A Novel and Mild Metal-Exchange Reaction in the Organometallic Cyclopentadienyl Series: 1,1′-Diaryl 2-Cymantrenyl 1-Butene as an Example

Siden Top,* El Bachir Kaloun, and Gérard Jaouen*

Laboratoire de Chimie Organométalliqu
Ecole Nationale Supérieure de Chimie de Paris
UMR C.N.R.S. 7576, 11, rue Pierre et Marie Curie
75231 Paris Cedex 05, France

Received June 9, 1999

The ($C_5H_5^-$) cyclopentadienyl ligand, because of its size, robustness, and electron count, is one of the most useful coordinating ligands in organometallic chemistry. Its almost ubiquitous nature has led to a number of articles on its functionalization.[1] The variety of preparation methods utilized demonstrates both the absence of a dominant synthetic strategy suitable for all cases and the necessity of seeking new approaches to deal with novel problems. Here we describe a new synthetic approach that gives access, starting from the same substrate, to different families of cyclopentadienyl organometallic complexes whose substituents possess a degree of complexity compatible with the production of fine chemicals.

This approach was dictated by the imperatives inherent in the new field of bioorganometallic chemistry.[2] Our work led us to attempt to introduce various CpM groups onto complicated substrates, for example $CpRe(CO)_3$ onto hormones[3] and antibodies,[4] CpFeCp′, CpCp′$TiCl_2$ onto antitumoral agents,[5] or $CpW(CO)_3R$ onto proteins,[6] for therapeutic, analytical or structural reasons, and we were faced with difficulties in preparation that needed to be solved.

Some years ago, we proposed a mild decomplexation method in the $Cr(CO)_3$ arene series, based on a photochemical oxidation in air and sunlight, at room temperature, producing quantitative amounts of substituted aromatics.[7] Curiously, this idea was not extrapolated to the metal cyclopentadienyls, where the breaking of bonds, either chemically (e.g., with Li on ferrocene)[8] or electrochemically,[9] leads to formation of unstable cyclopentadienyls that are difficult to manipulate. It would be altogether different if during the liberation of Cp^-, the intermediate could be kept in a stable form, for example a cyclopentadiene with four π electrons.

In fact to achieve the hypothetical result in Scheme 1, it is important to answer two preliminary questions concerning both the choice of organometallic and the conditions of decomplexation.

In terms of the initial choice of organometallic, it is clear that a easily oxidizable carbonylated half-sandwich complex, R−CpM(CO)*x*, is preferred for reasons of ease of bond-breaking and simplification of the reaction and the purification process (compared to a R−CpMCp′ sandwich). In addition, this substrate should demonstrate rich reactivity, and in particular should be amenable to the Friedel−Crafts reaction and be manipulable with a minimum of precautions. As for the recovery of the organic intermediate in the form of a cyclopentadiene, this should be possible with a mild decomplexation performed in the presence of a well-chosen protic solvent. These ideas were applied to the cymantrene complex **1** (Scheme 2).

This type of skeleton, with OH instead of OMe groups, recognizes the estrogen receptor and shows a strong estrogenic effect, while with an $-O-(CH_2)_3-NMe_2$ chain in place of an OMe group, it becomes an antiestrogenic entity.[5b] A simple exchange of metals would thus permit changes in the properties (structure, cytotoxicity, radiopharmaceutical properties) of this entity.

Scheme 2 shows the synthetic route used.

The approach consists of a McMurry coupling reaction between **2** and dimethoxybenzophenone. Heating an equimolar mixture of **2**[10] and dimethoxybenzophenone in THF in the presence of the McMurry reagent $Zn/TiCl_4$[11] furnishes compound **1** in a yield of 83% after chromatographic purification.

Compound **1** is a yellow solid, stable in air. It is known that light causes decomposition of manganese cyclopentadienyls, more or less rapidly depending on the compound. To our knowledge the organic products of this decomposition are not normally fully identified. A derivative of cyclopentadiene would be expected but, because dimerizations and polymerizations occur easily via the Diels−Alder reaction, the photochemical decomposition of manganese complexes leads to an unusable mixture of several products. To minimize the quantity of polymers, and especially to trap the liberated cyclopentadiene, the speed of decomplexation can be accelerated by using a UV irradiating lamp of appropriate strength in an ethyl ehter/methanol (1:2) ether mixture. With this

* To whom correspondence should be sent: Prof. G. Jaouen, Laboratoire de Chimie Organométallique, Ecole Nationale Supérieure de Chimie de Paris, UMR C.N.R.S. 7576, 11, rue Pierre et Marie Curie, 75231 Paris Cédex 05, France. Telephone: 33-1 43 26 95 55. Fax: 33-1 43 26 00 61. E-mail: Jaouen@ext.jussieu.fr.

