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A stable catalyst of the Pauson–Khand annelation

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Abstract—A practical catalytic-in-cobalt version of the PKA is clearly a desirable objective and there has been much research towards this goal in recent years. Systems developed to date, however, require either the use of high temperatures and high carbon monoxide pressures and/or the use of the sensitive cobalt catalyst, octacarbonyldicobablt(0). We report here a detailed account of PKA results obtained using the more robust cobalt compound, heptacarbonyl(triphenylphosphine)dicobalt(0), **1**, which indicate that 1 is an attractive alternative to octacarbonyldicobalt(0) as a catalyst of the PKA.

1. Introduction

Some of the most significant contributions to organic synthesis during the past years have been made by transition metal-mediated reactions. A prime example is the Pauson–Khand annelation (PKA), first described in 1971,[1] which involves the synthesis of cyclopentenone derivatives via the carbonylcobalt(0)-mediated cyclisation of an alkyne, an alkene and carbon monoxide. During its development and application, the PKA has mainly been applied using a stoichiometric amount of the transition metal complex, usually by prior formation of a stable (alkyne)hexacarbonyldicobalt(0) complex, even though the intermolecular catalytic Pauson–Khand annelation (CPKA) using $Co_2(CO)_8$ under mild conditions was reported as early as 1973.[2]

Interest in the CPKA was rekindled in the 1990s and significant improvements in the scope of this reaction were made during this decade. A typical example is the report from Livinghouse in 1996 which describes the application of a photochemically driven process requiring only mild temperatures (50–55°C) and one atmosphere of carbon monoxide to a wide range of intramolecular substrates.[3] In 1998, the same group reported that careful control of temperature within a narrow window (60–70°C) dispenses with the need for photolytic promotion.[4] Rigorous purification of the $Co_2(CO)_8$ catalyst is essential for the success of these systems, however, and Livinghouse recommends recrystallisation or sublimation immediately prior to use, or opening a fresh commercial sample in a glove-box.

The current state-of-the-art of CPKA is perhaps best illustrated by a summary of reports on the reaction in the last two years. Not surprisingly, in view of current interest in automation and environmental issues, there have been several reports concerning the immobilisation of PKA catalysts (see (1)–(3), Scheme 1). One system employs a polymer-supported cobalt carbonyl complex (see (1) Scheme 1)[5] whilst the other two (see (2) and (3) Scheme 1) use immobilised cobalt and require relatively high pressures of carbon monoxide to generate cyclopentenones.[6,7] In response to the difficulties associated with handling and using $Co_2(CO)_8$, Krafft has reported $Co_4(CO)_{12}$ as an alternative catalyst precursor using cyclohexylamine to induce catalyst formation via disproportionation of $Co_4(CO)_{12}$ and to preserve the active catalyst (see (4) Scheme 1).[8,9] Stabilisation of the active catalyst using a phosphane sulfide has been reported (see (5) Scheme 1)[10] and, remarkably, addition of BINAP leads to excellent enantioselectivity, albeit at the expense of turnover (see (6) Scheme 1).[11,12] Demanding substrates have been cyclised efficiently by the introduction of sulfur substituents, which presumably also stabilise key catalytic intermediates (see (7) Scheme 1).[13]

As a result of our interest in the use of carbonylcobalt(0) complexes immobilised on 'polymer-bound triphenylphosphine' (see (1), Scheme 1) in the CPKA,[5] we initiated an 'off-polymer' study of phosphorus derivatives of carbonyl-cobalt(0) species. Despite (a) the significant use of phosphine and phosphite substituted alkyne complexes in the stoichiometric PKA, where co-ordination leads to a reduction in the rate and overall efficiency of the reaction,[14] and (b) the observation that the use of triphenylphosphite as an additive in the $Co_2(CO)_8$ mediated CPKA leads to an improvement in reaction efficiency,[15] the performance of preformed complexes of phosphines and phosphites in the CPKA had not been assessed. We thus conducted a preliminary screening of phosphine and phosphite derivatives of $Co_2(CO)_8$ which revealed that these complexes were

