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A palladium catalysed cyclisation–carbonylation of bromodienes: control in carbonylation over facile β-hydride elimination†

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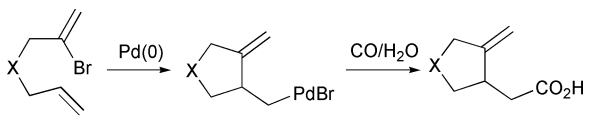
Conditions have been found for the efficient palladium mediated cyclisation–carbonylation of bromodienes to give γ,δ-unsaturated acids.

Palladium mediated cascade processes as developed by Trost,[1] Negishi,[2] Overman[3] and Grigg[4] often allow simple substrates to be converted directly into polycyclic functionalised products and as such the processes have been widely employed in highly efficient natural product synthesis. However, to ensure high yields, the substrates and trapping agents are usually designed/chosen so that only a single reaction pathway can be followed. Clearly it would be more useful if the particular reaction manifold could be controlled by choice of the palladium catalyst/co-catalyst/conditions rather than substrate structure as this would provide greater versatility in synthesis.

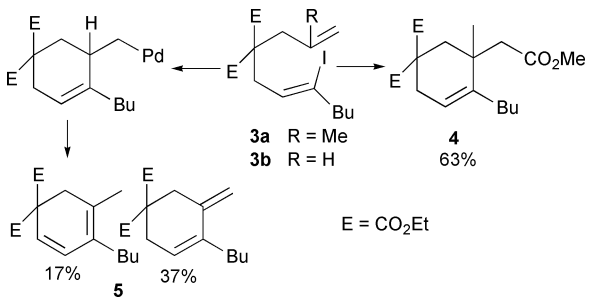
We chose to study the cyclisation–carbonylation of vinyl bromide **1** with the aim of producing the γ,δ-unsaturated acid **2** (Scheme 1).[5] Related work by Negishi[6] showed that whilst disubstituted alkenes provided high yields of unsaturated ester, monosubstituted alkenes only gave a mixture of dienes (Scheme 2).

Evidently in the case where β-hydride elimination can occur, it does so exclusively even in preference to an otherwise fast carbonylative process.[7] No doubt β-hydride elimination is facilitated by the presence of the alkene moiety which weakens the allylic C–H bond.[8] Our proposed palladium-mediated cascade process **1** → **2** is challenging as after oxidative addition, each of the proposed intermediates has at least one alternative pathway it can follow (Scheme 3). Our key concern was whether we could find conditions under which the alkyl palladium species **9** was trapped by CO faster than it underwent



1 **2**

Scheme 1 Desired process.



Scheme 2 Negishi's cyclisation–carbonylation protocol. *Reagents and conditions:* CO (1 atm) 5% $Cl_2Pd(PPh_3)_2$, NEt_3 (4 eq.), MeOH–DMF (1 : 2), 85 °C.

† Electronic supplementary information (ESI) available: experimental. See http://www.rsc.org/suppdata/cc/b2/b201311h/

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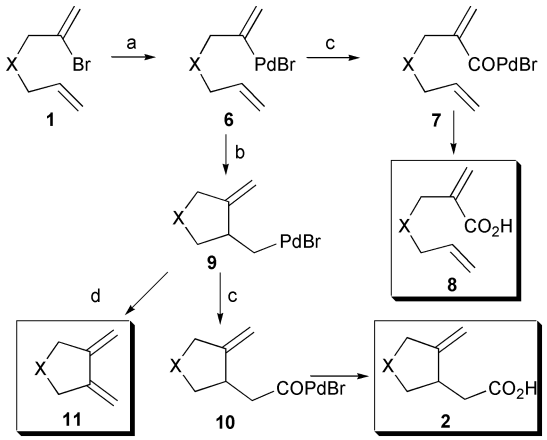

Scheme 3 Possible reaction routes, (a) Pd(0) (b) carbopalladation (c) carbonylation (d) β-hydride elimination.

