A Novel Approach to Synthesis of the Cinnoline Ring System *via* Organoiron(Cyclopentadienyl) Complexes

Ronald G. Sutherland*, Alaa S. Abd-El-Aziz, Adam Piórko
Udai S. Gill and Choi Chuck Lee*

Department of Chemistry, University of Saskatchewan,
Saskatoon, Saskatchewan S7N OWO Canada

Received December 18, 1987

An efficient synthesis of 3-mono or 3,4-disubstituted cinnolines from (*o*-dichlorobenzene)(cyclopentadienyl)iron hexafluorophosphate in three or four steps has been achieved. *o*-Chlorophenyl-alkyl or alkylaryl ketone complexes obtained from the *o*-dichlorobenzene complex upon treatment with enolate anions, react with hydrazine forming 3-mono or 3,4-disubstituted 1,4-dihydrocinnoline complexes. Treatment of the later with sodium amide leads to an aromatization-demetallation reaction resulting in formation of cinnolines, *i.e.* 3-methyl-, 3-phenyl- and 3,4-dimethylcinnoline. The influence of substituents bonded to the carbon atom adjacent to the complexed benzene ring in *o*-chlorophenyl -alkyl or -alkylaryl ketone prior to cyclization on the cyclization reaction is discussed.

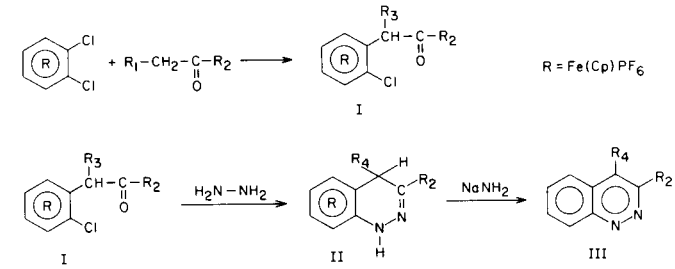
J. Heterocyclic Chem., **25**, 1107 (1988).

In 1957 Jacobs noted in his review on cinnoline and related compounds that this ring system is the least well known of the condensed bicyclic aromatic heterocycles containing two nitrogen atoms [1]. Since that time a significant interest in synthesis of compounds possessing the cinnoline ring system has developed and a number of them which exhibited biological activity have been used as drugs [2] or described as potential drugs or herbicides [3]. Traditional synthetic routes to the cinnoline ring system involve various cyclization reactions of diazonium salts of *o*-aminosubstituted benzenes, *N*-substituted phenylhydrazones [4] or the ring expansion of substituted indoles [4,5]. In present work we describe a new approach to the synthesis of the title compounds involving (arene)iron(cyclopentadienyl) complexes as starting materials.

For some time we have been involved in studies of nucleophilic substitution reactions of chloroarenes complexed by iron (cyclopentadienyl) moiety since such complexation is known to reverse the reactivity of arenes from the electrophilic to nucleophilic type [6]. Oxygen, sulfur, nitrogen or carbon nucleophiles efficiently replace chlorine in the presence of basic catalyst. Similar reactions of the *o*-dichlorobenzene complex cause the replacement of one or both chlorine substituents with oxygen or sulfur nucleophiles while nitrogen or carbon nucleophiles replace only one of the two ortho chlorines [7]. We have also reported that replacement of both chlorines in the *o*-dichlorobenzene complex take place with suitable *o*-disubstituted benzenes leading to formation of heterocycles possessing 9,10-diheteroanthracene system in the molecule [8]. Demetallation of these complexes leads to synthesis of heterocycles in an unique way.

In the present work we achieved the formation of the cinnoline ring system in two sequential reactions - formation of the hydrazone on a keto group in position 2 of the side chain of the *o*-chloro-substituted benzene which is followed by nucleophilic substitution of the *o*-chloro group by the second amino group of hydrazine (Scheme I).