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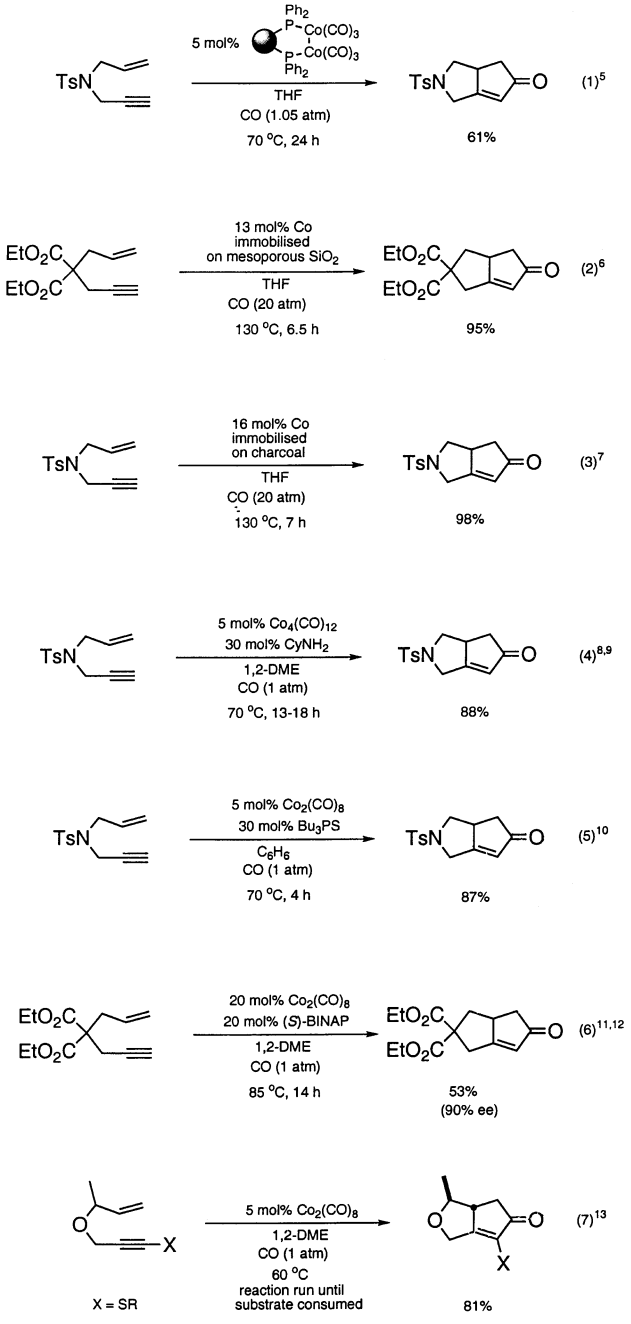
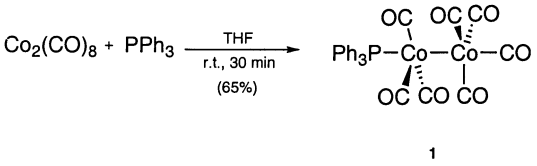


Scheme 1.

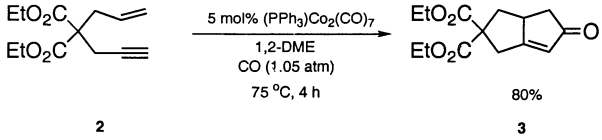
indeed catalysts of the PKA.[16] We have now examined more closely one of the catalysts identified by the screen, heptacarbonyl(triphenylphosphine)dicobalt(0), **1**. We report herein our study of its scope and limitations which reveals that this catalyst provides an attractive alternative to the PKA catalysts currently available.

2. Results and discussion

Heptacarbonyl(triphenylphosphine)dicobalt(0), **1**, was chosen for further development based on its activity in our initial screen and the relatively low cost of triphenylphosphine. Complex **1** is a stable solid,[17] easily prepared in good yield by stirring triphenylphosphine with



Scheme 2.



