Palladium-catalysed annulation of β-chloro-α,β-unsaturated esters with internal alkynes leading to 2*H*-pyran-2-ones

Ruimao Hua and Masato Tanaka*

National Institute of Materials and Chemical Research, Tsukuba, Ibaraki 305-8565, Japan.
E-mail: mtanaka@home.nimc.go.jp

Received* (*in Montpellier, France*) *15th September 2000, Accepted 6th October 2000
First Published as an Advance Article on the web 5th December 2000

Heteroannulation of β-chloro-α,β-unsaturated esters with internal alkynes proceeded in the presence of triethylamine and palladium complexes, bis(triphenylphosphine)palladium species in particular, to afford to 2*H*-pyran-2-ones. Treatment of methyl (*Z*)-3-chloro-2-heptenoate with $Pd(PPh_3)_4$ generates [(*Z*)-1-butyl-2-methoxycarbonylethenyl]chlorobis(triphenylphosphine)palladium *via* oxidative addition, which gives the corresponding 2*H*-pyran-2-one upon addition of 4-octyne. Terminal alkynes also reacted with β-chloro-α,β-unsaturated esters, but the major products were β-alkynylated α,β-unsaturated esters.

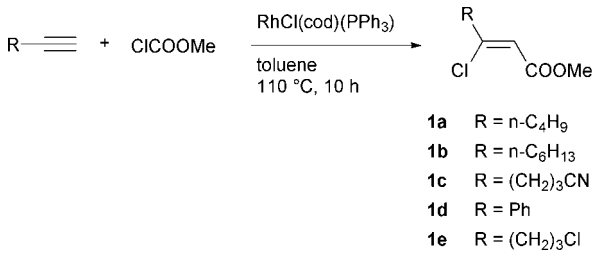
Introduction

2*H*-Pyran-2-one derivatives not only are valuable materials for organic synthesis, but also have physiological and biological activities in their own rights. For instance, some trisubstituted 2*H*-pyran-2-ones are claimed to be potent human immunodeficiency virus protease (HIV PR) inhibitors.[1] Although their synthetic methods have widely been explored,[2] those based on transition metal complex-catalysed reactions are very limited. Inoue,[2c–e] Walther[2f] and Tsuda *et al.*[2g] reported nickel-catalysed synthesis starting with alkynes and CO_2. Liebeskind and co-workers[2h,i] reported the formation of 2*H*-pyran-2-ones in rhodium(I)-catalysed carbonylation of cyclopropenyl esters and cyclopropenyl ketones and in palladium-catalysed carbonylative cross-coupling of 4-halogenocyclobutenones with organostannanes.

Recently we have reported the rhodium(I)-catalysed chloroesterification of alkynes with methyl chloroformate.[3] This new catalytic reaction provides a simple and efficient method to prepare (*Z*)-β-chloro-α,β-unsaturated esters (**1**) of great synthetic potential (Scheme 1). As a part of our studies on the synthetic application of **1**, we disclose herein that its palladium-catalysed reactions with internal alkynes successfully proceed in the presence of Et_3N to afford 4,5,6-trisubstituted 2*H*-pyran-2-ones. After we finished the experiments,[4] similar reactions starting with β-iodo, β-bromo-, and trifluoromethylsulfonyloxy-α,β-unsaturated esters were reported.[5]

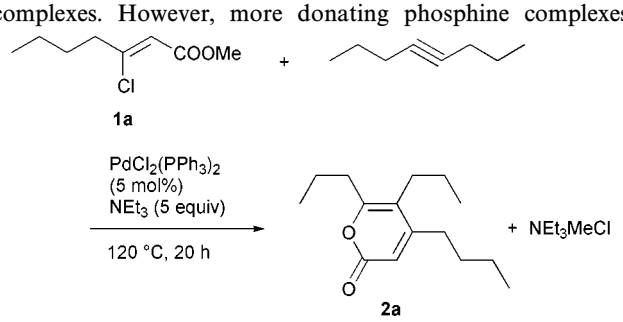
Results and discussions

We initiated the investigation with the reaction of compound **1a** with 4-octyne. In a sealed tube, a toluene (1 mL) solution of **1a**, 4-octyne (1.2 equiv.), Et_3N (5 equiv.) and $Pd(PPh_3)_2Cl_2$ (5 mol% relative to **1a**) was heated at 120 °C for 20 h. The corresponding heteroannulation product, 4-butyl-5,6-dipropyl-2*H*-pyran-2-one **2a**, was found by GC analysis to be formed in 83% yield, along with the precipitation of insoluble triethylammonium chloride (Scheme 2; Table 1, entry 1). The yield could be increased to 88% when a higher reaction temperature (*e.g.* 160 °C) was used (entry 2).[6]



