Regioselective Pauson–Khand Processes with Olefins Possessing Extended Phosphonates

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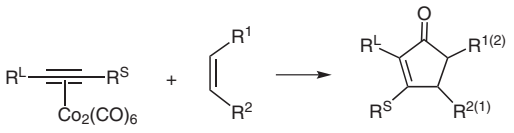
Dedicated to Professor Gerry Pattenden on the occasion of his 70th birthday

Abstract: Olefins possessing a tethered β-functionalised phosphonate functionality have been shown to be effective cyclisation partners within intermolecular Pauson–Khand processes. The optimised protocol described facilitates intermolecular cyclisations with high levels of olefinic regiocontrol.

Key words: alkyne complexes, annulations, β-functionalised phosphonates, Pauson–Khand reaction, regioselectivity

Over the last few decades, transition-metal-mediated cyclisations have provided vast synthetic value to the preparative chemistry community and continue to be applied as direct and highly efficient methods for the construction of many challenging carbon skeletons. Of particular note is the Pauson–Khand (P–K) reaction, which has evolved as an invaluable tool for the preparation of functionalised cyclopentenones.[1] First discovered in 1971 by Pauson and co-workers, the reaction involves the cycloaddition of an alkyne, present as its hexacarbonyldicobalt complex, an alkene, and carbon monoxide, in a formal [2+2+1] fashion, to furnish functionalised cyclopentenones directly (Scheme 1).



Scheme 1

Over recent years there has been enormous progress in enhancing the efficiency of the P–K annulation to the extent that this method can now be employed under relatively mild reaction conditions for the expedient synthesis of cyclopentenones and their derivatives.[2] Having stated this, it is the *intra*molecular variant of the P–K reaction that has shown the greatest effectiveness, to date, and which has found prominence as the key step in a number of natural product total syntheses.[3] In contrast, limitations still remain within the realm of the *inter*molecular P–K cyclisation process. More specifically in relation to this two-component annulation, the regiochemical outcome with regard to the alkene partner is difficult to predict. Indeed and as illustrated in Scheme 1, with simple unsymmetrical alkene substrates, it is common to see 1:1 mixtures of olefin insertion products.[2c,i,4] In an attempt to establish regiochemical control within such intermolecular P–K reactions, Krafft employed a potentially chelating heteroatom, tethered to the olefin in the homoallylic or bishomoallylic position, to direct the outcome of the cyclisation process.[5] Indeed, it was shown that the use of soft sulfur or nitrogen donor atoms induced appreciable levels of regioselectivity with respect to the alkene reaction partner. More recently, studies within our laboratories have shown how such regioselective intermolecular P–K processes can be further extended with the use of allylphosphonates. Again, with the phosphonate unit acting as the potentially chelating moiety, cyclopentenone products were delivered with high levels of regiochemical control.[6]

Following on from the success of our previous work involving allylphosphonates as cyclisation partners, we were keen to investigate further the efficiency of phosphonate ester directing groups and more extensively establish the scope of this functional unit within intermolecular P–K annulations. Additionally, due to the wide use of β-functionalised phosphonates as key reagents within olefination chemistry,[7] the use of olefins with suitably positioned phosphorus components would allow the incorporation of such a moiety onto the cyclopentenone framework. Based on all of this, we herein report the use of alkenes possessing such extended phosphonates within regioselective intermolecular P–K processes.

Our preliminary efforts in this programme focused on P–K cyclisations involving phenylacetylene cobalt complex **1** and, the relatively easily prepared,[8] olefin **2**, possessing the tethered phosphonate ester unit (Scheme 2). At the outset, a series of conditions were screened with well-established chemical promoters of the P–K reaction. Initial use of the long-chain odourless sulfide additive, dodecyl methyl sulfide (DodSMe), under conditions previously established within our laboratory,[9] in refluxing 1,2-DCE led only to decomposition of the starting complex (Scheme 2, Table 1, entry 1). In contrast, use of the same promoter at room temperature delivered the desired cyclopentenone products, as a mixture of isomers, in 19% yield (entry 2). Despite this relatively low reaction efficiency, we were encouraged by the moderate 5:1 regioselection