Scheme 3.

$Co_2(CO)_8$ at room temperature for 30 min, followed by a straightforward chromatographic purification (Scheme 2).

In order to compare the activity of catalyst **1** across a range of PKA substrates, we chose to develop a standard set of conditions and then apply them to all substrates, rather than varying the reaction conditions to optimise the yield of each individual reaction. We chose to identify our standard conditions using the diethyl malonate derivative **2** (Scheme 3) as the reaction of this substrate is easily followed by GC analysis. At this stage, we performed our reactions on a relatively small scale (0.5 mmol) and we chose to use 1,2-DME as solvent as preliminary experiments using THF and 1,2-DME as solvent had indicated that the latter solvent gave cleaner reactions. We chose to work under 1 atm of CO in order to determine the scope and limitations of **1** under relatively mild conditions. A series of experiments in which the conversion of **2** into **3** was followed over 10 h varying the temperature, and using a range of catalyst loadings led to the results depicted in Fig. 1. Use of 3 mol% **1** at 70 and 75°C (runs A and B) revealed that although the same conversion (60%) was achieved eventually, the higher temperature led to a faster turnover of catalyst in the early stages of the reaction. A temperature of 75°C was thus adopted for the remaining experiments. Reduction of the catalyst loading to 1 mol% (run C) led to conversion of 20%, whilst addition of an extra 2 mol% of **1** after 4 h increased conversion to 80% (run D). Adding the catalyst in portions (3 mol% at t=0 and 2 mol% at t=4 h) proved to be less effective than adding it all at the beginning of the reaction as 5 mol% of **1** added at t=0 gave a conversion of essentially 100% (run E). The use of 6 mol% of catalyst **1** improved the conversion in the early stages of the reaction (run F). Taking into account conversion, reaction time and catalyst loading, we decided to adopt the following conditions as our standard conditions: 5 mol% catalyst loading added at t=0, a reaction time of 4 h and a reaction temperature of 75°C. Under our standard conditions, substrate **2** was converted to cyclopentenone **3** in 94% NMR yield and 80% isolated yield.

In order to define the scope and limitations of catalyst **1** for the PKR, a series of intramolecular cyclisations were initially screened under our standard conditions. Malonate and amine derivatives of mono-substituted alkenes and