Scheme 1

As Table 1 shows, the reaction appears to be best catalysed by bis(triphenylphosphine)palladium species, independent of the structure of the precursor complex. Thus, the catalyst systems generated with *cis*-$PdMe_2(PPh_3)_2$, $PdCl_2 + 2PPh_3$, and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2 + 4PPh_3$ (entries 3–5) all performed nearly equally well to form **2a**. On the other hand, the $Pd(PPh_3)_4$-catalysed reaction gave **2a** in only 9% yield under the same reaction conditions (entry 6), suggesting the importance of the vacant coordination site for the oxidative addition of the Cl–C bond (*vide infra*). The species generated from $PdCl_2 + 4PPh_3$ also resulted in a similar performance (entry 7). The use of phosphine-free palladium compounds such as $PdCl_2$, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and $Pd(OAc)_2$ (entries 13–15) did not form the product at all,[7] presumably associated with the instability of intermediates and/or the lack of oxidative addition with **1a** due to the low electron density at the palladium center as compared with phosphinepalladium species. Accordingly, addition of only equiv. of PPh_3 greatly improved the catalytic performance of the palladium complex (entry 8). Palladium complexes ligated by less donating phosphorus ligand such as etpo (entry 9) and dppf (entry 10) also catalysed the reaction, albeit less actively than the bis(triphenylphosphine) complexes. However, more donating phosphine complexes



Scheme 2

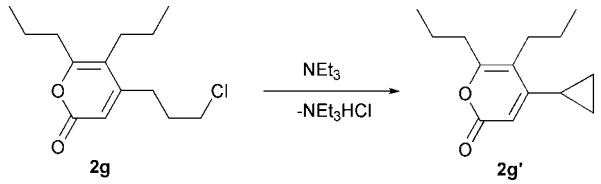
Table 1 Reaction of methyl (*Z*)-3-chloro-2-heptenoate **1a** with 4-octyne in the presence of Group 10 metal complex catalysts and Et_3N[a]

Entry	Catalyst	Recovery of **1a**(%)	**2a** (%)[b]
1	$PdCl_2(PPh_3)_2$	~0	83
2[c]	$PdCl_2(PPh_3)_2$	~0	88
3	*cis*-$PdMe_2(PPh_3)_2$	~0	81
4	$PdCl_2 + 2PPh_3$	~0	76
5	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$[d] + $4PPh_3$	~0	78
6	$Pd(PPh_3)_4$	84	9
7	$PdCl_2 + 4PPh_3$	78	3
8	$PdCl_2 + 1PPh_3$	27	59
9	$PdCl_2$ + 2etpo[e]	41	44
10	$PdCl_2$(dppf)[f]	nd	56
11	$PdCl_2$(dppb)[g]	nd	0
12	*cis*-$PdMe_2(PMe_2Ph)_2$	75	0
13	$PdCl_2$	>70	0
14	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$[d]	>70	0
15	$Pd(OAc)_2$	>70	0
16	$Ni(cod)_2 + 2PPh_3$	80	12
17	$Ni(cod)_2$ + 1.2dppf[f]	71	19
18	$Pt(PPh_3)_4$	nd	0
19	$Pt(PPh_3)_2(CH_2{=}CH_2$	nd	0
20[h]	*cis*-$PdMe_2(PPh_3)_2$	63	14
21[i]	*cis*-$PdMe_2(PPh_3)_2$	51	27