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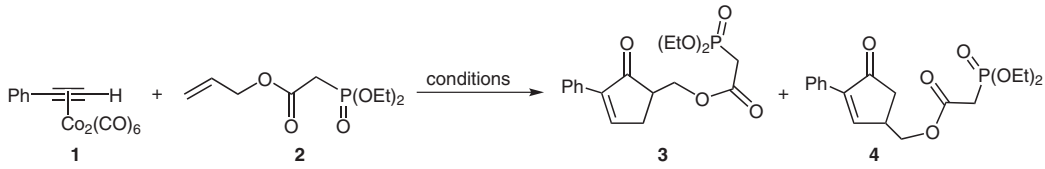


Scheme 2

observed. This sulfide-promoted process was repeated using dichloromethane as the reaction medium resulting in a 24% yield and a more appreciable 10:1 regioselectivity (entry 3). In an attempt to further enhance this reaction process, alternative amine *N*-oxide promoters were investigated.[10] In this regard, both trimethylamine *N*-oxide (TMANO·2H_2O) and *N*-methylmorpholine *N*-oxide (NMO·H_2O) unfortunately provided no improvement in cyclisation efficiencies with the key phosphonate containing olefin **2** (entries 4 and 5). Similarly, use of the cyclohexylamine additive[11] led to no cyclopentenone being isolated (entry 6).

Table 1 Initial Reactions of Phenylacetylene Complex **1** with Olefin **2**

Entry	Conditions	Yield (%)	Selectivity (**3**/**4**)
1	1,2-DCE, DodSMe, reflux, 16 h[a]	0	–
2	1,2-DCE, DodSMe, r.t., 16 h[a]	19	5:1
3	CH_2Cl_2, DodSMe, r.t., 16 h[a]	24	10:1
4	TMANO·2H_2O, CH_2Cl_2, r.t., 24 h[b]	5	–
5	NMO.H_2O, CH_2Cl_2, r.t., 24 h[b]	5	–
6	$CyNH_2$, CH_2Cl_2, reflux, 24 h[c]	0	–

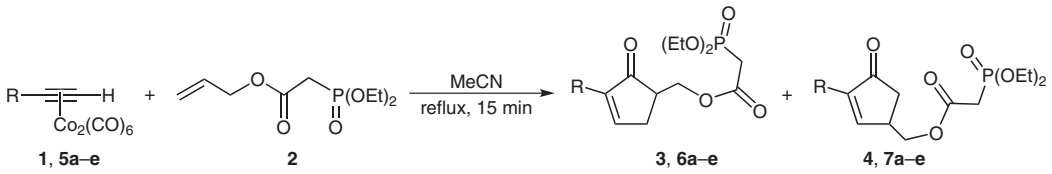
[a] Conditions: 3.5 equiv of DodSMe were employed.
[b] Conditions: 5.0 equiv of *N*-oxide were employed.
[c] Conditions: 2.0 equiv of amine additive were employed.

Following these initial investigations, we were encouraged by the, at least, acceptable levels of regioselectivity that could be obtained in some instances with the phosphonate-containing olefin **2**. However, the levels of cyclic product recovery were somewhat disappointing. In an effort to enhance the effectiveness of this process, we reconsidered the findings of our previous investigations into regioselective P–K processes involving allylphosphonate esters and, in particular, the observation that the omission of sulfide promoter did not have a detrimental effect on reaction yield and, indeed, led to enhanced olefin-insertion regioselectivity.[6] With this in mind, our attention turned to establishing the most effective solvent for our emerging P–K process, without the presence of a chemical promoter. In relation to this, the reaction between complex **1** and olefin **2** was carried out in a dichloromethane–acetonitrile mixture, as was shown to be optimal in our previous studies. Pleasingly, an elevated yield of our desired products was obtained in conjunction with a regioisomeric ratio of 7:1 (Scheme 2, Table 2, entry 1). A further simplification of the reaction conditions, using only acetonitrile as the reaction medium, resulted in an additional increase to both the yield and the selectivity obtained (entry 2). Extended reaction solvent investigations, employing 1,2-dichloroethane and toluene (entries 3 and 4), led to no further improvements in the efficiency of this cyclisation process.