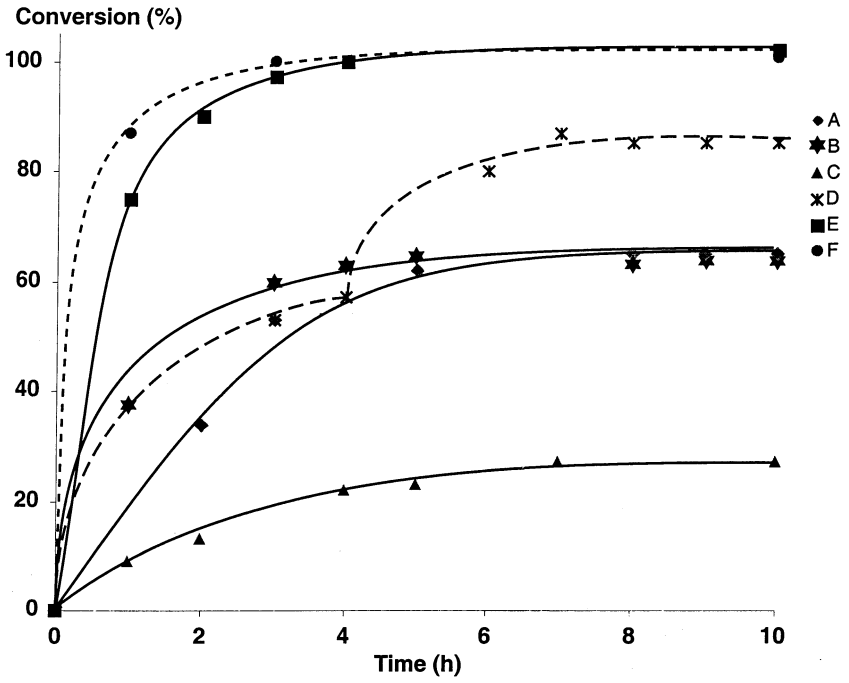


Figure 1. Effect of temperature and catalyst loading on the conversion of enyne **2** into cyclopentenone **3** over 10 h. All reactions run in 1,2-DME (10 mL) under 1.05 atm CO using 1.0 mmol of **2**. (A) 3 mol% **1**, 70°C; (B) 3 mol% **1**, 75°C; (C) 1 mol% **1**, 75°C; (D) 3 mol% **1** (0 h)+2 mol% **1** (4 h), 75°C; (E) 5 mol% **1**, 75°C; (F) 6 mol% **1**, 75°C.

alkynes, substrates known to undergo PKA relatively readily, gave very good yields of products using catalyst **1** under our standard conditions (Table 1, entries 1–3). Enynes disubstituted either at the alkyne or alkene functionality, substrates generally accepted as being more challenging than their monosubstituted counterparts, gave good to very good yields of annelation products (Table 1, entries 4–6). Our attention then turned to intermolecular PKAs and, again we found that catalyst **1** used under our standard conditions gave good to very good isolated yields (Table 1, entries 7–9).

Finally, as catalyst **1** had given reliable and promising results on a modest-but-typical CPKA scale (0.5 mmol), we conducted some preliminary experiments to test whether or not the CPKA could be readily scaled up using catalyst **1**. We were delighted to find that the intramolecular reaction leading to the production of **7** and the intermolecular reaction leading to the production of **14** could both be performed without significant loss of isolated yield on a 10 mmol scale (92 and 90% of **7** and **14**, respectively). From a practical point of view, it is also of note that a sample of **1** stored at 4°C in air for 18 months gave identical results in PKA reactions to a freshly prepared sample of **1**.

3. Conclusion

Heptacarbonyl(triphenylphosphine)dicobalt(0), **1**, catalyses a range of PKAs. The catalyst gives good yields after 4 h with 5 mol% loading, can be used under mild conditions, has been used successfully on a 10 mmol scale, and displays none of the sensitivities and handling problems characteristic of $Co_2(CO)_8$.[9]

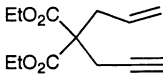
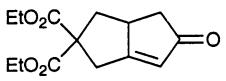
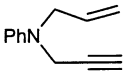
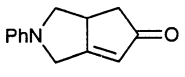
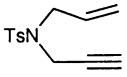
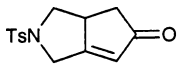
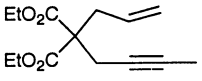
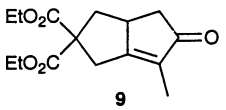
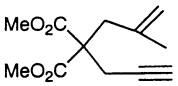
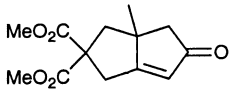
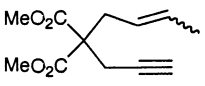
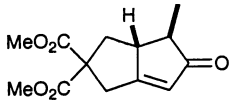
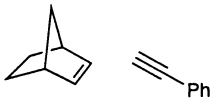
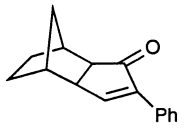
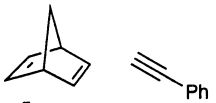
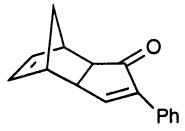
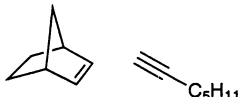
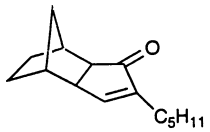
4. Experimental

