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Synthesis of Polymer-Bound Fischer Chromium Alkoxy and Aminocarbene Complexes

Stefano Maiorana,*[a†] Pierfausto Seneci,*[b] Tino Rossi,[b] Clara Baldoli,[a] Manuela Ciraco',[a] Elisabetta de Magistris,[b] Emanuela Licandro,[a] Antonio Papagni,[a] and Stefano Provera[b]

[a]Dipartimento di Chimica Organica e Industriale e Centro CNR. Universita' degli Studi di Milano, Via C. Golgi 19, I-20133 Milano, Italy. [b]GlaxoWellcome Medicines Research Centre, Via Fleming 4, I-37100 Verona, Italy

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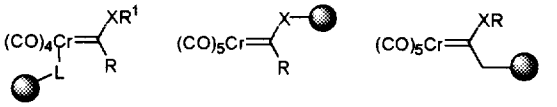
Abstract: A series of polymer-bound Fischer chromium alkoxy and amino carbene type I complexes were synthesized by the thermal exchange of a CO ligand in chromium pentacarbonyl carbenes **2** with triphenyl phosphine resin **1**. The supported alkoxycarbene **3a** proved to be reactive towards primary amines, and afforded the polymer-bound aminocarbenes **5**. Type **II** aminocarbenes were also prepared by reacting polymer-supported aminoacids with alkoxycarbene **2a**.

Keywords: Solid phase synthesis, polymer-bound Fischer carbenes, phosphino chromium carbonyls

The simple and versatile chemistry of Fischer carbene complexes has been widely exploited for organic synthetic applications,[1] but its particular and complementary nature in terms of reactivity and stereoselectivity is especially important in relation to the behaviour of the corresponding isolobal esters or amides. The strong electron-withdrawing power of the $Cr(CO)_5$ moiety makes the carbene carbon electrophilic, and the hydrogens α to this carbon strongly acidic. Deprotonation is easily performed and the resulting "metal enolate" is usually very reactive with electrophilic reagents, thus allowing the preparation of a wide range of new complexes. Solid phase organic synthesis is of growing importance because of its potential application to combinatorial chemistry,[2] which has rapidly emerged as a powerful strategy for the discovery of lead compounds. To the best of our knowledge Fischer carbenes have never previously been used for these purposes,[3] and so we decided to generate polymer-bound metal-carbene systems in order to study the solid phase chemistry of Fischer complexes with the aim of creating libraries of organic compounds. In principle, Fischer complexes have three positions suitable for anchorage to a polymeric skeleton, as shown in formulas **I**, **II** and **III**, in which X can be any appropriate heteroatom.



I **II** **III**

Structure **I** is particularly suitable for the purposes of combinatorial chemistry in view of the sequential structural diversification of the Fischer carbene. Moreover, the use of one of the chromium ligands (L, structure

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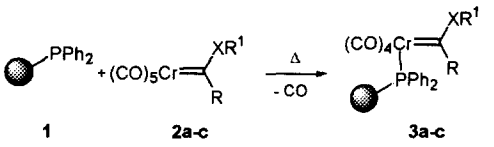
I) to hook the carbene onto the solid phase could lead to a class of traceless linkers.[4] Structures **II** and **III** also have some potential for developing interesting solid phase organic synthetic routes.

We report here the first example of polymer-bound Fischer carbenes of type **I** and **II**. Following one of the known methods used in solution for preparing triphenylphosphine metal tetracarbonyl carbenes,[5] our approach to the synthesis of compounds **I** used the thermal exchange of a CO ligand in complexes **2a-c** with triphenylphosphine resin **1** to give polymer-bound carbenes **3a-c**[6] (Scheme 1). In a typical experiment, deoxygenated toluene (2.7 ml) was added under argon to a mixture of **1**[7] (0.432 mmol, loading 1.21 mmol/g) and **2** (1.08 mmol). The suspension was gently stirred at 50° C for 5 hrs, and then cooled to room temperature and filtered. The resin was repeatedly washed with CH_2Cl_2 until a colorless washing solution was obtained, and then dried under vacuum (Table 1). ^{31}P NMR and IR proved to be easy analytical means for checking the resin-bound products **3a-c**, which were detected only as *cis* isomers. As shown in Table 1, the best yield was obtained in the case of methoxymethyl carbene **3a**.[8]

