Polymer supported cobalt carbonyl complexes as novel traceless alkyne linkers for solid-phase synthesis

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The immobilisation of functionalised alkynes onto 'polymer-bound triphenylphosphine', their chemical manipulation and subsequent release has been demonstrated for the first time, thus illustrating that cobalt carbonyl complexes can be used as 'traceless' π-alkyne linkers.

Solid-phase synthesis continues to excite ever-greater interest,[1] particularly as a means to facilitate the elaboration of compound libraries *via* combinatorial chemistry.[2] Of especial importance to this technology is the linker, the structural motif which joins the substrate under chemical manipulation to the polymeric support. A legacy of solid-phase peptide synthesis is the release of compounds bearing carboxylic acid or amide functionality derived from an ester linkage. While appropriate for some target molecules, this has rather limited appeal in a more general synthetic sequence. Efforts to address this problem have stimulated the evolution of 'traceless' linkers,[3] those which leave minimal vestige of the solid support upon release of the product. A good example is the tethering of compounds containing an aromatic ring by means of an aryl–silicon bond.[4] The linker is cleaved to reveal only a hydrogen atom at the former aromatic linkage site.

In this respect, transition metals offer a very alluring solution: the temporary and reversible immobilisation of an unsaturated substrate *via* π-interactions to the molecular scaffold dispenses with the functional group transformation necessarily required by a covalent system. In recent months this concept was illustrated for the first time with the immobilisation of arenes through a chromium carbonyl linker.[5] Liberation of the product by oxidative decomplexation returns the aromatic ring unchanged.

Surprisingly, there currently exists no method for the release of an alkyne from a polymeric support.[6] A system which allows the addition and later release of this functionality, without a compromise to its integrity, would thus represent a valuable extension to linker technology. The chemistry of cobalt carbonyl alkyne complexes is well established in the solution phase and has been applied to great effect in organic synthesis:[7] alkyne protection,[7a] the Nicholas reaction[7b] and Pauson–Khand cyclisations,[7c] for example, are amply documented. Given the ease of formation and tolerance to diverse reaction conditions of these complexes, it appeared to us that cobalt carbonyl species offered considerable potential as alkyne linkers for solid-phase synthesis.

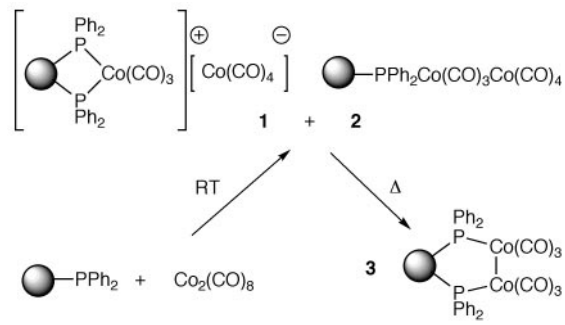
Our initial investigations involved the reaction of 'polymer-bound triphenylphosphine'† with $Co_2(CO)_8$ in THF at room temperature to generate a cobalt carbonyl resin, a support to which alkynes could be added directly (Scheme 1). The purple, stable resin was characterised on the basis of its IR and ^{31}P NMR spectra: strong absorptions ascribed to ionic **1** were accompanied by weaker peaks indicating a minor presence of the monophosphine-substituted complex **2**.[8] Heating of this resin at 60 °C in 1,4-dioxane cleanly converted it into a second form, assigned the structure of the neutral bisphosphine **3** on the basis of its IR and ^{31}P NMR spectra.[9]

The alkyne complexation of a phosphine-substituted cobalt carbonyl complex, $[(Bu_3P)Co(CO)_3]_2$, has been reported.[10] In view of the elevated temperature required, the simultaneous conversion of (**1** + **2**) into **3** *and* complexation of an alkyne becomes a feasible transformation (Scheme 2). Treatment of the resin bearing complexes **1** and **2** with hex-5-yn-1-ol in 1,4-dioxane at 70 °C generated the purple resin-bound alkyne complexes **4**, presumably *via* the intermediary carbonyl complex **3**. Comparison of overlapping sets of IR absorptions with literature data,[11] and data from samples of $Ph_3P(OC)_2CoCo(CO)_3$(hex-5-yn-1-ol) and $[Ph_3P(OC)_2Co]_2$(hex-5-yn-1-ol) prepared ourselves, indicates the presence of both mono- and bisphosphine substituted alkyne complexes, **4a** and **4b**, and that the latter is the major component.‡ The ^{31}P NMR spectrum of **4a**/**4b** supports alkyne complexation (with a 20% phosphorus site occupancy).