(1) (a) Macomber, D. W.; Hart, W. P.; Rausch, M. D. *Adv. Organomet. Chem*. **1982**, *21*, 1. (b) Janiak, C.; Schumann, H. *Adv. Organomet. Chem*. **1991**, *33*, 291. (c) Okuda, J. *Comments Inorg. Chem*. **1994**, *16*, 185. (d) Coville, N. J.; du Plooy, K. E.; Pikl, W. *Coord. Chem. Rev*. **1992**, *116*, 1. (e) Jutzi, P.; Dahlhauss, J. *Coord. Chem. Rev*. **1994**, *137*, 179. (f) Herberhold, M. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, Germany, 1995. (g) Plenio, H.; Warnecke, A. *Organometallics* **1996**, *15*, 5066. (h) Takahashi, T.; Sun, W.-H.; Xi, C.; Kotora, M. *Chem. Commun*. **1997**, *2069*. i) de Azevedo, C. G.; Boese, R.; Newman, D. A.; Vollhardt, K. P. C. *Organometallics* **1995**, *14*, 4980.

(2) (a) Jaouen, G.; Vessières, A.; Butler, I. S. *Accounts Chem. Res*. **1993**, *26*, 361. (b) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed*. **1998**, *37*, 1634.

(3) Top, S.; El Hafa, H.; Vessières, A.; Quivy, J.; Vessermann, J.; Hughes, D. W. McGlinchey, M. J.; Mornon, J.-P.; Thoreau, E.; Jaouen, G. *J. Am Chem Soc*. **1995**, *117*, 8372.

(4) Salmain, M.; Gunn, M.; Gorfti, A.; Top, S.; Jaouen, G. *Bioconjugate Chem.* **1993**, *4*, 424.

(5) (a) Top, S.; Tang, J.; Vessières, A.; Carrez, D.; Provot, C.; Jaouen, G. *J. C. S. Chem. Commun*. **1996**, 955. (b) Top, S.; Vessières, A.; Jin, L.; Quivy, J.; Leclercq, G.; Croisy, A.; Jaouen, G., **1999**, manuscript submitted for publication.

(6) Salmain, M.; Gorfti, A. Jaouen, G. *Eur. J. Biochem.* **1998**, *258*, 192.

(7) (a) Jaouen, G.; Dabard, R. *Tetrahedron. Lett*. **1971**, 1015. (b) Jaouen, G. Arene Complexes in Organic Synthesis. In *Transition Metal Organometallics in Organic Synthesis*; Alper, H., Ed.; Acad. Press: 1978; Vol. 2, pp 65, Chapter 2. (c) Top, S.; Jaouen, G. *J. Org. Chem*. **1981**, *46*, 18.

(8) Osgerby, J. M.; Pauson, P. L. *J. Chem. Soc*. **1961**, 4605.

(9) Chaloyard, A.; El Murr, N. *Inorg. Chem*. **1980**, *19*, 3217.

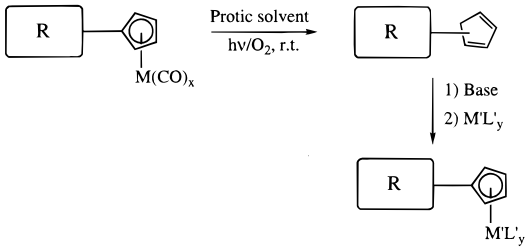
(10) Fischer, E. O.; Fellmann, W. *J. Organomet. Chem*. **1963**, *1*, 191.

(11) McMurry, J. E. *Acc. Chem. Res*. **1983**, *16*, 405.

