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Palladium catalysed cyclisation–carbonylation of enynes to give cyclic γ,δ-unsaturated acids†

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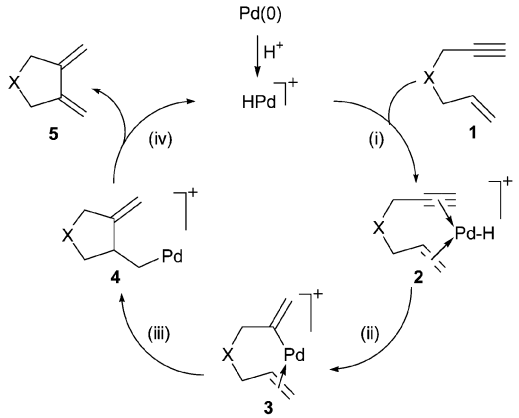
In the presence of acetic acid, trifurylphosphine and CO (2 atm), palladium catalyses the conversion of a range of enynes to cyclic δ,γ-unsaturated carboxylic acids in good yield.

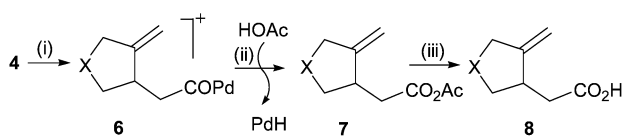
Cycloisomeristion of linear enynes using Pd(0) and an acid to give cyclic dienes is a well established process and has been extensively exploited in total synthesis, most notably by Trost.[1]



Scheme 1 Cycloisomerisation of enynes: (i) complexation, (ii) hydridopalladation, (iii) carbopalladation, (iv) β-H elimination.

A possible catalytic cycle for this process is shown in Scheme 1. Palladium hydride (PdH), which is initally formed from Pd(0) and acetic acid,[2] complexes with the enyne **1** to give **2**. Following hydridopalladation and carbopalladation the alkyl palladium intermedeate **4** is formed which finally undergoes β-hydride elimination to give the diene product **5** and reforms the active catalyst.

A valuable extension of this elegant process would be to couple the alkyl palladium intermedeate **4** with another reagent to generate even more functionalised products.[3] We considered the possibility of trapping **4** with CO as the acyl palladium intermedeate **6** could react further with AcOH[4] to furnish the anhydride **7** and return the active PdH catalyst (Scheme 2). Thus the acetic acid would be required to have a dual role in the catalytic process as a source of H^+ to form the PdH catalyst and as a nucleophile to trap the acyl palladium intermedeate **6**. It is likely that the anhydride would hydrolyse to the corresponding acid **8** under the reaction conditions.



Scheme 2 Desired process: (i) carbonylation, (ii) transformation of acylpalladium, (iii) hydrolysis.

† Electronic supplementary information (ESI) available: data for novel compounds. See http://www.rsc.org/suppdata/cc/b3/b300719g/

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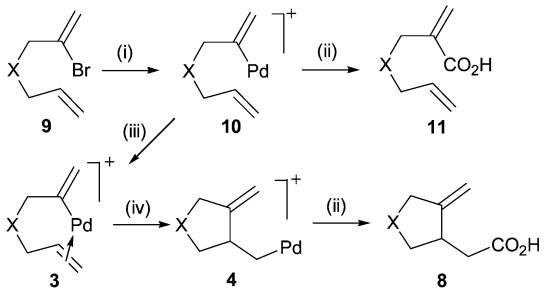


Scheme 3 Competing pathways: (i) oxidative addition by Pd(0), (ii) carbonylation then transformation of the acyl palladium species, (iii) complexation, (iv) carbopalladation.

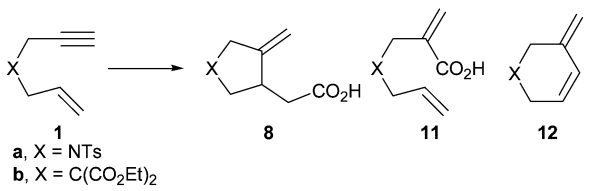
Although we had previously shown that bromodiene **9** could be converted to the same unsaturated acid **8** through careful choice of conditions that limited β-hydride elimination from **4** (Scheme 3),[5] we felt that the use of enynes offered several advantages:

(i) The starting materials are less functionalised and would be easier to prepare.