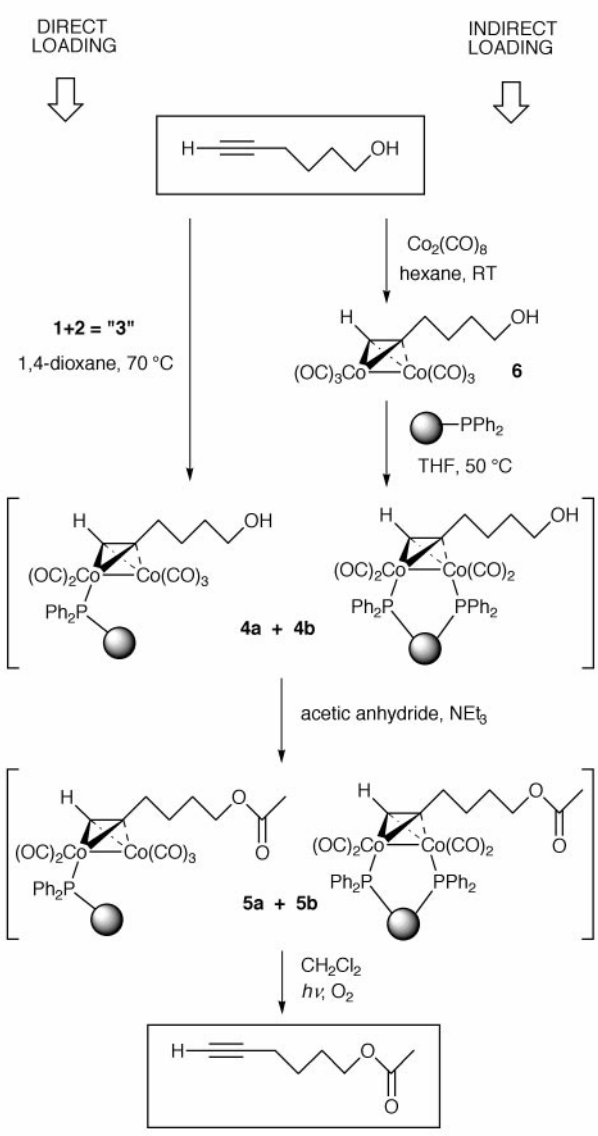
Acetylation of resin **4** to afford **5** using acetic anhydride–NEt_3 is supported by an additional acetate absorption at 1734 cm^{-1}. Decomplexation was achieved by aerial oxidation in CH_2Cl_2 under white light for 72 h. Filtration and washing of the brown polymeric residue delivered hex-5-yn-1-yl acetate as the sole product in 70 ± 20% yield from **4**.

A second approach with the same overall objective involved the reaction of 'polymer-bound triphenylphosphine' with a preformed alkyne complex (indirect loading) (Scheme 2). Designed to permit comparison between the two routes, hex-5-yn-1-ol was complexed with $Co_2(CO)_8$ to give **6**, a deep red oil (85%). Loading onto the polymer was effected in THF at 50 °C to afford **4**§ possessing similar IR characteristics to the resin prepared by the direct method. A comparison of the strengths of bands attributed to the mono- and bisphosphine derivatives[11] identifies the former as the major component *via* this route.‡ ^{31}P NMR spectroscopy is extremely valuable here.¶ A well-resolved resonance integrates to an 80% complexation of phosphorus sites (the benign phosphine oxide, polymer-$P(O)Ph_2$, occupying the remaining 20%) and a loading of 0.94 ± 0.02 mmol[hexynol] g^{-1}. Acetylation proceeded as before: that the metal carbonyl stretches and the ^{31}P NMR spectrum undergo no change demonstrates the stability of this linker to these conditions. Hex-5-yn-1-yl acetate (12 mg, 60 ± 10% from **4**) was recovered from the resin following acetylation of resin **4** (150 mg) and decomplexation over 72 h.

