New polymer-bound haloarene chromium dicarbonyl isocyanide complexes: a successful study validating their use in solid-phase chemistry

Stefano Maiorana,[a,*] Clara Baldoli,[a] Emanuela Licandro,[a] Laura Casiraghi,[a] Elisabetta de Magistris,[b,*] Alfredo Paio,[b] Stefano Provera[b] and Pierfausto Seneci[b]

[a]*Dipartimento di Chimica Organica e Industriale, Universita' di Milano e CNR-Centro Studio Sintesi, Stereochimica Speciali Sistemi Organici, Via C. Golgi 19, I-20133 Milano, Italy*
[b]*GlaxoWellcome Medicine Research Centre, Via Fleming 4, I-37135 Verona, Italy*

Abstract

New fluorobenzene chromium dicarbonylisocyanide complexes have been synthesized and evaluated in terms of their 'in solution' reactivity towards some nucleophiles. For the first time the polymer-bound isocyanides have been found to be valuable ligands for anchoring haloareneCr(CO)$_3$ complexes by means of their substitution for a CO group. The supported fluorobenzene complex reacted with nitrogen-nucleophiles. © 2000 Elsevier Science Ltd. All rights reserved.

New interest has recently emerged concerning the study of polymer-bound organometallics and their application in solid-phase chemistry, mainly directed toward the preparation of supported catalysts or reagents[1] in view of their exploitation in combinatorial chemistry technologies.[2] We have recently published the first synthesis of a series of polymer-bound Fischer chromium carbenes[3] as potential traceless linkers. Arene chromium tricarbonyl complexes can also be used as viable scaffolds in solid-phase and combinatorial chemistry applications, because they undergo a wide range of 'in-solution reactions', including nucleophilic or electrophilic attack, regio- and stereoselective transformations involving the ring or side chain carbon atoms. Their versatile chemistry has been extensively exploited in organic synthesis[4] including biotransformations.[5] In principle, a chromium tricarbonyl arene complex possesses two positions suitable for anchorage to a polymeric support as shown in structures **A** and **B**. Structure **A** is particularly suitable for combinatorial chemistry purposes because the metal fragment is a 'traceless linker'[6] that allows a greater number of diversifications on the aromatic ring.

* Corresponding authors. Fax: +39 02 7063 6857; e-mail: stefano.maiorana@unimi.it; fax: +39 045 9218196; e-mail: edm@glaxowellcome.co.uk.
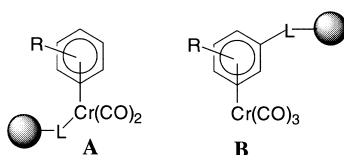
The possibility of using a metal carbonyl fragment to attach an aromatic ring to a solid support has recently been considered by other authors.[7–9] Gibson has successfully bound chromium tricarbonyl complexed aryl ketones to a polymer-supported triphenylphosphine.[8,9] However, it is worth noting that the polymer-bound arene complexes prepared by Gibson have the reactive functional group in a position far from the complexed aromatic ring, and so the peculiar reactivity of the aromatic ring or its substituents in such complexes has not yet been investigated. It is known from 'in-solution' chemistry that the presence of a phosphine group adjacent to the metal greatly reduces the reactivity of the aromatic ring to nucleophilic attack except in particular cases.[7] For this reason, we considered the ligands whose electronic properties are more similar to those of the CO group. Maleimido[10] and isocyanide groups appeared to be suitable candidates for this purpose, particularly because both could, in principle, be bound to a resin. Some preliminary experiments showed that a maleimido ligand was not suitable for solid-phase chemistry, we then moved on to consider isocyanide ligands. A series of arene chromium dicarbonyl N-acylisocyanide complexes have already been synthesized and studied in solution.[11,12] As acylisocyanide complexes could themselves be reactive toward nucleophiles, we turned our attention to N-alkyl or aryl isocyanide complexes. Few examples of such complexes are known,[13] and their reactivity has not been investigated. We started by studying the in-solution synthesis, of haloarene chromium dicarbonyl isocyanide complexes and their reactivity towards nucleophiles. Two commercially available isocyanides (2,6-dimethylphenyl- and benzylisocyanide **2** and **3**) were used in a two-step photochemical exchange reaction[14] for a CO ligand of fluorobenzeneCr(CO)$_3$ complex **1** (Scheme 1).

