ferguson, W.J. J. Heterocycl. Chem. 1982, 19, 845.
6. (a) Somei, M.; Saida, Y.; Komura, N. Chem. Pharm. Bull. 1986, 34, 4116; (b) Somei, M.; Yamada, F.; Naka, K. ibid, 1987, 35, 1322; (c) Somei, M.; Amari, H.; Makita, Y. ibid. 1986, 34, 3971.
7. Hegedus, L.S. Angew. Chem. Int. Ed. Eng. 1988, 27, 1113.
8. Semmelhack, M.F. Ann N.Y. Acad. Sci. 1977, 295, 36.
9. Jaouen, G.; In Transition Metal Organometallics in Organic Synthesis, Alper, H.; Ed. (Academic Press, New York) 1978, vol. 2, pp. 65-120.
10. Collman, J.P.; Hegedus, L.S. "Principles & Applications of Organotransition Metal Chemistry" University Science Books: Mill Valley CA, 1980, Chapters 12, 13,15.
11. Astruc, D. Tetrahedron 1983, 39, 4027.
12. Sutherland, R.G.; Iqbal, M.; Piorko, A. J. Organometal. Chem. 1986, 302, 307.
13. Moriarty, R.M.; Gill, U.S.; Ku, Y.Y. J. Organometal. Chem. 1988, 157, 350.
14. (a) Moriarty, R.M.; Gill, U.S. Organometallics 1985, 5, 253; (b) Gill, U.S.; Moriarty, R.M. Synth. React. Inorg. Met. - Org. Chem. 1986, 16, 485; (c) Gill, U.S.; Moriarty, R.M. Synth. React. Inorg. Met. - Org. Chem. 1986, 16, 1103; (d) Gill, U.S. Inorg. Chem. Acta 1986, 114, L25; (e) Sutherland, R.G.; Abd-EL-Aziz, A.S.; Piorko, A.; Lee, C.C. Synth. Commun. 1987, 17, 393; (f) Piorko, A.; Abd-EL-Aziz, A.S.; Lee, C.C.; Sutherland, R.G. J. Chem. Soc. Perkin Trans 1. 1989, 469; (g) Sutherland, R.G.; Zhang, C.H.; Piorko, A.; Lee, C.C. Can. J. Chem. 1989, 67, 137.
15. Beswick, P.J.; Leach, S.J.; Masters, N.F.; Widdowson, D.A. J. Chem. Soc. Chem. Commun. 1984, 46.
16. Card, R.J.; Trahanovsky, W.S. J. Org. Chem. 1980, 45, 2560.
17. Semmelhack, M.F.; Clark, G.R.; Farina, R.; Saeman, M. J. Amer. Chem. Soc. 1979, 101, 217.
18. Jaouen, G.; Meyer, A. J. Amer. Chem. Soc. 1975, 97, 4667.
19. Top, S.; Jaouen, G. J. Org. Chem. 1981, 46, 78.

20. Reetz, M.T.; Sauerwald, M. Tet. Lett. 1983, 24, 2837.
21. Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higushi, T.; Hayashi, Y. J. Org. Chem. 1983, 48, 2349.
22. Uemura, M.; Isobe, K.; Hayashi, Y. Tet. Lett. 1985, 26, 767; ibid, Chem. Lett. 1985, 91.
23. Kundig, E.P.; Desobry, V.; Simmons, D.P. J. Amer. Chem. Soc. 1983, 105, 6962.
24. Uemura, M.; Nishikawa, N.; Tokuyama, S.; Hayashi, Y. Bull. Chem. Soc. Japan, 1983, 53, 293.
25. Uemura, M.; Isobe, K.; Take, K.; Hayashi, Y. J. Org. Chem. 1983, 48, 3855.
26. Uemura, M.; Minami, T.; Hayashi, Y. J. Chem. Soc. Chem. Commun. 1984, 1193.
27. Semmelhack, M.F.; Zask, A. J. Amer. Chem. Soc. 1983, 105, 2034.
28. Jaouen, G.; Top, S.; Laconi, A.; Couturier, D.; Brocard, J. J. Amer. Chem. Soc. 1984, 106, 2207.
29. Davies, S. G. Chem. & Ind. 1986, 506.
30. (a) Semmelhack, M.F.; Clark, G.R.; Harrison, J.L.; Thebtaranonth, Y.; Wulff, W. Tetrahedron, 1981, 23, 3957; (b) Semmelhack, M.F.; Wulff, W.; Garcia, J.L. J. Organometal. Chem. 1982, 240, C5.
31. French Patent 1984, 2539428, Chemtech. May 1986, 320.
32. Moriarty, R.M.; Ku, Y.Y.; Gill, U.S. J. Chem. Soc. Chem. Commun. 1987, 1493; ibid, Organometallics 1988, 7, 660.
33. Fischer, E.O.; Goodwin, H.A.; Krieter, C.G.; Simmons, H.D.; Sonogashira, J.K.; Wild, S.B. J. Organometal. Chem. 1968, 14, 359.
34. Gill, T.P.; Mann, K.R. Organometallics 1982, 1, 485.
35. Fairhurst, G.; White, C. J. Chem. Soc. Dalton 1979, 1531.
36. Kozikowski, A.P.; Greco, M.N.; Springer, J.P. J. Amer. Chem. Soc. 1982, 104, 7622.
37. (a) Moriarty, R.M.; Ku, Y.Y.; Guo, L. J. Chem. Soc. Chem. Commun. 1988, 1621; (b) Moriarty, R.M.; Ku, Y.Y.; Guo, L.; Gill, U.S. unpublished results.
38. Masters, N.F.; Mathews, N.; Nechvatal, G.; Widdowson, D.A. Tetrahedron 1989, 45, 5955.
39. Moriarty, R.M.; Gill, U.S.; Ku, Y.Y. unpublished results.
40. (a) Moriarty, R.M.; Ku, Y.Y.; Gill, U.S. J. Chem. Soc. Chem. Commun. 1987, 1837; (b) ibid, J. Organometal. Chem. 1989, 362, 187; (c) Moriarty, R.M.; Ku, Y.Y.; Gill, U.S.; Gilardi, R.; Perrier, R.E.; McGlinchey, M.J. Organometallics 1989, 8, 960; (d) Jaouen, G.; Vessieres, A.; Top, S.; Ismail, A.A.; Butler, I.S. J. Amer. Chem. Soc. 1985, 107, 4778.