4.1. General

All reactions and manipulations involving organometallic species were performed under nitrogen or carbon monoxide using standard vacuum line and Schlenk tube techniques.[18] THF and 1,2-dimethoxyethane (1,2-DME) were distilled over sodium benzophenone ketyl. All other reagents were dried, distilled and stored according to standard procedures.[19] PK substrates **2**,[20] **4**,[21] **6**,[22] **8**,[23] and **10**,[24] were prepared according to literature procedures. Melting points, which are uncorrected, were recorded in open capillaries on a Buchi 510 melting point apparatus. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer. NMR spectra were recorded at RT on Bruker Avance 360, Bruker Avance 400 and Bruker DRX 500 instruments. Chemical shifts are reported in ppm relative to residual undeuterated solvent as the reference and J values are reported in Hz. Mass spectra were recorded on a JEOL AX 505W mass spectrometer and elemental analyses were performed by the North London University microanalytical services. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh). GC analyses were performed on a Unicam 610 gas chromatograph equipped with a FID (column: DB-225, 0.25 mm×30 m).

4.1.1. Heptacarbonyl(triphenylphosphine)dicobalt(0) 1. Octacarbonyldicobalt(0) (2.00 g, 5.86 mmol) and triphenylphosphine (1.53 g, 5.83 mmol) were dissolved in anhydrous THF (15 mL) in a dry Schlenk flask under nitrogen. The mixture was stirred in the dark at room temperature for 30 min and concentrated in vacuo after checking for the disappearance of the CO absorption at 1845 cm^{-1} by IR spectroscopy. The resultant brown residue was adsorbed

Table 1. Pauson–Khand reaction with various substrates

Entry	Substrate	Product	Yield (%)[a]
1	 **2**	 **3**	80 (94)
2	 **4**	 **5**	65 (89)
3	 **6**	 **7**	85 (97)
4	 **8**	 **9**	57 (70)
5	 **10**	 **11**	85 (90)
6	 **12**	 **13**	45 (62)[b]
7	 5 eq.	 **14**	96 (100)
8	 5 eq.	 **15**	73
9	 5 eq.	 **16**	64

All reactions run using 5 mol% of $(PPh_3)Co_2(CO)_7$ under 1.05 atm CO in 1,2-DME at 75°C for 4 h using 0.5 mmol of alkyne substrate.
[a] Isolated (NMR) yield.
[b] de 70%.

onto neutral alumina (Grade II) under nitrogen and then charged onto a chromatography column of silica. The column was eluted under nitrogen first with hexane to remove any unreacted octacarbonyldicobalt(0) and then with hexane/diethyl ether (9:1) to collect the title compound as a brown-red solid (2.17 g, 3.77 mmol, 65%); mp 120–125°C; IR ($CHCl_3$): ν 2077m, 2023w, 1988s, 1958w (C≡O) cm^{-1}; ^1H NMR (500 MHz; $(CD_3)_2CO$): δ 7.50–7.70 (m, Ar-H); ^{13}C $\{^1H\}$ NMR (125.8 MHz; $(CD_3)_2CO$): δ 129.9 (d, $^3J_{CP}$=10 Hz, *m*-Ar-C), 132.4 (*p*-Ar-C), 133.3 (d, $^1J_{CP}$=49 Hz, *ipso*-Ar-C), 133.6 (d, $^2J_{CP}$=10 Hz, *o*-Ar-C) and 201.7 (brs, Co(CO)); ^{31}P $\{^1H\}$ NMR (162 MHz; $(CD_3)_2CO$): δ 65.3 ($CoPPh_3$); FAB-MS: *m/z* (%)=548 (2) $[M^+-CO]$, 492 (21) $[M^+-3CO]$, 405 (7) $[M^+-Co-4CO]$, 377 (13) $[M^+-Co-5CO]$, 349 (17) $[M^+-Co-6CO]$, 321 (100) ($CoPPh_3^+$); $C_{25}H_{15}Co_2O_7P$ (576.21): C, 52.11; H, 2.62; Found: C, 52.1; H, 2.7.