[a] All reactions were carried out using 0.2 mmol of **1a**, 0.24 mmol of 4-octyne, 1.0 mmol of Et_3N, 0.01 mmol of catalyst in 0.4 mL of toluene or toluene-d_8 at 120 °C for 20 h. [b] Determined by GC based on the amount of **1a** used. [c] Run at 160 °C for 7 h in ethylbenzene. [d] 0.005 mmol catalyst. [e] etpo = 4-ethyl-2,4,6-trioxa-1-phosphabicyclo[2.2.2]octane. [f] dppf = 1,1′-bis(diphenylphosphino)ferrocene. [g] dppb = 1,4-bis(diphenylphosphino)butane. [h] Run in a sealed glass tube without using NEt_3. [i] Run under atmospheric pressure of nitrogen in ethylbenzene without using NEt_3.

such as *cis*-$PdMe_2(PMe_2Ph)_2$ and $PdCl_2$(dppb) did not exhibit activity (entries 11 and 12). Nickel complexes also catalysed the reaction, but the activity was much lower than that of the palladium complexes (entries 16 and 17), and platinum complexes did not catalyse the reaction at all (entries 18 and 19). Based on the possible mechanism of the catalysis (*vide infra*), it appeared conceivable that the reaction could hopefully proceed in the absence of triethylamine as chloromethane trapping agent. Indeed, it proceeded even in a sealed glass tube although it was very sluggish (entry 20). Another reaction run in an open system that minimizes accumulation of chloromethane resulted in a better yield (entry 21).

To assess the scope of this annulation, the reactions of compounds **1** with several alkynes have been investigated. The results are summarized in Table 2. It can be seen that the reactions of **1a** and **1b** with symmetrical dialkyl-substituted alkynes work nicely to give the corresponding trisubstituted 2*H*-pyran-2-ones in good yields (entries 1, 2, 4). However, unsymmetrical alkynes end up with the formation of regioisomers. At the moment we are unable to control the regiochemistry. For examples the reaction of **1a** with 2-pentyne (entry 3) gave an approximately 1 : 1 mixture of two regioisomers. β-Chloro-α,β-unsaturated esters having cyano (**1c**) and phenyl (**1d**) substituents also reacted similarly (entries 5, 6). However, the reaction of **1e** having a chloro substituent at the terminus (entry 7) afforded only 9% isolated yield of the corresponding 2*H*-pyran-2-one (**2g**; M^+, $m/z = 256$ for ^{35}Cl isotope). Another pyranone (**2g′**), which was isolated in 35% yield as the major product of the reaction, revealed on the basis of mass spectroscopy (M^+, m/z 220) that the chloro substituent was not retained in this product. ^1H NMR displayed signals in a very high region (δ 0.2–0.5), characteristic of a cyclopropyl group, suggesting that initially formed **2g** partially cyclized to form the 4-cyclopropylpyranone (Scheme 3). The cyclization is presumably associated with the acidity of the



2g **2g′**

Scheme 3

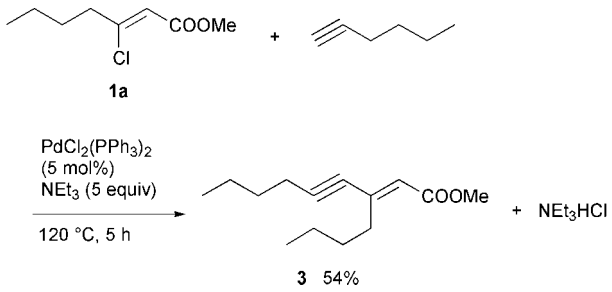
α-CH_2 in the γ-chloropropyl group bound to the pyranone ring in compound **2g**.[8]

More sterically congested alkynes also reacted with compound **1a**, albeit very sluggishly (entries 8 and 9). The starting materials were not completely consumed in these reactions even after heating for longer times (70–90 h). The product from 1-phenyl-1-butyne comprised two regioisomers in a ratio of approximately 1.2 : 1. 2,7-Dimethyloct-1-en-3-yne (90 h) also formed two regioisomers in an approximately 1 : 1 ratio.

The present procedure was not well applicable to terminal alkynes. However, a Hagihara–Heck type coupling product was formed readily (Scheme 4). Thus the reaction between compound **1a** and 1-hexyne run for 5 h under the standard conditions using Pd $Cl_2(PPh_3)_2$ as the catalyst gave methyl 3-butyl-(*Z*)-2-nonen-4-ynoate **3** in 54% yield.[9] GC-MS showed formation of the corresponding 2*H*-pyran-2-one derivatives only in a small quantity (<5%).