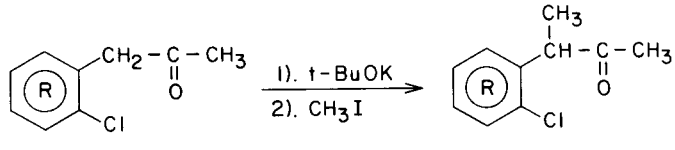
Scheme I



a). $R_1 = COCH_3$; $R_2 = CH_3$; $R_3 = R_4 = H$
b). $R_1 = COPh$; $R_2 = Ph$; $R_3 = COPh$; $R_4 = H$
c). $R_1 = COCH_3$; $R_2 = Ph$; $R_3 = R_4 = H$
d). $R_1 = COCH_3$; $R_2 = CH_3$; $R_3 = CH_3$; $R_4 = CH_3$

Substrates **Ia,b** and **c** have been obtained in a nucleophilc substitution reaction of the appropriate enolate anion with (*o*-dichlorobenzene)iron(cyclopentadienyl) hexafluorophosphate in the presence of base [7,9]. Under basic conditions such a reaction leads to monosubstitution only. Complex **Id** was obtained from **Ia** by deprotonation with potassium *t*-butoxide followed by methylation with methyl iodide using a methodology previously described [10] (Scheme II).

Scheme II



The key step involves two sequential reactions - formation of the hydrazone and nucleophilic substitution of chlorine by the amino group of hydrazine which leads to cyclization to form the 1,4-dihydrocinnoline system. We have not yet investigated the full mechanism, *i.e.* the sequence of the reactions because of our interest in the preparative significance of this work. Both reactions occur in the presence of glacial acetic acid which, according to the mechanism of hydrazone formation in the presence of acid warrants formation of ketone enolate while maintaining a sufficient concentration of free amino groups ready to enter both substitution and hydrazone formation [11].

The structure of 1,4-dihydrocinnoline complexes **IIa-d** has been established on the base of analytical and spectral data which are summarized in the experimental part. In proton nmr spectra, signals of the cyclopentadienyl protons appear for these complexes at 5.01-5.02 ppm (for cations **Ia,c,d** 5.30-5.40 ppm; for **Ib**, 4.80 ppm); signals of methyl protons in position 3 at 2.14-2.24 ppm (for **Ia**, 2.34; for **Id**, 2.36 ppm) and signals of protons bonded to carbon 4 of the ring in range 3.33-4.37 ppm (in cations **I** in the range 4.36-6.90 ppm). Carbon-13 spectra indicate disappearance of carbonyl carbon signals (range *ca.* 200 ppm) replaced by the signal of imine carbon appearing at 142-150 ppm. Also the signal of quaternary carbon atom of the complexed aromatic ring bearing chloro substituent (106-109 ppm) disappears and a new signal of a carbon bearing amino group appears (112-114 ppm) with signals of the two adjacent carbons of the ring shifted significantly upfield as found in the other amino complexes [7]. Both proton and carbon spectra indicate clearly for compound **IIb** the presence of only one uncomplexed phenyl group in the molecule and this compound is identical with **IIc** because of occurrence of debenzoylation.

It is interesting to note that starting complex **Ib** posesses two keto groups capable of being converted to hydrazone. However the cyclization product **IIb** do not have a benzoyl (or benzoyl hydrazone) group on the formed ring in position 4 which means that debenzoylation has occured. Further study involving similar complexes synthetized in our laboratory having the structure **I** with substituents R_3 and R_2, respectively: $R_3 = SO_2Ph$ and $R_2 = CH_3$; $R_3 = SO_2Ph$ and $R_2 = Ph$; $R_3 = CO_2Et$ and $R_2 = CH_3$; $R_3 = Ph$ and $R_2 = CH_3$ have been completed and in each case substitution of chlorine with hydrazine was observed but deacetylation (or debenzoylation) took place leading to formation of a CH_2R_3 type side chain [12]. Our conclusion is that deacylation under reaction conditions occurs as the first reaction and the presence of an electronwithdrawing substituent R_3 is a precondition for its occurence. If a hydrogen or an electrodonating methyl group are the substituent R_3 then no such reaction takes place and cyclization to the 1,4-dihydrocinnoline system occurs. Similar deacylation reactions in the presence of acidic catalysts have been described previously [7,9,13].

We also attempted reactions of cations **Ia** and **Ib** with phenylhydrazine instead of hydrazine. We found that the phenylhydrazones of **Ia** and of debenzoylated **Ib** were formed without subsequent replacement of chlorine and cyclization as determined by analytical and spectral data [12]. The reason is that phenylhydrazine is a weaker base than hydrazine and its strength is comparable with aniline [14] which has been reported not to enter substitution reaction with the chlorobenzene complexes [7,15].