4.1.2. Typical 0.5 mmol PKA reaction. Enyne **2** (119 mg, 0.5 mmol) and $Ph_3PCo_2(CO)_7$, **1**, (15 mg, 0.025 mmol) were dissolved at room temperature in CO saturated 1,2-DME (5 mL) under a carbon monoxide atmosphere (1.05 atm).

The mixture was heated at 75°C with vigorous stirring in the dark (aluminium foil around flask) for 4 h. The resulting brown mixture was cooled, filtered through a short pad of celite and concentrated in vacuo. (^{1}H NMR spectroscopy at this stage revealed a 94% conversion). Purification of the residue by flash column chromatography (SiO_2; hexane/EtOAc, 6:4) gave the known product **3**[20] (106.5 mg, 0.4 mmol, 80%) as a colourless oil; IR ($CHCl_3$): ν 1730s (C=O$_{ester}$), 1710s (C=O$_{ketone}$), 1636m (C=C) cm^{-1}; ^{1}H NMR (360 MHz; $CDCl_3$): δ 1.25 (6H, t, J=9 Hz, 2×CH_2CH_3), 1.72 (1H, dd, J=13, 13 Hz, C*H*HCO), 2.11 (1H, dd, J=18, 3 Hz, C*H*HC=), 2.61 (1H, dd, J=18, 6 Hz, CH*H*C=), 2.77 (1H, dd, J=13, 8 Hz, CH*H*CO), 3.07–3.10 (1H, m, C*H*CH_2CO), 3.23 (1H, dd, J=19, 1 Hz, C*H*HCHCH_2CO), 3.33 (1H, dd, J=19, 1 Hz, CH*H*CHCH_2CO), 4.16–4.25 (4H, m, 2×CH_2CH$_3$), 5.91 (1H, d, J=2 Hz, C=CH); ^{13}C {^{1}H} NMR (90.6 MHz; $CDCl_3$): δ 14.0 (2×CH_2CH_3), 35.1 (CH_2CHCH_2CO), 38.9 (CH_2CO), 42.1 (CH_2C=), 45.0 (*C*HCH_2CO), 60.8 (*C*(CO$_2$Et)$_2$), 62.0 (CH_2CH_3), 62.2 (CH_2CH_3), 125.6 (C=*C*H), 170.8 (CO_2), 171.5 (CO_2), 185.7 (*C*=CH) and 209.6 (C=CH*C*O).

PK products **3**,[20] **7**,[25] **9**,[20] **11**,[26] **13**,[26] **14**,[26] **15**[25] and **16**[27] were identified by comparison of their spectroscopic data with literature data.

Data for **5**: white solid, mp 145–6°C (decomp.); IR ($CHCl_3$): ν 1709s (C=O), 1650m (C=C) and 1601m (C=C$_{Ar}$) cm^{-1}; ^{1}H NMR (360 MHz; $CDCl_3$): δ 2.30 (1H, dd, J=4, 18 Hz, C*H*HCO), 2.73 (1H, dd, J=6, 18 Hz, CH*H*CO), 2.86 (1H, dd, J=8, 10 Hz, C*H*HCHCH_2CO), 3.43–3.52 (1H, m, C*H*CH_2CO), 3.98 (1H, dd, J=8, 8 Hz, CH*H*CHCH_2CO), 4.06 (1H, d, J=16 Hz, C*H*HC=), 4.43 (1H, d, J=16 Hz, CH*H*C=), 6.12 (1H, brs, C=CH), 6.64 (2H, d, J=8 Hz, *o*-Ar-H), 6.79 (1H, t, J=7 Hz, *p*-Ar-H), 7.29 (2H, dd, J=7, 8 Hz, *m*-Ar-H); ^{13}C {^{1}H} NMR (125.8 MHz; $CDCl_3$): δ 40.9 (CH_2CO), 44.6 (*C*HCH_2CO), 49.1 (CH_2C=), 52.5 (CH_2CHCH_2CO), 112.4 (*o*-Ar-C), 117.7 (*p*-Ar-C), 125.6 (C=*C*H), 129.8 (*m*-Ar-C), 147.6 (*ipso*-Ar-C), 182.4 (*C*=CH), 209.3 (C=O); EI-MS: *m/z* (%)=199 (99) [M$^+$], 170 (13) [M$^+$−CHO], 105 (100) ($C_6H_5NCH_2^+$), 94 (66) [M$^+$−$C_6H_5NCH_2$], 77 (36) [$C_6H_5^+$]; Acc. Mass. ($C_{13}H_{13}NO$): calcd 199.0997; Found:199.0999.