Scheme 1



1 **2a-c** **3a-c**

a: $XR^1 = OCH_3$, $R = CH_3$ **b**: $XR^1 = OCH_3$, $R = Ph$ **c**: $XR^1 =$  , $R = CH_3$

Table 1

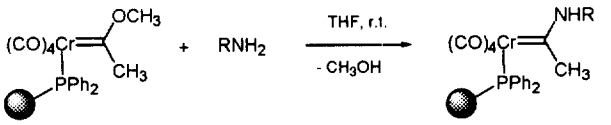
Product	Yield[a] (%)	^{31}P, ppm (C_6D_6)	IR ν_{CO}, cm^{-1}, (nujol)
3a	72	58.3	2008; 1888
3b	58	55.4	2010; 1887
3c	25[7]	58.9	1991; 1938; 1867

[a] Determined by ^{31}P-NMR analysis. [§]

In order to begin evaluating the reactivity of polymer-bound alkoxycarbenes, **3a** was submitted to aminolysis reactions with a series of amines **4a-d.** The reaction was run at room temperature and afforded the supported amino carbenes **5a-d** in good yields[9] (Scheme 2). It is worth noting that the ^{31}P signals for compounds **5a-d** (Table 2) are shifted about 3 ppm downfield from the ^{31}P signal of **3a**; this difference is diagnostic and allows solid phase reaction yields to be easily evaluated. In addition, enriched phenethyl-^{13}C amine **4a** was used to prepare **5a**: this enabled us to make a ^{13}C-NMR analysis of **5a,** which showed a single carbon atom signal at 48.4 ppm, thus also indicating that a single rotamer of this aminocarbene was probably present (at least at room temperature). Scheme 2 shows the first example of the solid phase reactions of a polymer-bound Fischer carbene. This is therefore a promising test of the reactivity of alkoxycarbenes **3**, and is currently the best way of synthesising polymer-bound amino carbenes. In fact the direct thermolysis of amino carbene **2c** with resin **1** gave low yields of **3c** (Table 1). Moreover to verify the possibility of recovering the

organic ligand from the resin, carbene **5d** was treated with I_2 in CH_2Cl_2 solution for 1 h at room temperature. The corresponding *N*-4-trifluoromethylphenyl acetamide was quantitatively isolated from the organic solution.

Scheme 2



3a **4a-d** **5a-d**

a : R = $^{13}CH_2CH_2Ph$ **c** : R = CH_2Php-OCH_3
b : R = CH_2Ph **d** : R = CH_2Php-CF_3

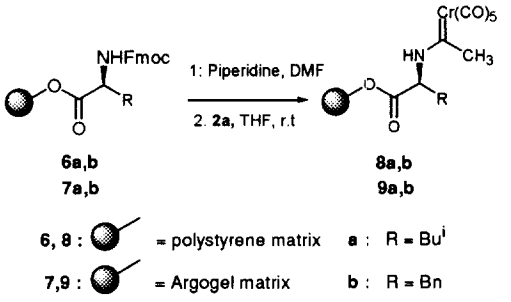
Table 2

Product	Yield[a] (%)	^{31}P, ppm (C_6D_6)	IR ν_{CO}, cm^{-1}, (nujol)
5a[b]	86	61.3	1994; 1937; 1865
5b	100	60.8	1996; 1937; 1872
5c	82	61.0	1995; 1937; 1867
5d[c]	100	60.9	1996; 1937; 1874

[a] Determined by ^{31}P-NMR analysis. [b] ^{13}C NMR δ (C_6D_6): 48.4 .
[c] ^{19}F NMR δ (C_6D_6): -63.2 .

As far as the compounds of general formula **II** are concerned, their preparation started from supported Fmoc-protected leucine and phenylalanine grafted onto a polystyrene (**6a,b**) or Argogel matrix (**7a,b**) [10] (Scheme 3). After the elimination of the Fmoc protecting group,[11] a 0.16 M solution of carbene **2a** (1.2 ml for **6** and 0.85 ml for **7**) in THF was added to the dry resins, and the slurry was slowly stirred at room temperature for 3 hours. The resulting resin was filtered, rinsed with DMF, MeOH and CH_2Cl_2 and dried under vacuum. The immobilized aminocarbenes **8a,b** and **9a,b** were then obtained and characterized.[12]

