

Chromium Carbonyl Complexes as Novel Traceless Linkers

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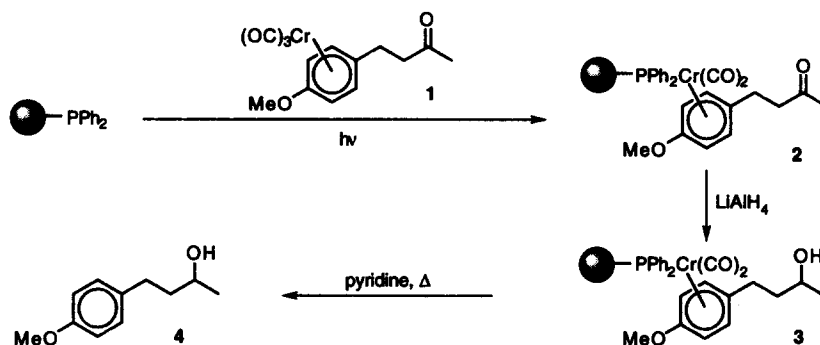
Abstract: Substrates containing aromatic rings have been attached to 'polymer supported triphenylphosphine' using a chromium carbonyl linker, chemically manipulated, and released from the polymer to demonstrate the use of π -arene chromium complexes as traceless linkers. © 1999 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry and multiple parallel synthesis (MPS) are very valuable methods of generating large numbers of molecules which can subsequently be screened for useful properties or effects. The development of combinatorial chemistry and MPS has been greatly facilitated by the use of solid phase synthesis in which substrate molecules are covalently attached to a solid support. Traditional methods for attaching the growing organic molecule to the solid support rely heavily on ester and amide functionality. While this may be suitable in some cases, in other cases the functional group left in the product is detrimental to the desired biological or chemical activity of the target molecule. For this reason, there has been significant interest in recent years in developing so-called 'traceless linkers'.¹ In a typical example, aromatic rings have been linked to solid supports by aryl-silicon bonds which are created by lithium-halogen exchange and chlorosilane quenching of an aryl bromide. After combinatorial development of the substrate, the aryl-silicon bonds are cleaved using anhydrous HF to leave aryl-hydrogen bonds in the products.^{1c}

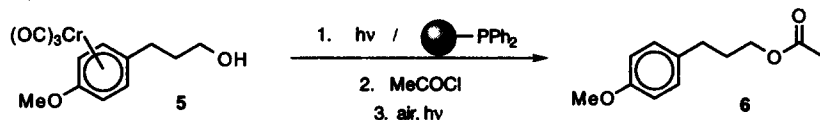
Attachment of organic molecules to a solid support through π -complexation with a polymer-bound transition metal is attractive in so much as the linkage would be truly traceless. In principle an aromatic ring, a 'functional group' present in many potential substrates for combinatorial chemistry, may be attached and removed from a chromium carbonyl fragment without any modification of the aromatic ring whatsoever. Semmelhack and coworkers have recently discussed this possibility.² We now present preliminary results of our work in which we have demonstrated that a π -arenechromium carbonyl complex can indeed be used as a traceless linker.

Commercially available 4-(4-methoxyphenyl)-2-butanone was heated with $\text{Cr}(\text{CO})_6$ in $\text{Bu}_2\text{O}/\text{THF}$ (10:1) to give the novel complex **1** as yellow air-stable crystals in 80% yield. An exploratory set of reactions was then carried out to determine whether or not this arene complex could be attached to a polymer support, manipulated and removed from the support. Thus 1.1 equivalents of complex **1** was irradiated in the presence of commercially available 'polymer supported triphenylphosphine' in THF. Subsequent filtration, washing and drying of the polymer gave a brown powder which was characterised as predominantly **2** on the basis of its IR and ^{31}P NMR spectra. The former contained strong absorptions at 1870, 1802 cm^{-1} [$\text{Cr}(\text{CO})_2\text{PPh}_3\text{C}_6\text{H}_5\text{OMe}^3$ strongly absorbs at 1886 and 1827 cm^{-1}] and 1710 cm^{-1} , whilst the latter contained a resonance at δ 90 [$\text{Cr}(\text{CO})_2\text{PPh}_3\text{C}_6\text{H}_5\text{OMe}$ resonates at δ 91.9³]. The ^{31}P NMR spectrum revealed that the polymer coverage with

the arene chromium dicarbonyl complex was ~40%, the remainder of the sites being made up of polymer- $\text{PPh}_2\text{Cr}(\text{CO})_5$ ($\delta = 56$, 20%), polymer- $\text{P}(\text{O})\text{Ph}_2$ ($\delta = 29$, 10%) and polymer- PPh_2 ($\delta = -5$, 30%).⁴ Polymer 2 was then reduced with LiAlH_4 giving, after work-up, a dark yellow powder which did not absorb at 1710 cm^{-1} . The ^{31}P NMR spectrum of the reduced material revealed that the loading of 3 on the polymer was 25% thus representing a yield for this step of 62%. The reduction product was released from the polymer by heating in pyridine for 2 h. Filtration, washing the polymer with THF and Et_2O , and concentration of the washings gave alcohol 4 of >95% purity. The yield for the release of 4 from the polymer was 90%.



In a second series of experiments, commercially available 3-(4-methoxyphenyl)propionic acid was reduced (LiAlH_4 , 94%) to its alcohol, which was readily converted to the novel yellow crystalline air-stable chromium complex 5 in good yield [$\text{Cr}(\text{CO})_6$, 98%]. Irradiation of 1.1 equivalents of complex 5 in the presence of 'polymer supported triphenylphosphine' gave a brown powder which analysis indicated had a ~30% loading of chromium arene complex. Acetylation produced material which within experimental error had the same loading of chromium arene complex as its precursor *i.e.* the acetylation had proceeded in essentially quantitative yield. In this case release of the organic product from the polymer was achieved by air oxidation which proceeded in 70% yield to give ester 6.



In summary, we have demonstrated the use of transition metal π -complexes as traceless linkers by 'traceless' attachment of the arene of a reaction substrate to a phosphine-containing polymer *via* a chromium carbonyl linker. Experiments to optimise and broaden the scope of this chemistry are underway.

- (a) A.R. Brown, D.C. Rees, Z. Rankovic and J.R. Murphy, *J. Am. Chem. Soc.*, 1997, **119**, 3288 and references therein; (b) P.H.H. Hermkens, H.C.J. Ottenheijm and D.C. Rees, *Tetrahedron Report No. 418*, *Tetrahedron*, 1997, **53**, 5643 and references therein; (c) M.J. Plunkett and J.A. Ellman, *J. Org. Chem.*, 1997, **62**, 2885; (d) L.M. Gayo and M.J. Suto, *Tetrahedron Lett.*, 1997, **38**, 211; (e) X. Zhao and K.D. Janda, *Tetrahedron Lett.*, 1997, **38**, 5437.
- M.F. Semmelhack, G. Hilt and J.H. Colley, *Tetrahedron Lett.*, 1998, **39**, 7683.
- T.E. Bitterwolf, *Polyhedron*, 1988, **7**, 1377.
- $\text{PPh}_3\text{Cr}(\text{CO})_5$, $\delta_{\text{P}} = 55.3$, S.O. Grim, D.A. Wheatland and W. McFarlane, *J. Am. Chem. Soc.*, 1967, **89**, 5573; polymer- $\text{P}(\text{O})\text{Ph}_2$, $\delta_{\text{P}} = 28.8$, polymer- PPh_2 , $\delta_{\text{P}} = -6.3$, M. Bernard and W.T. Ford, *J. Org. Chem.*, 1983, **48**, 326.