In a typical experiment, a toluene solution (40 mL) of complex **1** (1 mmol) was irradiated using a 125 W high-pressure Hg lamp at room temperature in the presence of cyclooctene (22 equiv.). The appropriate isocyanide **2** or **3** (1 mmol) was then added, and the solution heated to 55°C until the isocyanide was completely reacted. After standard work-up, the very stable complexes **4** and **5** were recovered by crystallization in good yields.[15] The reactivity of **4** in aromatic nucleophilic substitutions was then tested with a series of different nucleophiles **6a–e**. (Scheme 2)

The reactions were run in DMF at room temperature using an equimolar amount of nucleophiles **6c–e**, with amines **6a,b** being used as solvent. Complexes **7a–e** were isolated in good yields and completely characterized.[16] In addition to highlighting a new aspect of the chemistry of such organometallics, the remarkable reactivity of complex **4** also represents a good premise for their
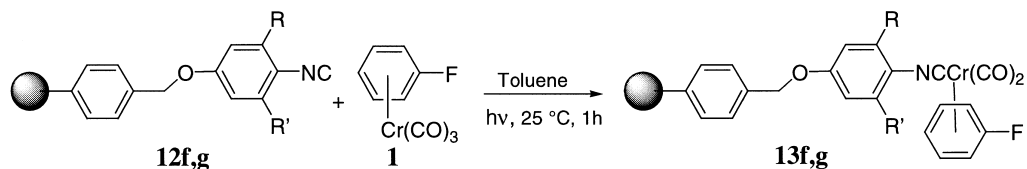

Scheme 1.

Scheme 2.

f: R=R'=H; g: R=R'=CH₃
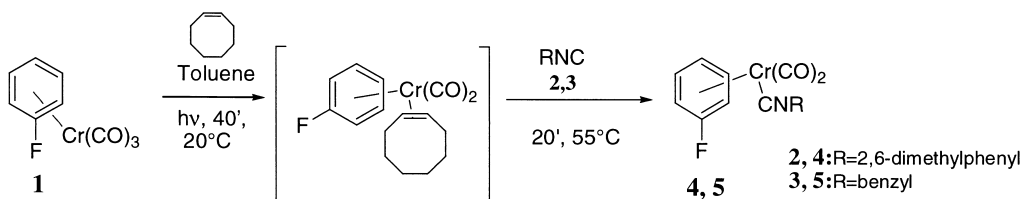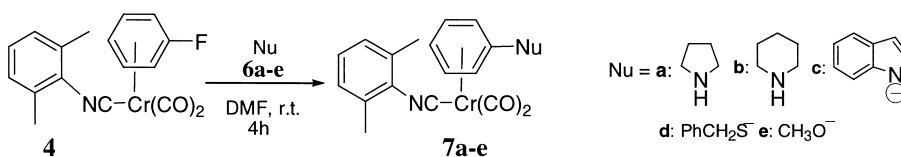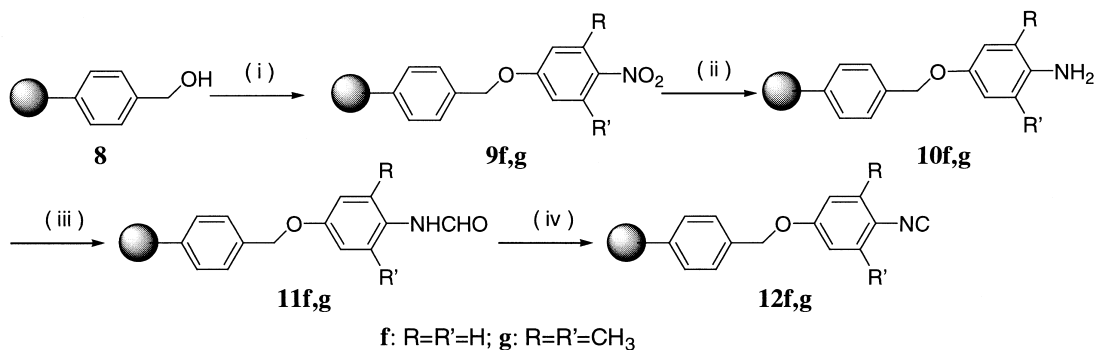
Scheme 3. *Reagents and conditions*: (i) hydroxymethylpolystyrene resin **8** (1 equiv.), PPh$_3$ (3 equiv.), DEAD (3 equiv.), *p*-NO$_2$ArOH (3 equiv.), THF, rt, 24 h; (ii) **9f,g** (1 equiv.), SnCl$_2$2H$_2$O (9 equiv.), DMF, rt, 24 h; (iii) **10f,g** (1 equiv.), Ac$_2$ O/HCO$_2$H (30 equiv.), THF, 60°C, 2 h; (iv) **11f,g** (1 equiv.), PPh$_3$ (5.5 equiv.), Et$_3$N (11 equiv.), CCl$_4$ (5.5 equiv.), CH$_2$Cl$_2$, rt, 36 h