Scheme 3



6a,b **8a,b**
7a,b **9a,b**

6, 8 : = polystyrene matrix **a** : R = Bu^i
7,9 : = Argogel matrix **b** : R = Bn

In conclusion, we have demonstrated that polymer-bound metal carbene complexes of type **I** and **II** can be readily prepared. Aminolysis of the supported oxacarbene **3a** affords a series of polymer-bound amino carbenes **5**. This represents the first example of the extension of the aminolysis reaction of oxacarbenes to a solid phase format.The newly prepared carbenes are resin-bound through one of the chromium ligands (compounds **3** and

5) or the heteroatom (compounds **8** and **9**). When stored under nitrogen at -20° C, the supported complexes are stable for several weeks.These polymer-bound organometallics appear to be suitable for developing solid phase synthetic chemistry and the reactivity of polymer-bound carbene complexes is now being further studied in our laboratories.

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† E-mail: MAIOR@ICIL64.CILEA.IT

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6. Unlike in solution[5b], all of the attempts to generate carbene complexes **3** from resin-bound $PPh_2Cr(CO)_5$ failed. Polymer-bound $PPh_2Cr(CO)_5$ was prepared by heating resin **1** with $Cr(CO)_6$ (80°C in DMF for 10h).
7. Resin **1** was obtained as reported by M. Bernard, W. T. Ford, *J. Org. Chem.* **1983**, *48*, 326-332, starting from PL-PBS, (2 mmol/g), Polymer Laboratories Inc.
8. All of the new compounds gave satisfactory elemental analysis.(Cr, N, P). ^{1}H MAS-NMR $\delta(CD_2Cl_2)$: **3a** 2.46 (bs, 3H, CH_3); 4.01 (bs, 3H, OCH_3). Compound **3c** proved to be the least stable of the polymer-bound carbenes, which could account for the low reaction yield.
9. The reaction was run by adding a THF solution of the appropriate amine **4** (1 ml of 0.6M THF solution) to dry **3a** (100 mg, loading 0.72 mmol/g). The slurry was slowly stirred for about 6 hrs at 23 °C, and its colour changed from deep red to yellow orange. The resin was filtered and rinsed with DMF, CH_3OH, CH_2Cl_2, and dried. . ^{1}H MAS-NMR $\delta(CD_2Cl_2)$: **5a** 2.26 (bs, 3H, CH_3); 2.49 (bs, 2H, CH_2Ph); 3.05 (bd, 2H, $J_{C\text{-}H}$ = 140 Hz, CH_2N); 8.07 (bs, 1H, NH). **5b** 2.45(bs, 3H, CH_3); 4.06 (bs, 2H, CH_2); 8.25 (bs, 1H, NH). **5c** 2.45 (bs, 3H, CH_3); 3.69 (bs, 3H, OCH_3); 3.99 (bs, 2H, CH_2); 8.17 (bs, 1H, NH). **5d** 2.45 (bs, 3H, CH_3); 4.12 (bs, 2H, CH_2); 8.25 (bs, 1H, NH).
10. Preparation of resins **6,7**: In a syringe, a solution of the appropriate aminoacid (10 eq.) in dry DMF (10 vol.) was added to the dry resin (1eq) **6** (Hydroxymethyl polystyrene, 0.87 mmol/g, Novabiochem) or **7** (Argogel™-OH, 0.45 mmol/g, Argonaut Technologies Inc.). After the resin was swollen, diisopropyl carbodiimide (10 eq.) and DMAP (0.2) were added to the slurry, which was stirred at room temperature for 24 hrs, filtered and the resin rinsed with DMF (5x20 ml) and CH_2Cl_2 (5x20 ml). The resin was then suspended in 10% (v/v) of Ac_2O/DMF solution (20 ml) and DMAP (0.2eq), stirred at room temperature for 15 hrs, and then filtered and rinsed as above.[9] Loading was evaluated using the Fmoc number.[13]
11. The Fmoc group was removed by treating resins **6a,b** (120 mg,0.66 mmol/g) and **7a,b** (120 mg, 0.38 mmol/g) with an excess of 20% solution of piperidine in DMF at room temperature for 1h.
12. FT-IR (nujol, cm^{-1}):. **8a**, 2055; 1971; 1916; 1740. **8b**, 2055; 1972; 1916; 1740. **9a**, 2053; 1970; 1928; 1741. **9b**, 2053; 1970; 1923; 1741.
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