Deprotonation of nitrogen in position 1 of the ring of the complexes **II** with sodium amide leads both to 1,4-deprotonation and demetallation of the complexes and we obtained the aromatic heterocycles directly: 3-methylcinnoline (**IIIa**), 3-phenylcinnoline (**IIIb** and **IIIc**; both complexes **IIb** and **IIc** being obtained from different starting complexes **Ib** and **Ic**, respectively, are identical) and 3,4-dimethylcinnoline (**IIId**). All these compounds have been synthesized previously by more difficult routes {[16,17], [18,19] and [20], respectively} and our analytical data are in full agreement with those published. In the experimental part yields, mass spectra and high resolution nmr spectral data for these compounds are given.

With the respect to the reactivity of (arene)iron(cyclopentadienyl) complexes three facts should be noted. While alkylations of alkylbenzene complexes *via* deprotonation/-alkylation route have been extensively studied [6] synthesis of the complex **Id** is the first report of such reaction on a side chain carrying a very reactive carbonyl function in direct proximity to the deprotonated carbon. Secondly, the cyclization described here is also the first example of nucleophilic substitution on complexed chloroarene system under acidic conditions with a nitrogen nucleophile and in the presence of alkyl substituent on that ring; such reactions are not observed under the basic conditions normally employed for nucleophilic substitution on complexed chloroarenes. Finally the deprotonation with sodium amide which in the case of aminobenzenes complexed by iron(cyclopentadienyl) moiety leads normally to stable (cyclohexylimino)iron(cyclopentadienyl) complexes [6,21] results in demetallation. These reactions are also the first examples of demetallation of cyclohexadienyl complexes with exocyclic double bond. We believe that deprotonation occurs but that the (cinnoline) iron(cyclopentadienyl) complex is unstable and decomposes with liberation of the free heterocycle. This is supported by the fact that no complexes of heterocycles such as quinoline or phenazine have been synthetized despite all the intensive efforts made; complexation was only possible when preceded by hydrogenation of phenazine to 9,10-dihydrophenazine [22].

Finally we would like to emphasize that the described

synthesis of cinnolines should be of considerable utillity in heterocyclic synthesis. Starting from readily available (*o*-dichlorobenzene)iron(cyclopentadienyl) hexafluorophosphate and using commercially available reagents we obtained 3-substituted or 3,4-disubstituted cinnolines with 35-70% overall yield from the starting cation in reactions carried out under very mild conditions. The synthesis may be extended to compounds bearing additional substituents on the starting dichlorobenzene complex.

EXPERIMENTAL

Starting complexes were prepared following literature procedures: (*o*-dichlorobenzene)(cyclopentadienyl)iron hexafluorophosphate [23]; **Ia** [7]; **Ib** [9]; **Ic** [9]. Mass spectra were obtained using electron impact ionization at 70 eV. The ^{1}H nmr (300.133 MHz) and ^{13}C nmr (75.469 MHz) spectra were recorded on Bruker AM 300 instrument; all chemical shifts are given in δ, ppm scale (internal TMS for proton; calculated from solvent signals in carbon-13 nmr spectra) where δ_{TMS} = 0 ppm.

Complex **Id**, [η^6-3-(*o*-chlorophenyl)butanone]iron(cyclopentadienyl)hexafluorophosphate was prepared using modified literature description [10] as follows:

To a solution of 2.17 g (5.0 mmoles) of **Ia** in 350 ml of THF equimolar amount (0.56 g) of potassium *t*-butoxide was added. The mixture immediately became red and was stirred for ½ hours. Methyl iodide (0.71 g, 0.31 ml, 5.0 mmoles) was then added *via* syringe and the mixture gently refluxed with stirring for 5 hours. The resulting solution was then filtered, concentrated to *ca.* 30 ml and 0.82 g (5.0 mmoles) of ammonium hexafluorophosphate in 100 ml of water was added. The product was extracted with methylene chloride, the combined organic extracts were dried (magnesium sulfate) and evaporated to dryness. The crude product containing a small amount of starting complex **Ia** was recrystallized from methylene chloride-diethyl ether giving 1.59 g (71%) of **Id** as orange-yellow microcrystals; ir (potassium bromide): 1710 cm^{-1} (CO); ^{1}H nmr (acetone-d_6): δ 1.87 (d, J = 7.3 Hz, 3H, C*H*$_3$CH), 2.36 (s, 3H, C*H*$_3$CO) 4.80 (q, J = 7.3 Hz, 1H, C*H*CH$_3$), 5.33 (s, 5H, cyclopentadienyl), 6.50 (t, J = 6.0 Hz, 1H, complexed aromatic), 6.57 (d, J = 5.9 Hz, 1H, complexed aromatic), 6.65 (t, J = 6.1 Hz, 1H, complexed aromatic), 6.87 (d, J = 5.9 Hz, 1H, complexed aromatic); ^{13}C nmr (acetone-d_6): δ 14.67 (CH$_3$), 28.31 (*C*H$_3$CO), 49.49 (CH), 79.54 (cyclopentadienyl), 86.35, 87.36, 88.20, 89.22, 105.35 (quaternary) and 108.24 (quaternary) (all complexed aromatic), 203.20 (CO).