Table 2 Solvent Study on Reactions of Phenylacetylene Complex **1** with Olefin **2**

Entry	Conditions	Yield (%)	Selectivity (**3**/**4**)
1	MeCN–CH_2Cl_2 (1:3), reflux, 3 h	31	7:1
2	MeCN, reflux, 3 h	39	10:1
3	1,2-DCE, reflux, 3 h	16	5:1
4	toluene, reflux, 3 h	18	2:3

During the solvent-optimisation studies it had become apparent that, in addition to cyclopentenones **3** and **4**, the mass balances of the reaction processes were generally made up of degradation products. As a result, our concerns focused on the stability of the desired cyclopentenones under the chosen reaction protocol (Table 2, entry 2). In relation to this, we subjected a sample of the cyclisation products **3** and **4** to the optimal refluxing acetonitrile conditions. As suspected, complete decomposition was observed after just a few hours, confirming our view that the desired products were not stable for prolonged periods under the conditions that delivered the most efficient cyclisation outcome. Consequently, attention turned to the overall reaction time. In all reactions performed to this stage in the programme, the addition of the cobalt complex (in the chosen reaction solvent) had been carried out over one hour. This mode of addition was maintained, however, the subsequent reaction time was reduced to just 15 minutes. Using this modified method, a 56% isolated yield of cyclopentenones **3** and **4**, with a 10:1 selectivity ratio, was achieved (Scheme 2, Table 3, entry 2). In an effort to enhance the reaction efficiency further, we subsequently investigated the effect of the number of equivalents of the olefinic phosphonate ester **2** employed. Pleasingly, increasing the number of equivalents of **2** from two to three resulted in a further improved 66% isolated yield, with an elevated selectivity of 12:1 being ob-



Scheme 3

tained (entry 3). In a final probe within this overall optimisation process, the reaction was performed in refluxing propionitrile to determine whether an elevated reaction temperature, over this shorter reaction time, would be beneficial. Unfortunately, this led to a slightly lower yield being obtained in this instance (entry 4).

Table 3 Reaction Time Study on P–K Cyclisations of Phenylacetylene Complex **1** with Olefin **2**

Entry	**2** (equiv)	Time (min)[a]	Yield (%)	Selectivity (**3**/**4**)
1[b]	2	180	39	10:1
2[b]	2	15	56	10:1
3[b]	3	15	66	12:1
4[c]	3	15	41	10:1

[a] Reaction time following alkyne complex addition over 1 h.
[b] Reaction performed in refluxing MeCN.
[c] Reaction performed in refluxing propionitrile.

With these optimised conditions in hand,[12] we set out to establish the scope of this new regioselective P–K process. Initially, we probed the effectiveness of our optimal conditions against a range of aryl alkyne substrates. Both electron-rich (Scheme 3, Table 4, entries 2 and 3) and electron-deficient (entry 4) aryl substrates resulted in good yields of the desired cyclopentenone products and in high regioisomeric ratios; the more sterically encumbered 1-naphthyl alkyne led to a lower cyclisation yield, whereas the selectivity remained high at 9:1 (entry 5). In addition to this, we also investigated the effectiveness of an alkyl-substituted alkyne substrate under our developed reaction conditions (entry 6). This, again, delivered the desired products, albeit in a more moderate 47% combined yield and with 7:1 regioselectivity.

