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Tandem cobalt mediated rearrangement and Pauson–Khand reaction for the synthesis of functionalised polycyclic systems†

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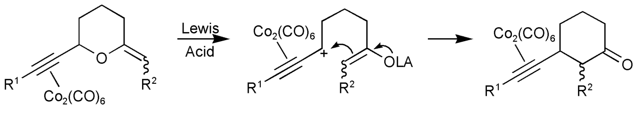
The cobalt mediated rearrangement of enol ether complex 2 furnishes cyclic ketone 6, which undergoes an intramolecular Pauson–Khand reaction allowing access to functionalised polycyclic systems.

The conjugate addition of organocuprate reagents to enone systems constitutes an effective and flexible method for the formation of new carbon–carbon bonds.[1] These synthetic transformations occur in high yield and have been accomplished in a highly stereoselective fashion. A powerful facet of 1,4-addition of organocuprates to cyclic enones is the option of further elaborating the intermediate copper enolate with a range of electrophiles. This allows regiospecific functionalisation at the ring α-position. This strategy has been used to great effect in the synthesis of complex molecular architectures and biologically active molecules. However, such protocols generally require transmetallation of the enolate counterion and subsequent quenching with a suitable electrophile.[2,3]

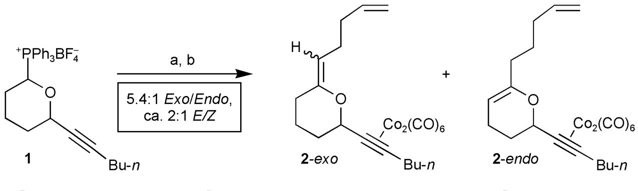
Generally, alkynylcuprate reagents will not transfer the versatile acetylenic function to enones in a 1,4-fashion.[4] In response to this problem, we have recently described a novel rearrangement of propargylic enol ether complexes to the corresponding ß-alkynyl cyclic ketone complexes (Scheme 1).[5] This rearrangement is of note due to the observed stereoselective and regiospecific incorporation of functionality within the newly formed alkynyl cycloalkanone at the α-position.



Scheme 1 Rearrangement of enol ether complexes to cyclic ketone complexes.

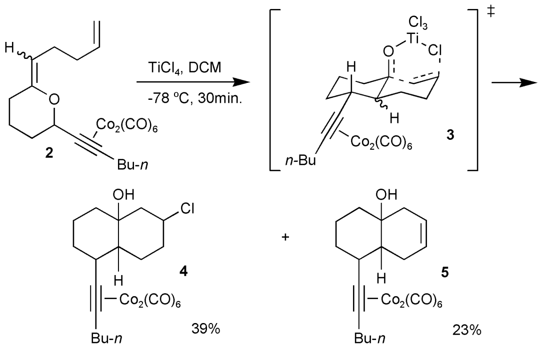
We now wish to report further studies on a system containing alkene functionality which can be used to exploit the synthetically valuable $Co_2(CO)_6$-alkyne moiety in an intramolecular Pauson–Khand reaction.

The required enol ether complex possessing a pendant olefin was synthesised using Wittig methodology[5,6] (Scheme 2) derived from phosphonium salt **1** and commercially available 4-pentenal. Accordingly, treatment of **1** with strong base and 4-pentenal followed by addition of octacarbonyldicobalt to the crude product furnished enol ether complex **2** as a 5.4 : 1 mixture of *exo-* and *endo*cyclic enol ether complexes. In the event, the **2**-*exo* and **2**-*endo* isomers were inseparable by flash column chromatography.[7]



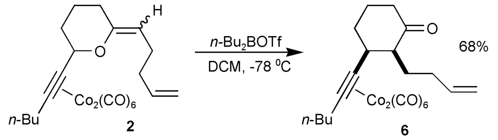
Scheme 2 *Reaction conditions*: (a) *n*-BuLi, THF, 4-pentenal, THF, −78 °C to RT. (b) $Co_2(CO)_8$, petrol, RT. Yield = 71% over two steps.

Treatment of the enol ether complexes **2** with $TiCl_4$, (DCM, −78 °C to RT)[5] resulted in the formation of a complex mixture of products. Unexpectedly, crude ^1H NMR analysis of the mixture revealed the complete loss of the terminal olefin functionality from the reaction products. A combination of FTIR and MS analysis of the major isolated complexes revealed the presence of OH and Cl groups, and these compounds were assigned the structures **4** and **5**. Examination of the literature revealed that Tokoroyama has observed tertiary chlorohydrin by-product formation from a $TiCl_4$ promoted Sakurai reaction bearing a similar pendant olefin.[8] Based on this precedent, we suspect that the initial rearrangement of enol ether complex **2** was successful, but that the intermediate ketone–$TiCl_4$ complex **3** then underwent carbonyl-ene/Prins type reaction leading to complexes **4** and **5** (*via* the forming titanium alkoxide **3**) (Scheme 3).‡ Indeed, during the course of these investigations Coates described[9] $TiCl_4$ promoted chloro-Prins reactions on cyclohexanones possessing a butenyl group, mirroring the reaction of our proposed intermediate cyclohexanone **3**. In Coates' work, predominantly *syn*-chlorohydrins were formed together with variable amounts of ene product. A similar product distribution was seen in our own case.§



Scheme 3 Titanium mediated tandem rearrangement and Prins/carbonyl-ene reactions.