application in solid-phase synthesis. We therefore approached the problem of preparing the appropriate isocyanide resins onto which to bind the arene complexes. Some polymer-bound isocyanides are reported in the literature[17] and examples of their use to anchor the organometallic species are known.[18] A silica-bound methylbenzoate chromium dicarbonyl isocyanide complex has also been reported.[19] We first synthesized the new polymer-bound isocyanide ligands **12f,g** from the hydroxymethyl polystyrene resin **8** as shown in Scheme 3.[17]

Both the resins **12f** (0.864 mmol/g) and **12g** (0.935 mmol/g) showed a sharp peak in the IR spectrum at 2122 cm^{-1} due to the isocyanide group.

The fluorobenzeneCr(CO)$_3$ complex **1** was supported on the resin by means of 1 h direct photochemical irradiation[20] of **12f,g** (1 mmol) suspended in a deoxygenated toluene solution (15 mL) of complex **1** (6 mmol) (Scheme 4). Subsequent filtration, MeOH/DMF/DCM washing and drying under vacuum gave the dark yellow resins **13f,g** which were subsequently characterized.[21]

Finally, in order to carry out a preliminary evaluation of the reactivity of polymer-bound fluorobenzene isocyanide complexes, resin **13f** (1 mmol) was reacted at room temperature in DMF with pyrrolidine (20 equiv., *c* 2.8 M), piperidine (25 equiv., *c* 3.0 M), and indole *N*-anion

Scheme 4.
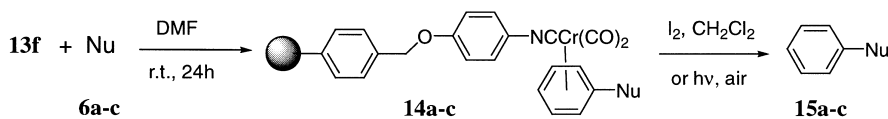
Scheme 5.

(10 equiv., c 0.5 M) (Scheme 5). The supported complexes **14a–c** thus obtained (which had no ^{19}F NMR signal) were decomplexed and cleaved with I$_2$ in dichloromethane for 1 h at room temperature, or by exposure to air and sunlight for 2 days. Products **15a–c** were recovered from the cleavage solution in 80% average yields. In conclusion, polymer-bound isocyanides can be considered suitable ligands for supporting haloarene chromium carbonyl complexes.

In more detail, the supported fluorobenzene derivative **13f** was prepared and found to undergo nucleophilic substitution with nitrogen nucleophiles, thus showing that the reactivity of the aromatic ring is only slightly affected by the replacement of a carbonyl group with an isocyanide moiety.

Acknowledgements

References

1. Bailey, D. C.; Langer, S. H. *Chem. Rev.* **1981**, *81*, 110–148. Andres, C. J.; Whitehouse, D. L.; Deshpande, M. S. *Curr. Opin. Chem. Biol.* **1998**, *2*, 353–368. Kingsbury, C. L.; Mehrman, S. J.; Takas, J. M. C*urrent Organic Chemistry* **1999**, *3*, 497–555.
2. Lorsbach, B. A.; Kurth, M. *Chem. Rev.* **1999**, *99*, 1549–1581.
3. Maiorana, S.; Seneci, P.; Rossi, T.; Baldoli, C.; Ciraco' M.; De Magistris, E.; Licandro, E.; Papagni, A.; Provera, S. *Tetrahedron Lett.* **1999**, *40*, 3635–3638.
4. Semmelhack, M. F. In C*omprehensive Organometallic Chemistry II*, vol. 12; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: New York, 1995; pp. 979–1038. Davies, S. G. *ibid.* pp. 1039–1070.
5. Baldoli, C.; Maiorana, S.; Del Buttero, P.; Ottolina, G.; Riva, S. *Tetrahedron: Asymmetry* **1998**, *9*, 1497–1504, and references cited therein.
6. James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946.
7. Semmelhack, M. F.; Hilt, G.; Colley, J. H. *Tetrahedron Lett.* **1998**, *39*, 7683–7686.
8. Gibson, S. E.; Hales, J. N.; Peplow, M. A. *Tetrahedron Lett.* **1999**, *40*, 1417–1418.
9. Gibson, S. E.; Hales, J. N.; Peplow, M. A.; Comely, A. C. International Patent, 2000, WO 00/07966.
10. Nasielski, J.; Denisoff, O. *J. Organomet. Chem.* **1975**, *102*, 65–70.
11. Fehlhammer, W.; Fritz, M. *Chem. Rev.* **1993**, *93*, 1243–1280.
12. Jaouen, G.; Le Maux, P.; Simmoneaux, G. *J. Organomet. Chem.* **1981**, *217*, 61–77. Dabard, R.; Jaouen, G.; Simmoneaux, G.; Cais, M.; Kohn, D. H.; Lapid, A.; Tatarsky, D. *J. Organomet. Chem.* **1980**, *184*, 91–101. Jaouen, G.; Simmoneaux, G.; Le Maux, P.; Dabard, R. *J. Org. Chem.* **1979**, *18*, 3167–3170.
13. Strohmeier, W.; Hellmann, H. *Chem. Ber.* **1964**, *97*, 1877–1885. Harris, G. W.; Albers, M. O.; Boeyens, J. C. A.; Coville, N. *Organometallics* **1983**, *2*, 609–614. Lentz, D.; Marschall, *Z. Anorg. Allg. Chem.* **1991**, *593*, 181–184.
14. Jaouen, G. *Tetrahedron Lett.* **1973**, *52*, 5159–5162.
15. The analytical data of **4** and **5** are consistent with the assigned structures: compound **4** (80%) IR ν_{CN}, (cm^{-1} CCl$_4$) 2056; NMR (ppm, C$_6$D$_6$): ^{19}F $= -136$; ^{1}H arom. Cr(CO)$_3$: 4.5–4.6 (m, 1H), 5.0–5.2 (m, 2H), 5.2–5.3 (m, 2H); m.p.