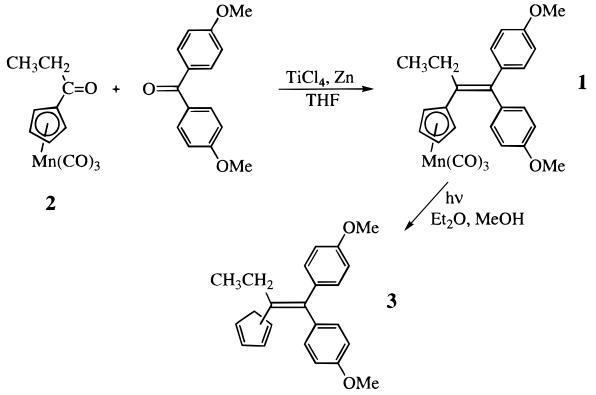
(12) Synthesis of **3** and **1**. 1.71 g (9 mmol) of $TiCl_4$ was added dropwise to a suspension of 1.17 g (12 mmol) of zinc powder in 30 mL THF at 0 °C. The blue mixture obtained was heated at reflux for 2 h, the solution became black. The oil bath was removed. A second solution was prepared by dissolving 0.882 g (3 mmol) of 4, 4′-dimethoxybenzophenone and 0.780 g (3 mmol) propionylcymantrene, **2**, in 15 mL THF. The latter solution was added dropwise to the first solution, and the resulting mixture was then heated again for 2 h. After cooling to room temperature, the mixture was hydrolyzed with 100 mL of a 10% Na_2CO_3 solution. After ether extraction and solvent removal, the crude product, 2.12 g, was chromatographed on silica gel plates (TLC) with ethyl ether/pentane 1/5 as eluent to give 1.25 g of **1** (83% yield). **1** was crystallized from ethyl ether/pentane to give yellow crystals, mp 91 °C. ^{1}H RMN (200 MHz, $CDCl_3$) δ 7.10, d, 7.01, d 6.84, d, 6.80, d (8H, aromatic ring), 4.54, t, 4.47, t (4H, C_5H_4), 3.81, s, 3.80, s (6H, 2 MeO), 2.31, q (2H, CH_2CH_3), 1.05, t (CH_2CH_3). Anal. ($C_{26}H_{23}O_5Mn$): calcd, C, 66.38, H, 4.93; found, C, 66.45, H, 5.00. 0.402 g of **1** were dissolved in 15 mL of technical grade ethyl ether and 30 mL of methanol. The long tube containing the solution was placed in front of the UV lamp (TQ150) for irradiation. Significant gas evolution was observed. After 1 h irradiation, a brown powder precipitated from the solution. The solution was filtered through a filter funnel filled with 0.5 mm thick silica gel and then removed by evaporation. Silica gel TLC with ethyl ether/pentane 1/6 as eluent gave 0.228 g of **3** as a beige oil (81% yield). ^{1}H RMN (200 MHz, $CDCl_3$) δ 7.14−6.67, m (8 H, aromatic ring), 6.40−5.94 (m, 3H of C_5H_5 ring), 3.83, s, 3.82, s, 3.78, s, 3.77, s (6H, 2 MeO), 3.01, m, 2.66, m (2H, CH_2 of C_5H_5 ring), 2.42, q, 2.41, q (2H, CH_2CH_3), 1.02, t, 1.01, t (CH_2CH_3) (mixture of two isomers).

10.1021/ja991915k CCC: $19.00
Published on Web 01/15/2000

Scheme 1



Scheme 2

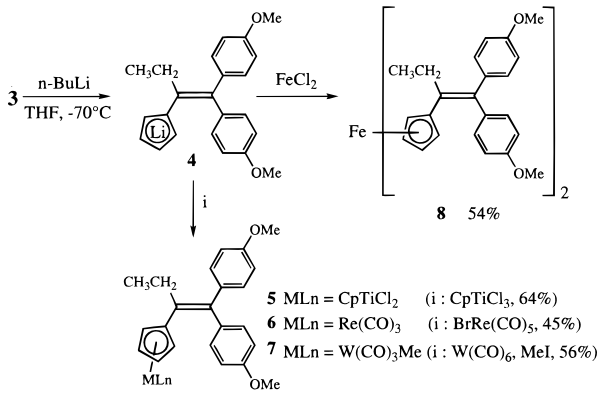


approach we were able to obtain in 1 h the cyclopentadiene **3** in 81% yield after purification.[12] Once pure, **3** proves relatively stable against polymerization, and it can be kept several days under refrigeration. The ^{1}H NMR spectrum showed that **3** is a mixture of at least two diene positional isomers. However, separation is not essential for the rest of the procedure.