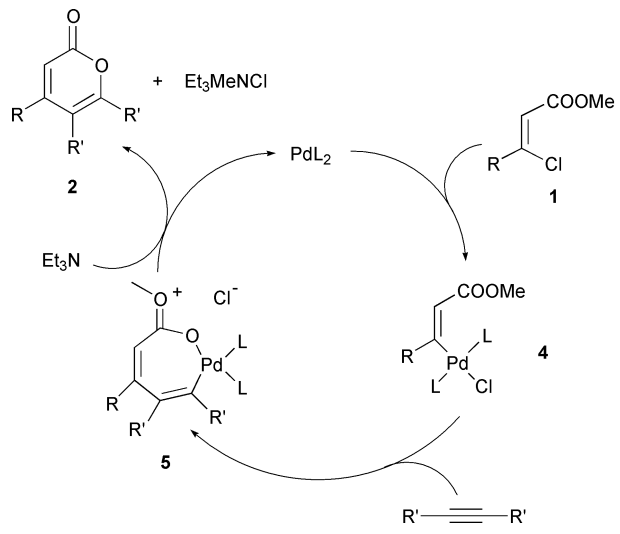
Under the standard reaction conditions, other functionalized alkynes, such as dimethyl acetylenedicarboxylate, methyl 2-octynoate, 3-hexyn-2-one and 2-butyn-1-yl acetate, did not form 2*H*-pyran-2-one derivatives in appreciable quantities. Oligomerization of these alkynes appeared to precede the annulation reaction.

On the basis of the results and the known palladium chemistry, a possible mechanistic explanation for the formation of compound **2** can be summarized as shown in Scheme 5. This proposal is closely related to one for isocoumarin formation.[5b] It involves oxidative addition of **1** to bis(phosphine)-palladium(0) species, generating the (β-methoxycarbonyl-



3 54%

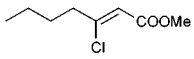
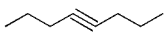
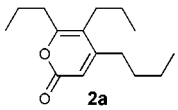
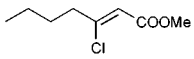
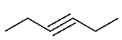
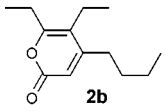
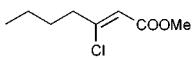
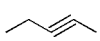
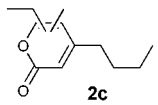
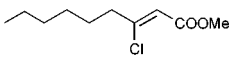
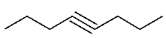
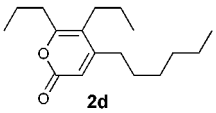
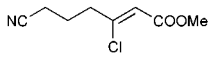
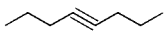
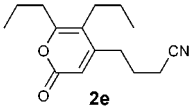
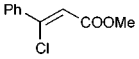
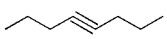
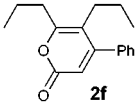
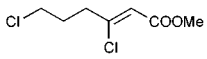
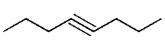
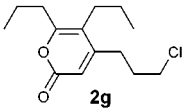
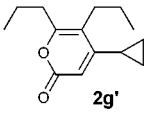
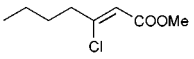
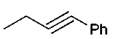
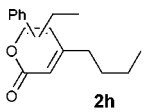
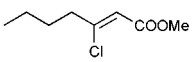
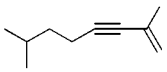
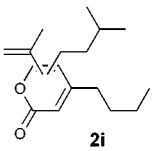
Scheme 4



2 **1** **5** **4**

Scheme 5

Table 2 Pd-catalysed reactions of β-chloroacrylates (**1**) with alkynes in the presence of Et_3N[a]

Entry	β-Chloro ester	Alkyne	Time /h	Product	Yield (%)[b]
1	 **1a**		20	 **2a**	74 (83)[c]
2	 **1a**		20	 **2b**	72
3	 **1a**		20	 **2c**	67[d]
4	 **1b**		20	 **2d**	62
5	 **1c**		20	 **2e**	56
6	 **1d**		20	 **2f**	57
7	 **1e**		20	 **2g**	9 (19)
				 **2g'**	35 (51)
8	 **1a**		70	 **2h**	65[e,f]
9	 **1a**		90	 **2i**	47[d,e]