4.1.3. 10 mmol Intramolecular PKA reaction. Enyne **6** (2.5 g, 10 mmol) and (PPh_3)$Co_2(CO)_7$, **1**, (288 mg, 0.5 mmol) were dissolved at room temperature in carbon monoxide saturated 1,2-DME (100 mL) under a carbon monoxide atmosphere (1.05 atm). The mixture was heated at 75°C with vigorous stirring in the dark (aluminium foil around the flask) for 4 h. The resulting brown mixture was cooled, filtered through a short pad of celite and concentrated in vacuo. (^{1}H NMR spectroscopy revealed total conversion.) Purification of the residue by flash column chromatography (SiO_2; hexane/EtOAc, 6:4) gave the known cyclopentenone **7**[3,25] (2.54 g, 9.2 mmol, 92%) as a white solid; mp 147–149°C (lit.[3] 145–148°C); IR ($CHCl_3$): ν 1714s (C=O), 1651m (C=C), 1600w (C–C$_{Ar}$), 1350s and 1162s (NSO_2) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.99 (1H, dd, J=4, 18 Hz, C*H*HCO), 2.32 (3H, s, CH_3), 2.48–2.58 (2H, m, CH*H*CO and C*H*HC=), 3.05–3.15 (1H, m, C*H*CH_2CO), 3.93–3.98 (2H, m, CH*H*C= and C*H*HCHCH_2CO), 4.27 (1H, d, J=17 Hz, CH*H*CHCH_2CO), 5.92 (1H, s, C=CH), 7.28 (2H, d, J=8 Hz, *m*-Ar-H), 7.66 (2H, d, J=8 Hz, *o*-Ar-H); ^{13}C {^{1}H} NMR (90.6 MHz; $CDCl_3$): δ 21.6 (CH_3), 39.8 (CH_2CO), 44.0 (*C*HCH_2CO), 47.7 (CH_2CHCH_2CO), 52.5 (CH_2C=), 126.2 (C=*C*H), 127.5 (*o*-Ar-C), 130.1 (*m*-Ar-C), 133.3 (*p*-Ar-C), 144.2 (*ipso*-Ar-C), 178.6 (*C*=CH), 207.2 (C=O).