The organo-lithium reagent **4** reacts with $CpTiCl_3$, $BrRe(CO)_5$, $W(CO)_6$, and $FeCl_2$ to form compounds **5**, **6**, **7**, and **8**, respectively, in yields ranging from 45 to 64%.[13]

Scheme 3 calls for several comments. It illustrates the fact that

Scheme 3



the cymantrene complex **1** is a stable and unique source for several series of organometallic complexes of varied interest. In this respect the strategy recalls and complements the fixation onto a substrate by using a hydroxylated cyclopentene as a masked cyclopentadiene[1i], a strategy which was not successful in our case. In special cases, nitroferrocenyl compounds,[14] nickelocene[15] and manganocene[16] can also produce free substituted cyclopentadiene. A complex of Re similar to **6** could be used, in radioactive form, as a radiopharmaceutical. There is a current revival of interest in the rapid fixation of isotopes 186 and 188 of Re, and even of ^{99m}Tc, onto bioligands.[3,17] A compound such as **7** containing a heavy metal could find an application in the X-ray structural determination of the receptor protein.[6] However although **6** and **7** are obtainable by other routes, the same cannot be said for **5**. Access to this molecule requires the formation of Cp′$CpTiCl_2$ in the last step of the synthesis, which is permitted by the strategy described here. A biological study of the products derived from **5**, **6**, and **7** is underway. We are also studying the potential and limits of this new decomplexation−recomplexation reaction for a variety of applications.

Acknowledgment. We thank the "Centre National de la Recherche Scientifique" and DeBiopharm company for their financial support, and Barbara McGlinchey for translating the manuscript.

JA991915K

(13) ^{1}H RMN of **5** (200 MHz, $CDCl_3$) 7.20, 7.00, 6.88, 6.81 (4d, 8H, 2 C_6H_4); 6.49 (s, 5H, C_5H_5); 6.27, 6.15 (2m, 4H, C_5H_4); 3.82, 3.81 (2s, 6H, 2MeO); 2.44 (q, 2H, CH_2CH_3); 1.00 (t, 3H, CH_2CH_3). Mass spectrum (DCI) *m*/*z*: 532 $(M + NH_4)^+$, 333. ^{1}H RMN of **6** (200 MHz, $CDCl_3$) δ 7.08, 7.03, 6.85, and 6.80 (4d, 8H, 2 C_6H_4), 5.11, 5.07 (2t, 4H, C_5H_4), 3.80, and 3.79 (2s, 6H, 2 MeO), 2.27, q (2H, CH_2CH_3), 1.07, t (CH_2CH_3). MS (70 eV) *m*/*z*: 602 $[M^+]$, 518 $[M^+ - 3CO]$. ^{1}H RMN of **7** (200 MHz, $CDCl_3$) δ 7.11, 7.03, 6.87, 6.81 (4d, 8H, 2 C_6H_4), 5.14, 4.96 (2t, 4H, C_5H_4), 3.81, s, 3.80, s (6H, 2 MeO), 2.32, q (2H, CH_2CH_3), 1.05, t (CH_2CH_3). MS (70 eV) *m*/*z*: 614 $[M^+]$, 529, 515 $[M^+ - 3CO - Me]$, 484.^{1}H RMN of **8** (200 MHz, $CDCl_3$) δ 7.07, 6.94, 6.85, 6.76 (4d, 8H, 2 C_6H_4), 4.05 and 3.80 (2m, 4H, C_5H_4), 3. 81 and 3.80 (2s, 6H, 2 MeO), 2.59 (q, 2H, CH_2CH_3), 1.02 (t, 3H, CH_2CH_3). MS (70 eV) *m*/*z*: 718 $[M^+]$, 387.

(14) Salter, R.; Pickett, T. E.; Richards, C. J. *Tetrahedron Asymmetry* **1998**, *9*, 4239.

(15) Moberg, C. *J. Organomet. Chem.* **1976**, *108*, 125.

(16) Unseld, D.; Krivykh, V. V.; Heinze, K.; Wild, F.; Artus, G.; Schmalle, U.; Berke, H. *Organometallics* **1999**, *18*, 1525.

(17) (a) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, P. A.; Abram, U.; Kaden, T. A. *J. Am. Chem Soc.* **1998**, *120*, 7987. (b) Minutolo, F.; Katzenellenbogen, J. A. *Organometallics* **1999**, *18*, 2519.