[a] Reactions were carried out using 0.5 mmol of **1**, 0.6 mmol of alkyne, 2.5 mmol of Et_3N and 0.025 mmol of $PdCl_2(PPh_3)_2$ in 1.0 mL of toluene at 120 °C. [b] Unless otherwise noted, the yields refer to isolated yields based on the amount of **1** used. [c] The figure in parentheses is GC yield. [d] Mixture of two regioisomers in a ratio of *ca.* 1 : 1. [e] ^1H NMR yield. [f] Mixture of two regioisomers in a ratio of *ca.* 1 : 1.2.

vinyl)palladium intermediate **4**, insertion of alkyne into the Pd–C bond and nucleophilic attack of the carbonyl oxygen on the palladium center to result in the palladacycle **5**. Finally, elimination of triethylmethylammonium chloride and reductive elimination furnish 2*H*-pyran-2-one and regenerate Pd^0.[10] Among the elemental processes involved in the catalytic cycle, those relevant to the oxidative addition and the reactivity of the resulting complex are substantiated by the following experiments. Thus, treatment of $Pd(PPh_3)_4$ with **1a** at 90 °C for 3 h in toluene caused the solution to change from yellow to pale yellow and very cleanly generated *Z*-**4**, which was isolated in 83% yield after recrystallization. Complex *Z*-**4**, when used as the catalyst (5 mol%) for the reaction of **1a** and 4-octyne under the standard conditions, afforded **2a** in 87% yield. In addition, when *Z*-**4** was treated in toluene with 4-octyne (5 equiv.) in the presence of Et_3N (5 equiv.) at 120 °C for 10 h, **2a** was obtained in 65% yield, supporting that the generation of *Z*-**4** triggered the catalysis. We have been unsuccessful in isolating or spectroscopically characterizing the intermediates that follow *Z*-**4**. However, according to the mechanistic proposal, it was envisaged that an external nucleophile added to the reaction between complex **4** and

alkyne could retard the conversion of **4** into **2** by suppressing nucleophilic attack of the carbonyl oxygen on the palladium(II) center at the intermediate stage like **5**. Indeed, when the foregoing reaction of *Z*-**4** with 4-octyne (5 equiv.) in the presence of Et_3N (5 equiv.) was repeated in the presence of 1 equiv. of triphenylphosphine the yield of **2a** decreased to 23% (*vs.* 65% observed in the absence of the extra PPh_3). Another similar reaction in the presence of tetrahydrofuran (50 equiv. relative to *Z*-**4**) also resulted in a lower yield of **2a** (44%).[11] The $PdCl_2(PPh_3)_2$-catalysed reaction of **1a** with 4-octyne (entry 1, Table 1) was also retarded when run in the presence of THF (5 equiv. relative to **1a**) to give only 54% GC yield of **2a**. The low catalytic activity of $Pd(PPh_3)_4$ as compared with $PdCl_2(PPh_3)_2$ is presumably associated with the oxidative addition step. However, if we consider that the oxidative addition of **1a** with $Pd(PPh_3)_4$ could proceed even at 90 °C (*vide supra*), we cannot rule out the possibility that the low activity of $Pd(PPh_3)_4$ is due at least partially to the free PPh_3 generated from it under the catalytic conditions, which causes a similar negative effect on the nucleophilic attack of the carbonyl oxygen.

In summary, we have developed a new palladium-catalysed annulation reaction to furnish 4,5,6-trisubstituted 2*H*-pyran-2-ones, starting with internal alkynes and β-chloro-α,β-unsaturated esters **1**, the latter of which can readily be obtained by rhodium-catalysed addition of chloroformates to terminal alkynes. Further study of the synthetic elaboration of **1** is in progress.

Experimental

General

All ^1H, ^{31}P-{H} and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer at 300, 121.5 and 75.5 MHz, and referenced to $SiMe_4$ (^1H), appropriate solvent resonances (^{13}C) and H_3PO_4 (^{31}P), respectively. GC-MS was performed on a Shimadzu GC-17A/QP-5000 mass spectrometer by using EI (70 eV) with an OV-1701 (25 m) column. Infrared spectra were obtained on a JASCO FT/IR-5000 spectrometer.