In an effort to circumvent the ene/Prins side reaction, a range of alternative Lewis acids were examined. We were pleased to find the use of dibutylboron triflate at −78 °C efficiently rearranged the exocyclic enol ether complexes **2** to ketone complex **6** in 68% yield (Scheme 4).¶ A single diastereomer



Scheme 4 Rearrangement of butenyl substituted enol ether complex.

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† Electronic supplementary information (ESI) available: experimental procedures and data for all new compounds. See http://www.rsc.org/suppdata/cc/b2/b204616b/

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was isolated from this reaction and assigned as **6** on the basis of 250 MHz ^{1}H NMR spectroscopy.‖

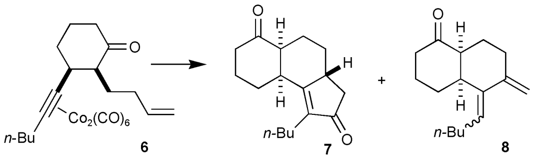
We next turned our attention to the investigation of **6** in a Pauson–Khand cycloaddition reaction. Addition of the enyne complex to 4 Å molecular sieves in toluene at 0 °C (conditions A, Table 1),[10] warming to room temperature and stirring overnight resulted in formation of a new polar compound. Isolation *via* chromatography followed by ^{13}C NMR and mass spectral analysis revealed the correct mass ion and the presence of two carbonyl carbons, indicative of successful formation of the desired fused tricyclic system **7**. To our surprise, ^{13}C NMR data indicated the presence of only one set of signals, revealing the clean formation of **7** as a *single diastereomer* (Scheme 5). Tricycle **7** was assigned as possessing the *cis*-decalone and *endo*-cyclopentenone arrangement as shown. This reaction represents a novel route to functionalised linearly fused polycyclic scaffolds and its application in target synthesis is currently underway and will be reported in due course.

Pleased with this outcome, we were nevertheless concerned by the presence of various olefin containing by-products. Accordingly, we examined alternative methods in an effort to improve cyclisation efficiency. Utilisation of Kerr's polymer supported sulfide resin[11] (conditions B, Table 1) led to cleaner formation of the desired cyclopentenone **7** which was recovered in 71% chemical yield, again as a single diastereomer. In this instance, a second compound was isolated cleanly from the reaction mixture. GCMS and ^{1}H NMR analysis revealed the presence of two isomeric compounds that were assigned as **8** (Scheme 5). It is known that electron deficient olefins participate abnormally in the Pauson–Khand reaction furnishing conjugated dienes.[12] However, Krafft has observed similar conjugated diene formation using enynes with olefins not possessing a conjugated electron withdrawing group.[13] Furthermore, she has described conditions whereby the diene may be formed as the major product through addition of a dilute toluene solution of enyne complex to toluene at reflux under nitrogen. Indeed, employment of these conditions allowed the recovery of *bis*-exocyclic diene **8** (72%) (conditions C, Table 1) as the major product together with trace amounts of cyclopentenone **7**.

Table 1 Pauson–Khand reaction of enyne complex **7**

Entry	Solvent	Temp.	Time	**7**	**8**
A[a]	Toluene	0 °C to RT	16 h	42%	13%[b]
B[c]	1,2-DCE	83 °C	1.5 h	71%	21%[d]
C	Toluene	110 °C	0.5 h	[e]	72%[f]

[a] 9 Equiv. of TMANO dihydrate used. [b] Estimated yield based on ^{1}H NMR analysis of crude material. [c] 3.5 Equiv. of resin supported alkyl methyl sulfide used. [d] Observed as a 2.5 : 1 mixture of olefin isomers. [e] Trace amount observed by GCMS analysis. [f] Observed as a 3 : 1 mixture of olefin isomers.



Scheme 5 Intramolecular Pauson–Khand and diene formation.

In conclusion, cobalt complexed enol ether **2** undergoes a rearrangement reaction in which the product distribution was found to rely markedly on the choice of Lewis acid. The product cobalt–enyne complex **6** was found to undergo a very efficient intramolecular Pauson–Khand reaction in the presence of Kerr's polymer supported sulfide resin. We are currently examining the scope of this polycycle forming strategy further and are investigating the potentially useful carbon–carbon bond formations observed in the carbonyl-ene and diene forming side reactions.

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Notes and references

‡ *Endo*cyclic enol ether **2**-*endo* was recovered from this reaction (37%).

§ A full assignment of the stereochemistry of complexes **4** and **5** has not yet been accomplished but will form part of a full study of the chloro-Prins reaction.

¶ *Endo*cyclic enol ether **2**-*endo* was recovered from this reaction (18%).

‖ The ring propargylic proton was observed as a ddd, consistent with 1 axial and 2 equatorial vicinal protons (couplings of 10.1, 4.9 and 4.4 Hz).

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