Anal. Calcd. for $C_{15}H_{16}ClF_6FeOP$: C, 41.55; H, 3.72. Found: C, 41.39; H, 3.63.

Cyclization. General Procedure.

To a solution of 1 mmole of complex **I** in 25 ml of methylene chloride and 2 ml of DMF ten drops of glacial acetic acid followed by 1 ml of anhydrous hydrazine were added. The mixture which immediately became dark red was stirred under nitrogen for 24 hours. The solution with a white precipitate was filtered through sintered glass, washed with water (3 x 20 ml) dried (magnesium sulfate) and evaporated to dryness. The resulting brown oil was washed with diethyl ether and purified on a short column (5 cm) filled with deactivated alumina (F20, Alcoa Chimica). Impurities were washed out with hexane and carbon tetrachloride and the product was eluted with methylene chloride-acetonitrile 4:1. After evaporation the crude product was recrystallized from methylene chloride-ether.

(4a,5,6,7,8,8a-η^6-1,4-Dihydro-3-methylcinnoline)iron(cyclopentadienyl) Hexafluorophosphate (**IIa**).

This complex was obtained as orange-brown powder, yield 0.33 g (80%); ^{1}H nmr (acetone-d_6): δ 2.14 (s, 3H, C*H*$_3$), 3.33 and 3.70 (AB quartet, J = 10.0 Hz, C*H*$_2$), 5.02 (s, 5H, cyclopentadienyl), 6.16-6.22 (m, 4H, complexed aromatic), 9.03 (s, 1H, N*H*); ^{13}C nmr (acetonitrile-d_3): δ 22.90 (CH$_3$), 29.61 (CH$_2$), 77.18 (cyclopentadienyl), 72.47, 82.35 (quaternary), 83.50, 85.10, 86.30, 113.75 (quaternary) (all complexed aromatic), 146.54 (*C*=N).

Anal. Calcd. for $C_{14}H_{15}F_6FeN_2P$: C, 40.79; H, 3.67; N, 6.79. Found: C, 40.47; H, 3.58; N, 6.70.

(4a,5,6,7,8,8a-η^6-1,4-Dihydro-3-phenylcinnoline)iron(cyclopentadienyl) Hexafluorophosphate (**IIb** and **IIc**).

Complexes **IIb** and **IIc** are identical although obtained from different starting complexes **Ib** and **Ic**, respectively, as an orange-brown powder, yield 0.33 g (70%) for **IIb** and 0.34 g (72%) for **IIc**; ^{1}H nmr (acetone-d_6): δ 3.75 and 4.37 (AB quartet, J = 9.5 Hz, C*H*$_2$), 5.01 (s, 5H, cyclopentadienyl), 6.23-6.37 (two m's, 4H, complexed aromatic), 7.49-7.54 (m, 3H, phenyl), 7.93-7.97 (m, 2H, phenyl), 9.69 (s, 1H, N*H*); ^{13}C nmr (acetone-d_6): δ 25.95 (C*H*$_2$), 76.99 (cyclopentadienyl), 72.41, 83.42, 83.42 (quaternary [24]), 85.21, 86.14, 112.27 (quaternary) (all complexed aromatic), 126.26, 126.26, 129.21, 129.21, 130.31, 136.25 (quaternary) (all phenyl), 142.76 (*C*=N).

Anal. Calcd. for $C_{19}H_{17}F_6FeN_2P$: C, 48.02; H, 3.61; N, 5.89. Found: C, 48.30; H, 3.67; N, 5.81.

(4a,5,6,7,8,8a-η^6-1,4-Dihydro-3,4-dimethylcinnoline)iron(cyclopentadienyl) Hexafluorophosphate (**IId**).