(ii) Increased atom economy.

(iii) If the enyne was complexed to Pd (Scheme 1, intermedeate **2**), premature capture of the vinyl palladium species **10** to give the linear acid **11** could be avoided. This side reaction (Scheme 3) plagued the synthesis of unsaturated acids **8** from bromodiene substrates which did not have a high proclivity towards cyclisation.[5]

We began our investigations of the enyne cyclisation process on **1a** using conditions that had successfully been used in



Scheme 4 Schematic for Table 1.

Table 1 Solvent and acid effects on product distribution (Scheme 4)

					Yields (%)[b]		
Entry	Substrate	Solvent	Conditions[a]	Additive	**8**	**1**	**12**
1	**1a**	DMF	A	—	17	76	—
2	**1b**	DMF	B	—	10	78	—
3	**1b**	DME	B	—	55	23	—
4	**1b**	Dioxane	B	—	32	8	—
5	**1b**	CH_3CN	B	—	—	< 10	32
6	**1b**	DME	B	TFA (1 eq.)	57	14	18

[a] All reactions were run at 80 °C for 24 h under 2 atm pressure of CO in the presence of (A) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), P(2-furyl)$_3$ (0.3 eq.), HOAc (2 eq.) at a substrate concentration of 0.25 M, (B) $Pd(OAc)_2$ (10 mol%), P(2-furyl)$_3$ (60 mol%) and HOAc (10 eq.) at a substrate concentration of 0.33 M. [b] Determined by NMR against an internal standard.

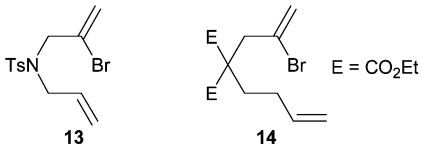
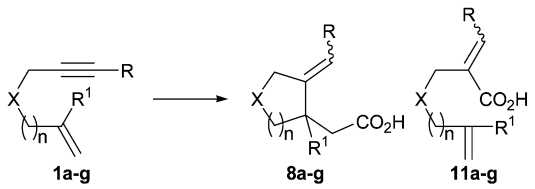


Fig. 1

bromodiene cyclisation–carbonylation [$Pd_2(dba)_3$·$CHCl_3$ (2.5 mol%), P(2-furyl)$_3$ (0.3 eq.), NaOAc (2 eq.), DMF, 80 °C, CO (2 atm)] except that NaOAc was replaced by AcOH. This first attempt was indeed partially successful: the cyclised product was formed, albeit in low yield, without formation of the linear acid but a large quantity of starting material remained (Table 1, entry 1). In fact when these conditions were employed with the corresponding bromodiene **13** (Fig. 1), a 1 : 1 ratio of linear and cyclised acids was formed.[5] This highlights the considerable advantage of the palladium complexed enyne intermediate **2**, as this clearly avoids premature capture of the vinyl palladium intermediate **10** by CO. However the yield was low and large amounts of starting material remained. In fact when these conditions were applied to **1b**, very little conversion occurred. As **1b** showed even less tendency to react, further investigations were directed towards this substrate so that we could arrive at a more general solution. Variation in source of Pd, amount of acid and concentration finally led to a set of conditions (B) which did indeed furnish a small amount of the desired product, but again a large amount of starting material **1b** remained (Table 1, entry 2). To promote the reaction, we needed to promote complexation of the PdH with the enyne, the first step in the cascade process. We felt that DMF might be coordinating strongly to Pd,[2] thus preventing enyne complexation, and so we sought less polar/coordinating solvents (Table 1). Indeed, changing from DMF to DME produced a considerable improvement in yield of the desired product (entry 3). Dioxane was also effective but several side-products were observed (entry 4) and MeCN changed the course of the reaction to give the diene **12** (entry 5).[6] Attempts to increase the reactivity of the PdH species by using a stronger acid did lead to increased conversion of the enyne but also resulted in increased quantities of diene **12** (Table 1, entry 6).