Having established an effective protocol that delivered cyclopentenone products in generally good yields and, importantly, with high regioisomeric ratios, favouring the 2,5-disubstitued isomers, our thoughts turned to the factors driving this regioselective P–K annulation process. To investigate the role of the tethered phosphonate, an equivalent substrate without this functional group was

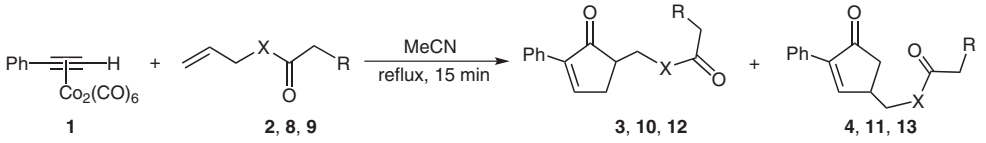
Table 4 P–K Cyclisations of a Range of Alkyne-$Co_2(CO)_6$ Complexes with Olefin **2**[a]

Entry	R	Yield (%)	Selectivity (**6**/**7**)
1	**1** Ph	66	12:1[b]
2	**5a** 4-MeC_6H_4	71	12:1
3	**5b** 4-$MeOC_6H_4$	65	12:1
4	**5c** 4-ClC_6H_4	63	10:1
5	**5d** 1-naphthyl	42	9:1
6	**5e** *n*-Bu	47	7:1

[a] All reactions were carried out following the general procedure outlined in ref. 12.
[b] This represents the ratio for **3**/**4**.

employed under our optimised protocol. Upon reaction of allylic ester derivative **8** with our standard phenylacetylene cobalt complex **1**, the desired cyclopentenone products were isolated in a combined 81% yield and with a diminished regioisomeric ratio of 6:1 (Scheme 4, Table 5, entry 2). The somewhat elevated yield may be attributed to the use of a less sterically encumbered olefin or, indeed, could be accredited to potentially higher product stability under the developed reaction conditions. In terms of reaction selectivity, the depleted regiochemical ratio in this case would support the concept that the phosphonate ester (in **2**) is acting as a potentially ligating unit involved in the regioselective outcome of this process, as in our previously published and related studies with allylphosphonates.[6] Having stated this, the moderate levels of selectivity that remain when allylic ester **8** is employed would appear to indicate that the carbonyl functionality may also play an important role within the regiochemical outcome of this general annulation process.

To probe this theory further, the reaction was repeated with β-ketophosphonate **9**. Replacement of the oxygen atom with a methylene unit creates a less Lewis basic carbonyl group. Indeed, if the carbonyl functionality is inherently involved in the regiochemical outcome of this annulation process, a reduced selectivity could be anticipated with this substrate **9**. As shown in Table 5, entry 3,



Scheme 4

Table 5 Probing the Alkene Functionality in P–K Cyclisations of Phenylacetylene Complex **1**[a]

Entry	X	R	Yield (%)	Selectivity
1	O	**2** $P(O)(OEt)_2$	66	12:1 (**3/4**)
2	O	**8** H	81	6:1 (**10/11**)
3	CH_2	**9** $P(O)(OMe)_2$	28	3:1 (**12/13**)

[a] All reactions were carried out following the general procedure outlined in ref. 12.

when phosphonate **9** was employed, a significantly diminished 3:1 regioisomeric ratio was obtained, as well as a low 28% isolated yield. This result supports the hypothesis that the carbonyl functional unit, as well as the phosphorus component, plays an influential role in the regiochemical outcome of the P–K annulations with extended phosphonate systems as described here.

In summary, as part of an ongoing programme of work within our laboratory to increase the efficiency and applicability of intermolecular Pauson–Khand reactions, we have now demonstrated the use of an extended class of olefins possessing a tethered phosphonate ester unit. Under optimised reaction conditions, and without the requirement for any additional promoters or additives, these phosphorus-possessing alkenes act as effective P–K cyclisation partners and deliver functionalised cyclopentenones, of obvious further synthetic utility, with good levels of regiochemical control.