(pentane) 107–109°C; compound **5** (70%) IR ν_{CN} (cm^{-1} CCl$_4$) 2097; NMR (ppm, C$_6$D$_6$): ^{19}F = –137; ^{1}H arom. Cr(CO)$_3$: 4.4–4.5 (m, 1H), 4.9–5.0 (m, 2H), 5.05–5.1 (m, 2H); m.p. (pentane) 50–52°C. Using isocyanide **2**, we also prepared the complexes of benzene (**4a**), and 1,2- and 1,3-dichlorobenzene (**4b,c**). Compound **4a** (63%), IR ν_{CN} (cm^{-1} CCl$_4$) 2045, m.p. (pentane) 114–116°C; compound **4b** (95%), IR ν_{CN} (cm^{-1} CCl$_4$) 2062, m.p. 92–93°C; compound **4c** (88%), IR ν_{CN} (cm^{-1} CCl$_4$) 2064, m.p. 105–106°C.

16. Selected data of **7**: [(Y, m.p. (pentane), IR ν_{NC} (CCl$_4$)]. Compound **7a**: 88%, 144–146°C (dec.), 2002 cm^{-1}; compound **7b**: 60%, 95–97°C, 2009 cm^{-1}; compound **7c**: 95%, oil, 2053 cm^{-1}; compound **7d**: 81%, oil, 2050 cm^{-1}; compound **7e**: 66%, 102–104°C, 2042 cm^{-1}.

17. Hulme, C.; Peng, J.; Morton, G.; Salvino, M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227–7230. Bheemashankar, A. K.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5633–5636. Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 7489–7492.

18. Howell, J. A.; Berry, M. *J. Chem. Soc., Chem. Commun.* **1980**, 1039–1040. Giannandrea, R.; Mastrorilli, P.; Zaccaria, G.; Nobile, C. F. *J. Mol. Cat. A: Chem.* **1996**, *109*, 113–117.

19. Andersson, C.; Larsson, R.; Yom-Tov, B. *Inorg. Chim. Acta* **1983**, *76*, L185–187.

20. Attempts to anchor complex **1** onto resin **12f,g** 'via' cyclooctene intermediate gave **13f,g** in very low yields.

21. Resin **13f**: loading 0.296, FT-IR (cm^{-1}: 1877, 2006 ν_{CO}, 2054, 2141 ν_{NC}), ^{19}F NMR (C$_6$D$_6$, ppm:–136.3) and ^{1}H MAS–NMR (C$_6$D$_6$, ppm: 4.9, 5.1, 5.2, 7.37, 7.39). Compound **13g**: loading 0.521, FT-IR (cm^{-1}: 1864, 2000 ν_{CO}, 2054, 2136 ν_{NC}), ^{19}F NMR (C$_6$D$_6$, ppm: –138.4) and ^{1}H MAS-NMR (C$_6$D$_6$, ppm: 2.2, 5.2, 5.3).