Further optimisation of the enyne reaction in DME was performed and it was found that changing from $Pd(OAc)_2$ to $Pd_2(dba)_3$·$CHCl_3$ and increasing the amount of acid led to complete consumption of enynes **1a/b** (Table 2). Indeed when these optimised conditions were applied to a number of 1,6-enynes good yields of the desired cyclised products were obtained (Table 2, entries 1 to 3). Application to enynes bearing non-terminal alkynes was not successful and starting material was largely reisolated (entries 4 and 5). The 1,7-enyne **1f** gave the desired product **8g** in reasonable yield together with 20% of the linear product **11g** (entry 6). This compares with the bromodiene methodology in which the corresponding bromodiene **14** (Fig. 1) gave the acid products in 90% combined yield as a 4.6 : 1 mixture of the linear to cyclic product. A less highly substituted 1,7-enyne **1g** gave linear acid **11g** as the predominant product with only a small amount of **8g** (entry 7) indicating the limitation to the substrates which can be employed.



Scheme 5 Schematic for Table 2.

Table 2 Application of reaction conditions (Scheme 5)

						Yields (%)[a]	
Entry	Substrate	X	*n*	R	R^1	**8**	**11**
1	**1a**	NTs	1	H	H	68	—
2	**1b**	$C(CO_2Et)_2$	1	H	H	72	—
3	**1c**	$C(CO_2Et)_2$	1	H	Me	77	—
4	**1d**	NTs	1	Me	H	Trace	—
5	**1e**	NTs	1	TMS	H	—	—
6	**1f**	$C(CO_2Et)_2$	2	H	H	45	20
7	**1g**	NTs	2	H	H	11	53

Reagents and conditions: All reactions were run at 80 °C for 38 h under 2 atm. pressure of CO in the presence of $Pd_2(dba)_3$·$CHCl_3$ (5 mol%), P(2-furyl)$_3$ (60 mol%) and HOAc (15 eq.) at a substrate concentration of 0.33 M in DME.[a] Purified by column chromatography.

There are two possible linear starting materials which lead to cyclic γ,δ-unsaturated acids *via* the common palladium intermediate **3**: bromodiene **9** or enyne **1**. The difference between the two processes in relation to the ratio of cyclic : linear acids formed appears to result from the method of formation of the key vinyl palladium intermediate **3**. Once this intermediate is formed carbopalladation can ensue and the cyclic acid will be produced. In the case of the bromodienes intermediate **3** is reached only after formation of vinyl palladium species **10**, allowing carbonylation to compete with association and cyclisation. In the case of enynes both the alkyne and alkene are proposed to coordinate to the metal *before* addition of the PdH across the alkyne and hence the vinyl palladium species **3** is formed directly and not *via* intermediate **10**. For premature carbonylation to occur from the enyne substrate, dissociation of the alkene from the palladium centre (**3** → **10**) must proceed at a rate comparable with carbopalladation. This clearly does not occur with 1,6-enynes where carbopalladation is fast but does occur with 1,7-enynes, resulting in formation of significant quantities of linear acids.

In conclusion we have developed a novel cyclisation–carbonylation–capture process for the conversion of enynes into γ,δ-unsaturated cyclic acids in good yields. This study also demonstrates that enynes may well be superior substrates to bromodienes for cascade processes as one possible competing pathway (premature capture) is severely retarded.

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Notes and references

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3 When generated from an enyne, **4** has previously been trapped with: (*a*) a hydride source such as PMHS to effect a cyclisation reduction strategy: B. M. Trost and F. Rise, *J. Am. Chem. Soc.*, 1987, **109**, 3161; (*b*) an organostannane to effect a cyclisation cross-coupling strategy: H. Yamada, S. Aoyagi and C. Kibayashi, *Tetrahedron Lett.*, 1997, **38**, 3027.

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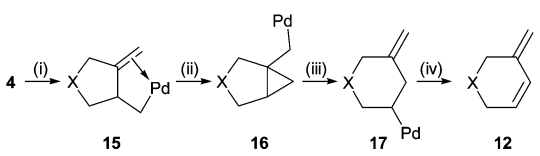
5 V. K. Aggarwal, P. W. Davies and W. O. Moss, *Chem. Commun.*, 2002, 972.

6 A likely pathway for the formation of diene **12** is shown in Scheme 6:



Scheme 6 Formation of **12**: (i) complexation, (ii) carbopalladation, (iii) rearrangement, (iv) β-H elimination.

See E. Negishi, C. Copéret, S. Ma, T. Mita, T. Sugihara and J. M. Tour, *J. Am. Chem. Soc.*, 1996, **118**, 5904.