This complex was obtained as an orange-brown powder, yield 0.32 g (75%); ^{1}H nmr (acetone-d_6): δ 1.30 (d, J = 7.2 Hz, C*H*$_3$CH), 2.24 (s, 3H, C*H*$_3$), 3.75 (q, J = 7.2 Hz, C*H*), 5.02 (s, 5H, cyclopentadienyl), 6.26-6.36 (m, 4H, complexed aromatic), 9.13 (s, 1H, N*H*); ^{13}C nmr (acetone-d_6): δ 18.56 (C*H*$_3$CH), 20.86 (C*H*$_3$), 34.91 (C*H*), 76.77 (cyclopentadienyl), 73.31, 83.67, 84.67, 86.23, 88.31 (quaternary), 113.12 (quaternary) (all complexed aromatic), 150.05 (*C*=N).

Anal. Calcd. for $C_{15}H_{17}F_6FeN_2P$: C, 42.17; H, 4.01; N, 6.56. Found: C, 42.01; H, 4.08; N, 6.60.

Demetallation-Aromatization. General Procedure [21].

To a solution of 1 mmole of the complex **II** in 250 ml of methylene chloride (0.39 g, 10 mmoles) of sodium amide was added. The mixture was stirred under nitrogen for 3 hours then filtered through sintered glass and evaporated to dryness. Crude product was purified on short column (5 cm) filled with Silica Gel (70-300 mesh, Merck & Co) and the product was eluted with chloroform. Evaporation of the chloroform solution gave product, identified by melting point, ms and nmr spectra.

3-Methylcinnoline (**IIIa**).

This compound was previously characterized as the picrate [16] and the hydrochloride [17] while we obtained it as brownish oil, yield 0.11 g (78%); ^{1}H nmr (chloroform-d): δ 2.95 (s, 3H, C*H*$_3$), 7.68-7.78 (m, 4H, aromatic), 8.47 (d, J = 8.1 Hz, 1H, aromatic); ^{13}C nmr (chloroform-d): δ 21.96 (C*H*$_3$), 121.43, 126.07, 126.41 (quaternary), 129.49, 129.60, 130.99, 149.25 (quaternary), 153.79 (quaternary) (all aromatic); ms: m/e 144 (M$^+$, 57.3), 115 (100), 89 (8.9), 63 (8.1).

Anal. Calcd. for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.15; H, 5.42; N, 19.16.

3-Phenylcinnoline (**IIIb** and **IIIc**).

This compound was obtained as a white-brownish solid, mp 117-119° (lit 118.5-119 [18], 119-120 [19]), yield 0.16 g (78%); ^{1}H nmr (chloroform-d): δ 7.46-7.57 (m, 3H), 7.69-7.86 (m, 3H), 8.14 (s, 1H), 8.24 (d, 7.3 Hz, 2H), 8.54 (d, 8.3 Hz, 1H) (all aromatic); ^{13}C nmr (chloroform-d): δ 118.35, 126.00 (quaternary), 126.67, 126.81, 126.81, 128.62, 128.62, 129.00, 129.18, 129.85, 130.80, 136.43 (quaternary), 149.44 (quaternary), 152.92 (quaternary) (all aromatic); ms: m/e 206 (M$^+$, 100%), 178 (45.4), 66 (8.5).

3,4-Dimethylcinnoline (**IIId**).

This compound was obtained as a white-brownish solid, mp 117-119° (lit 118-120° [20]), yield, 0.125 g (79%); ^{1}H nmr (chloroform-d): δ 2.62 (s,

3H, CH_3), 2.94 (s, 3H, CH_3), 7.65-7.76 (m, 2H, aromatic), 7.98 (d, J = 7.5 Hz, 1H, aromatic), 8.45 (d, J = 8.0 Hz, d, J = 2.7 Hz, 1H, aromatic); ^{13}C nmr (chloroform-d): δ 12.94 (CH_3), 20.41 (CH_3), 122.34, 125.79 (quaternary), 128.68, 128.70, 129.98 (quaternary), 130.26, 148.66 (quaternary), 152.47 (quaternary) (all aromatic); ms: m/e 158 (M^+, 76.6), 144 (22.7), 129 (37.4), 128 (26.4), 115 (100).

Acknowledgments.

Financial support given by Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

REFERENCES AND NOTES

[1] T. L. Jacobs, "Cinnolines and Related Compounds", Vol **6**, "Heterocyclic Compounds", R. C. Elderfield, ed, John Wiley and Sons, New York, 1957, pp 146-173.