4.1.4. 10 mmol Intermolecular PKA reaction. Phenylacetylene (1.02 g, 10 mmol), norbornene (4.70 g, 50 mmol) and $Ph_3PCo_2(CO)_7$, **1**, (288 mg, 0.5 mmol) were dissolved at room temperature in carbon monoxide saturated 1,2-DME (100 mL) under a carbon monoxide atmosphere (1.05 atm). The mixture was heated at 75°C with vigorous stirring in the dark (aluminium foil around the flask) for 4 h. The resulting brown mixture was cooled, filtered through a short pad of celite and concentrated in vacuo. (^{1}H NMR spectroscopy revealed total conversion.) Purification of the residue by flash column chromatography (SiO_2; hexane/EtOAc, 19:1) gave the known cyclopentenone **14**[26] (2.02 g, 9.0 mmol, 90%) as a white solid; mp 92–93°C (lit.[26] 95°C); IR ($CHCl_3$): ν 1696s (C=O) cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$): δ 1.02 (1H, ddd, J=11, 1, 1 Hz, CHC*H*HCHCHCO), 1.15 (1H, ddd, J=11, 2, 2 Hz, CHCH*H*CHCHCO), 1.32–1.42 (2H, m, CH_2C*H*HCHCHCO and CH_2C*H*HCHCHC=C), 1.61–1.67 (1H, m, CH_2CH*H*CHCHCO), 1.71–1.77 (1H, m, CH_2CH*H*CHCHC=C), 2.30 (1H, brd, J=4 Hz, CH_2C*H*CHC=C), 2.39 (1H, brd, J=5 Hz, CHCO), 2.53 (1H, brd, J=4 Hz, CH_2C*H*CHCO), 2.73 (1H, brdd, J=5, 3 Hz, CHC=C), 7.33–7.42 (3H, m, *m*-Ar-H and *p*-Ar-H), 7.67 (1H, d, J=3 Hz, C=CH), 7.71–7.74 (2H, m, *o*-Ar-H); ^{13}C {^{1}H} NMR (125.8 MHz; $CDCl_3$): δ 28.8 (CH_2CH_2CHCHCO), 29.6 (CH_2CH_2CHCHC=C), 31.7 (CH*C*H_2CHCHCO), 38.8 (CH_2*C*HCHC=C), 39.9 (CH_2*C*HCHCO), 48.1 (*C*HC=C), 55.4 (*C*HCO), 127.5 (*o*-Ar-C), 128.8 (*m*-Ar-C and *p*-Ar-C), 131.9 (*ipso*-Ar-C), 146.5 (Ph*C*=CH), 160.6 (C=*C*H), 209.5 (C=O).

4.1.5. 2-But-2-enyl-2-prop-2-ynyl-malonic acid dimethyl ester 12. 2-But-2-enyl malonic acid dimethyl ester (1.6 g, 8.6 mmol) was added over 5 min to a solution of sodium methoxide (540 mg, 10 mmol) in dry methanol (15 mL). The mixture was stirred under nitrogen for 15 min. Propargyl bromide (80% solution in toluene, 1.6 g, 10.8 mmol) was added over 15 min and the resulting mixture was stirred at room temperature for 16 h. The mixture was washed with water (20 mL), extracted with diethyl ether (3×15 mL) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, hexane/diethyl ether 9:1) of the residual oil gave the title compound **12** (0.771 g, 3.44 mmol, 40%) as a colourless oil (*E*/*Z*, 85:15); IR ($CHCl_3$): ν 3308w (C≡C–H), 3030w (C=C–H), 1734s (C=O) cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$): δ 1.67 (3H, brd, J=7 Hz, C=CHCH_3(*E*)), 2.02 (1H, t, J=3 Hz, C≡CH), 2.75 (2H, dm, J=8 Hz, CH_2CH=CHCH$_3$), 2.79 (2H, d, J=3 Hz, CH_2C≡C), 3.75 (6H, s, 2×OCH$_3$), 5.20–5.26 (1H, m, C=C*H*CH$_3$), 5.58–5.65 (1H, m, C*H*=CCH$_3$); ^{13}C {^{1}H} NMR (125.8 MHz; $CDCl_3$): δ 18.4 (C=CH*C*H$_3$(*E*)), 22.9 (CH_2C≡), 35.7 (CH_2C=CHCH$_3$), 53.1 (2×OCH$_3$), 57.4 (*C*(CO$_2$Me)$_2$), 71.7 (≡*C*H), 79.3 (*C*≡CH), 124.2 (CH=*C*HCH$_3$), 131.1

(*C*H=CHCH$_3$), 170.7 (2×*C*O$_2$Me); EI-MS: *m*/*z* (%)=224 (8) [M$^+$], 185 (54) [M$^+$−CH$_2$C≡CH], 165 (42) [M$^+$−CO$_2$Me], 164 (100) [M$^+$−HCO$_2$Me], 153 (84), 105 (63) [M$^+$−H(CO$_2$Me)$_2$]; Acc. Mass. ($C_{12}H_{16}O_4$): calcd 224.1049; Found: 224.1044.

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