β-hydride elimination;[9] the latter being the main reaction pathway in the related Negishi work.[6,9] Unfortunately the simple expedient of increasing the CO pressure to promote carbonylation over β-hydride elimination cannot be employed as this would result in trapping the vinyl palladium species **6**. Instead, we considered the possibility of tuning the reactivity of alkyl palladium **9** through choice of phosphine ligand. We reasoned that the rate of carbonylation could be increased by using electron rich phosphines, which should favour binding of CO to palladium because it is a strong π-acceptor. Thus, we should be able to control the course of the reaction towards the desired product through the correct choice of phosphine.

Treating bromodiene **1a** with a palladium catalyst under an atmosphere of carbon monoxide led to the formation of a mixture of products consisting of the γ,δ-unsaturated acid **2a**, the α,β-unsaturated acid **8a** and the diene **11a**. Brief optimisation of solvent, base, temperature and pressure led us to the following standard conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), NaOAc (2 eq.) dry DMF (0.2 M) at 80 °C under 2 atmospheres of CO[10] for 24 h with a phosphine co-catalyst (0.4 eq.).[11]

We then varied the phosphine ligand and analysed the ratio of products obtained (Table 1) and we were pleased to note that our analysis was broadly correct: highly electron rich phosphines promoted carbonylation. However, carbonylation was so fast with the electron rich alkyl phosphines (entries 1–3) that this process competed with carbopalladation leading to significant amounts of the linear acid. It transpired that aryl phosphines possessed the right balance between promoting carbonylation, but not too fast so that none of the linear acid was detected, and inhibiting the rate of β-hydride elimination (entries 4 and 5). Of the aryl phosphines, P(2-furyl)$_3$ gave more of the carbonylated product **2** over the β-hydride eliminated diene **3**. The bisphosphine dppb was also tested but gave large amounts of diene **11**.

Having achieved good yields and high selectivity in favour of the cyclised acid, we decide to investigate alternative substrates using the two optimum phosphines from our screening studies (Table 2).

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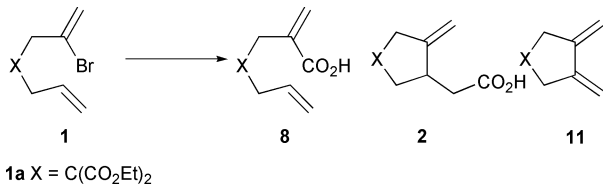
Table 1 Effect of phosphines on the reaction distribution (Scheme 4)

Entry	Phosphine	Yield (%)[a]	Ratio[b] **2a**:**8a**
1	P^tBu_3	65	1:3:7
2	P^tBu_2BiPh	48	2.1:1
3	PCy_2BiPh	42	1.9:1
4	PPh_3	65	>20:1
5	P(2-furyl)$_3$	79	>20:1
6	dppb[c]	26	>20:1
7	P^tBu_3[d]	42[e]	2.4:1

[a] Isolated yields of acids, the remainder of materials is diene **11**. [b] Determined from ^{1}H NMR. [c] 0.2 eq. [d] 1 atm CO. [e] Purified by column chromatography.



Scheme 4 *Reagents and conditions*: substrate (0.25 mmol, 1 eq.), $Pd_2dba_3.CHCl_3$ (2.5 mol%), phosphine (0.4 eq.), NaOAc (2 eq.), dry DMF (0.2 M), 80 °C, CO (2 atm), 24 h.