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(12) **General Experimental Procedure**
A 25 mL three-necked round-bottomed flask was fitted with a condenser, flame-dried under vacuum, and allowed to cool under nitrogen. The vessel was charged with dry MeCN (7.5 mL) and the phosphonate ester (0.75 mmol). The reaction mixture was heated slowly to reflux and a solution of the desired cobalt complex (0.25 mmol) in dry MeCN (2.5 mL) was then added over 1 h via syringe pump. Following complete addition, heating was continued at reflux for 15 min. After this time, the reaction mixture was concentrated to dryness, dissolved in EtOAc, and filtered through Celite to remove cobalt residues. The filtrate was concentrated, and the crude product was purified by silica column chromatography to yield the desired regioisomeric cyclopentenones.
Sample Compound Data
Compound **6e**: IR (CH_2Cl_2): ν = 1027, 1053, 1256, 1275, 1703, 1740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, $^3J_{HH}$ = 7.2 Hz), 1.28–1.37 (m, 8 H), 1.42–1.50 (m, 2 H), 2.15–2.19 (m, 2 H), 2.50–2.53 (m, 1 H), 2.67–2.80 (m, 2 H), 2.92 (d, 2 H, $^2J_{PH}$ = 21.6 Hz), 4.09–4.19 (m, 4 H), 4.28 (dd, 1 H, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.3 Hz), 4.46 (dd, 1 H, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 4.0 Hz), 7.30 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.6, 165.8 (d, $^2J_{PC}$ = 6.2 Hz), 156.5, 146.1, 64.8, 62.8 (d, $^2J_{PC}$ = 6.9 Hz), 62.7 (d, $^2J_{PC}$ = 6.7 Hz), 44.6, 34.2 (d, $^1J_{PC}$ = 134.0 Hz), 30.8, 29.7, 24.5, 22.4, 16.34, 16.28, 13.8 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 19.41 ppm. HRMS (EI): *m/z* calcd for $C_{16}H_{28}O_6P$ $[M^+ + H]$: 347.1618; found: 347.1623.

Compound **7e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, $^3J_{HH}$ = 7.3 Hz), 1.25–1.50 (m, 10 H), 2.14–2.20 (m, 3 H), 2.59 (dd, 1 H, $^2J_{HH}$ = 18.9 Hz, $^3J_{HH}$ = 6.6 Hz), 2.99 (d, 2 H, $^2J_{PH}$ = 21.5 Hz), 3.14–3.23 (m, 1 H), 4.12–4.24 (m, 6 H), 7.23 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 166.0 (d, $^2J_{PC}$ = 6.3 Hz), 156.1, 148.5, 67.3, 63.1 (d, $^2J_{PC}$ = 6.0 Hz), 38.38, 38.36, 34.5 (d, $^1J_{PC}$ = 133.5 Hz), 30.5, 24.7, 22.6, 16.60, 16.56, 14.0 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 19.35 ppm.

The ratio of **6e/7e** in the unseparated mixture was calculated from the relative integral values of the proton NMR signals at δ = 7.30 ppm (**6e**) and 7.23 ppm (**7e**). All other regioisomeric ratios were established in a similar fashion. Isomer **7e** was identified specifically as the 2,4-disubstituted cyclopentenone through the use of two-dimensional NMR experiments. Firstly, HSQC and HMBC techniques were used to determine the representative signals for the individual proton and carbon atoms. The regiochemistry of **7e** was then determined by coupling correlations in the COSY spectrum and, specifically, with respect to the cyclopentenone C-4 methine proton showing direct coupling interactions with the C-3 olefinic proton, as well as the C-5 methylene unit and the *O*-methylene protons in the pendant side chain. The COSY spectrum for the 2,5-isomer **6e** shows no coupling between the C-5 methine unit and the C-3 olefinic proton, whereas the same olefinic proton in this isomer does show a coupling interaction with the C-4 methylene unit. In all other cases (**3**, **4**, **6a–d**, **7a–d**, **10**, **11**, **12**, **13**), the identity of the specific regioisomers was established more routinely through characteristic olefinic coupling patterns.