Each loading technique has its own advantage: overall yields *via* indirect loading are significantly higher than those obtained from direct loading. The latter, however, obviates pre-formation of a cobalt alkyne complex and thus offers convenience: once



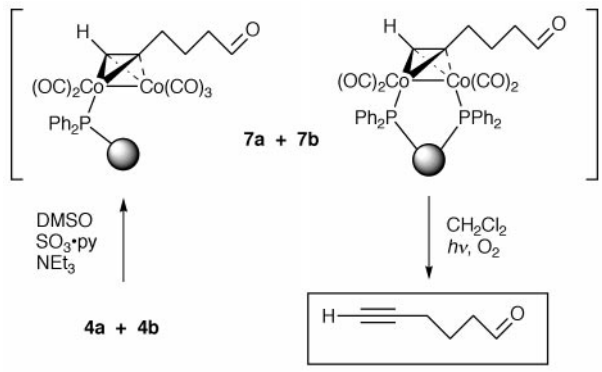
Scheme 1



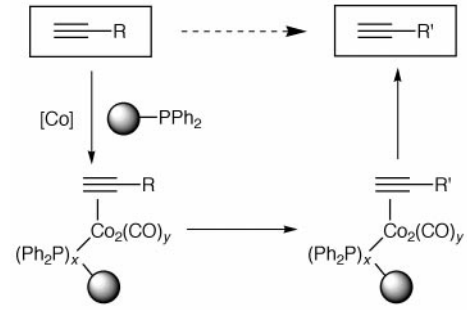
Scheme 2

prepared, the resin-linker complex (**1** + **2**) can be stored and used as required.

Finally, in preliminary experiments to explore the versatility of this linker, alcohol **4** (prepared by direct loading) was oxidised in the presence of SO_3·py-activated DMSO and NEt_3[12] to afford the aldehyde complex **7** (Scheme 3), displaying a diagnostic aldehyde stretch at 1723 cm^{-1}. Significantly, all other data (IR and ^{31}P NMR) of resin **7** are unchanged from those of **4**, thus demonstrating the linker's stability to these oxidising conditions. Hex-5-yn-1-al was isolated in 17 ± 5% yield after decomplexation as before (the low yield here is attributed to the volatility of the aldehyde).



Scheme 3



Scheme 4

In conclusion, we have demonstrated for the first time the utility of cobalt carbonyl complexes as linkers for the 'traceless' immobilisation and subsequent release of alkyne substrates (Scheme 4). The linker is stable to certain widely-used reaction conditions and the work described herein is applicable to various combinatorial methods.

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Footnotes and references

† 'Polymer-bound triphenylphosphine' (commercially available from Fluka, ~1.6 mmol P g^{-1}) describes a diphenylphosphino polystyrene polymer crosslinked with 2% divinylbenzene.

‡ Details of estimates used in this study are as follows: **4a**:**4b** ratios were estimated from IR intensities (3:7 and 6:4 for direct and indirect routes respectively). Solution calibration studies verify this estimate. Solid phase ^{31}P NMR spectra can be accurately integrated but show no resolution of mono- and bisphosphine derivatives. The error margins for yield and loading calculations are estimated as follows: IR spectra, 5%; ^{31}P NMR spectra, direct method, 10%; ^{31}P NMR spectra, indirect method 5%.

§ The experimental procedure for indirect formation of **4** is as follows: polymer-bound triphenylphosphine (1 g, ~1.6 mmol P) was suspended in oxygen-free anhydrous THF (10 cm^3) and allowed to swell for 30 min under nitrogen agitation. A solution of hexacarbonyl(hex-5-yn-1-ol)dicobalt(0) complex (1.2 g, 3.2 mmol) in anhydrous THF (5 cm^3) was added and the black suspension was heated to 50 °C for 4 h. After cooling, the resin beads were filtered, washed with alternate aliquots of THF and Et_2O until the filtrate became colourless, and dried *in vacuo* to afford deep purple beads of **4** (1.46 g, 80% P site occupancy, 0.94 ± 0.02 mmol[hexynol] g^{-1}).

¶ Polymer samples for ^{31}P NMR were swollen in THF and scanned with a D_2O capillary lock at 145.7 MHz for 2 h. Different phosphine species are readily distinguished: polymer-PPh_2-[Co], δ_P = 50–80; polymer-P(O)Ph_2, δ_P = 28.8; polymer-PPh_2, δ_P = −6.3.

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