[2] For example: Cinnopentazone, Cinnoxacine, Index Nominum 1980, Societe Suisse de Pharmacie, Zurich, 1979, p 205; D. Lednicer, L. A. Mitscher, "The Organic Chemistry of Drug Synthesis", Vol **2**, John Wiley and Sons, New York 1980, pp 387-390.

[3] Recent examples: J. T. A. Boyle, R. S. Todd, British Patent, GB 2,160,201; *Chem. Abstr.*, **105**, 208903r (1986); Grelan Pharmaceutical Co., Ltd., Japan Patent, JP 57,131,700; *Chem. Abstr.*, **98**, 34591g (1983) for drugs; J. S. Badmin, R. F. Jones, Brazilian Patent, PI 7800,098; *Chem. Abstr.*, **90**, 49667v (1979) for insecticides; ICI Australia Ltd., Japan Patent, JP 82 45,167; *Chem. Abstr.*, **97**, 72380z (1982) for herbicides.

[4] G. R. Newkome and W. W. Paudler, "Contemporary Heterocyclic Chemistry", John Wiley and Sons, New York, 1982, pp 214-217.

[5] M. Somei and Y. Kurizuka, *Chem. Letters*, 127 (1979).

[6] R. G. Sutherland, *J. Organomet. Chem. Library*, **3**, 311 (1977); R. G. Sutherland, M. Iqbal and A. Piórko, *J. Organomet. Chem.*, **302**, 307 (1986).

[7] C. C. Lee, A. S. Abd-El-Aziz, R. L. Chowdhury, U. S. Gill, A. Piórko and R. G. Sutherland, *J. Organomet. Chem.*, **315**, 79 (1986) and references cited therein.

[8] R. G. Sutherland, A. Piórko, U. S. Gill and C. C. Lee, *J. Heterocyclic Chem.*, **19**, 801 (1982); R. G. Sutherland, A. Piórko, C. C. Lee, S. H. Simonsen and V. M. Lynch, in preparation.

[9] R. G. Sutherland, A. S. Abd-El-Aziz, A. Piórko and C. C. Lee, *Synth. Commum.*, **17**, 393 (1987) and R. M. Moriarty and U. S. Gill, *Organometallics*, **5**, 253 (1986).

[10] R. G. Sutherland, B. R. Steele, K. J. Demchuk and C. C. Lee, *J. Organomet. Chem.*, **181**, 411 (1979).

[11] T. H. Lowry and K. Schueller Richardson, "Mechanism and Theory in Organic Chemistry", Harper and Row Publishers, New York, 1987, pp 702-709.

[12] R. G. Sutherland, A. S. Abd-El-Aziz, U. S. Gill, A. Piórko and C. C. Lee, unpublished results.

[13] U. S. Gill and R. M. Moriarty, *Synth. React. Inorg. Met.-Org. Chem.*, **16**, 1103 (1986).

[14] P. J. Krueger, "Chemistry of the Hydrazo, Azo and Azoxy Groups", S. Patai, ed, John Wiley and Sons, New York, 1975, pp 159-164.

[15] P. L. Pauson and J. A. Segal, *J. Chem. Soc., Dalton Trans.*, 1677 (1975).

[16] H. J. Haas, and A.-M. Seliger, *Chem. Ber.* **96**, 2427 (1963).

[17] H. Lund and N. H. Nilsson, *Acta Chem. Scand.*, **B30**, 5 (1976).

[18] H. E. Baumgarten and J. L. Furnas, *J. Org. Chem.*, **26**, 1536 (1961).

[19] C. M. Atkinson and C. J. Sharpe, *J. Chem. Soc.*, 2858 (1959).

[20] D. I. Haddlesey, P. A. Mayor and S. S. Szinai, *J. Chem. Soc.*, 5269 (1964).

[21] J. F. Helling and W. A. Hendrickson, *J. Organomet. Chem.*, **168**, 87 (1979).

[22] C. C. Lee, B. R. Steele and R. G. Sutherland, *J. Organomet. Chem.*, **186**, 265 (1980); R. G. Sutherland, B. R. Steele, A. Piórko and C. C. Lee, unpublished results.

[23] I. U. Khand, P. L. Pauson and W. E. Watts, *J. Chem. Soc. C.*, 2261 (1968).

[24] Found in gated decoupling experiment.