Table 2 Effect of substituents on product distribution (Scheme 5, R = H)

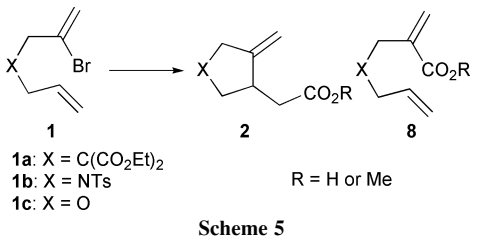
Entry	X	Phosphine[a]	Yield (%)[b]	Ratio **2**:**8**[c]
1	$(EtO_2C)_2C$	A	68	>20:1
2	$(EtO_2C)_2C$	B	52	>20:1
3	TsN	A	62	1:1[d]
4	TsN	B	50	9:1
5	O	A	69	1:6
6	O	B	37	0:1[e]

Reagents and conditions: substrate (0.25 mmol, 1 eq.), $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%), phosphine (0.3 eq.), NaOAc (2 eq.), dry DMF (0.2 M), 80 °C, CO (2 atm), 24 h.[a] A = P(2-furyl)$_3$, B = PPh_3. [b] Isolated yield of acid mixtures purified by column chromatography. [c] Determined by ^{1}H NMR. [d] Ratio of isolated products and ^{1}H NMR. [e] Direct capture product only.

The sulfonamide linked substrate **1b** gave a 1:1 mixture of cyclised:linear acids **2b**:**8b** using P(2-furyl)$_3$ but a much improved 9:1 ratio with PPh_3 (Table 2, entries 3 and 4). The ether linked substrates were much poorer and provided mostly the linear acids. The ratio of linear:cyclised acids for the different substrates reflects their relative rates of cyclisation which is increased with increasing substitution in the linking chain.[12]

The yield of the cyclised acid was especially low for substrate **1c** bearing the oxygen linker which is undoubtedly the most challenging substrate. If we could increase the yield for **1c** this would provide a general solution to the cyclisation–carbonylation of essentially any related bromodiene. Having explored how variation in the phosphine altered the course of the reaction we decided to investigate solvent effects. As a starting point we chose Negishi's solvent system [DMF–MeOH–H_2O (20:10:1)], which was effective in cyclisation of **3a** to give **4**, and chose to initially study substrate **1b** where improved yields and selectivity were desirable. Although some product was obtained using these conditions, we found that with added PPh_3 and at the higher pressure of 2 atm of CO, a good yield of the cyclised methyl ester was achieved (Table 3, entry 1). The reaction could also be conducted in DMF–H_2O and an even higher yield of the cyclised acid was obtained (entry 2). Using these conditions, improved yields of cyclised esters/acids were also obtained with the most difficult oxygen linker **1c** (entries 3 and 4). In particular, use of P(2-furyl)$_3$ gave a 48% isolated yield of the cyclic ester **2c** (entry 5).

In summary, we have found conditions under which a cascade cyclisation–carbonylation can be efficiently conducted on monosubstituted alkenes. These substrates are particularly difficult as the alkyl palladium intermediate is prone to undergoing facile β-hydride elimination. We have been able to achieve moderate to good yields of cyclic γ,δ-unsaturated esters and acids even from substrates that do not have an inherent proclivity towards cyclisation.



Scheme 5

Table 3 Effects of solvent on product distribution (Scheme 5)

			Yield of esters (acids)(%)[b]	
Entry	Substrate	Conditions[a]	**2**	**8**
1	**1b**	A	69	—
2	**1b**	B	(74)	(7)
3	**1c**	A	36	21
4	**1c**	B	(29)	(23)
5	**1c**	C	48	23

[a] All reactions were run at 85 °C for 24 h under 2 atm of CO pressure in the presence of NEt_3 (4 eq.), A = 5% $Cl_2Pd(PPh_3)_2$, PPh_3 (0.2 eq.), MeOH–DMF–H_2O (1:2:0.1), B = 5% $Cl_2Pd(PPh_3)_2$, PPh_3 (0.2 eq.), DMF–H_2O (20:1), C = 5% $PdCl_2$, P(2-furyl)$_3$ (0.3 eq.), MeOH–DMF–H_2O (1:2:0.1). [b] Isolated yield of acid or ester mixtures after column chromatography.

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