Synthesis and product characterization

General procedure for palladium-catalysed annulation of compounds 1 with alkynes. In a thick-walled Pyrex tube was placed a mixture of compound **1** (0.5 mmol), alkyne (0.6 mmol), Et_3N (2.5 mmol), palladium catalyst (0.025 mmol) and toluene (1.0 mL) under nitrogen. The tube was then flame-sealed and heated at 120 °C. The progress of the reaction could be followed visually by the precipitation of insoluble ammonium chloride. After cooling, removal of precipitate by filtration and evaporation of volatiles *in vacuo*, the residue was extracted with hexane (5.0 mL) (except for **2e**, which was extracted with diethyl ether). The extract, after concentration (to *ca.* 1 mL), was chromatographed on alumina with an appropriate eluent to afford pure product **2**.

The experiments summarized in Table 1 were conducted on an 0.2 mmol scale (with respect to compound **1a**). After removal of precipitate by filtration, the filtrate was diluted with toluene to 2.0 mL and analysed by gas chromatography after addition of an appropriate amount of ferrocene as internal standard.

4-Butyl-5,6-dipropyl-2*H*-pyran-2-one 2a. Chromatography on alumina with hexane as eluent gave a pale yellow oil (87.0 mg, 0.37 mmol, 74%), which was distilled on Kugelrohr to furnish an analytically pure colorless oil; bath temperature 120 °C/0.9 Torr. ^1H NMR (C_6D_6): δ 5.92 (s, 1H, olefinic CH), 2.13 (t, 2H, $J = 7.4$ Hz), 1.95–1.90 (m, 4H), 1.52 (m, 2H), 1.12 (m, 6H) and 0.77–0.72 (m, 9H). ^{13}C NMR (C_6D_6): δ 161.6, 160.9, 159.4, 114.7, 111.4, 32.8, 32.0, 30.7, 28.0, 24.1, 22.6, 21.1, 14.1, 13.9 and 13.8. IR (neat): 2964, 2936, 2876, 1729, 1632 and 1545 cm^{-1}. GC-MS: *m/z* (% relative intensity) 236 (M^+, 21), 207 (11), 194 (24), 179 (40), 166 (100), 151 (56), 137 (41) and 71 (72). Calc. for $C_5H_8O_2$: C, 76.27; H, 10.17. Found: C, 76.30; H, 10.31%. HRMS: calc. for $C_{15}H_{24}O_6$ *m/z* 236.1775, found 236.1795.

4-Butyl-5,6-diethyl-2*H*-pyran-2-one 2b. Chromatography on alumina with hexane as eluent gave a pale yellow oil (75.0 mg, 0.36 mmol, 72%), which was distilled from Kugelrohr to furnish an analytically pure colorless oil; bath temperature 110 °C/1.2 Torr. ^1H NMR (C_6D_6): δ 5.90 (s, 1H, olefinic CH), 2.05–1.79 (m, 6H) and 1.10–0.67 (m, 13H). ^{13}C NMR (C_6D_6): δ 161.8, 161.7, 159.3, 115.4, 111.5, 31.8, 32.6, 24.1, 22.6, 19.1, 15.0, 13.9 and 12.1. IR (neat): 2962, 2936, 2876, 1723, 1634 and 1547 cm^{-1}. GC-MS: *m/z* (% relative intensity) 208 (M^+, 13), 166 (23), 138 (100), 123 (40), 109 (51) and 57 (84). Calc. for $C_{13}H_{20}O_2$: C, 75.00; H, 9.62. Found: C, 75.10; H, 9.74%.

Reaction of compound 1a with 2-pentyne. Chromatography on alumina with hexane as eluent gave a pale yellow oil (65.0 mg, 0.34 mmol, 67%), which was a 1 : 1 regioisomeric mixture **2c**. Kugelrohr distillation furnished an analytically pure colorless oil; bath temperature 105–110 °C/1.5 Torr. ^1H NMR (C_6D_6): δ 5.88 (s, 1H, olefinic CH) and 2.05–0.48 (m, 17H). ^{13}C NMR (C_6D_6): δ 161.7, 161.6, 161.3, 159.7, 159.1, 157.4, 116.0, 111.4, 111.0, 109.1, 32.7, 31.8, 30.6, 30.0, 24.6, 22.6, 22.5, 19.3, 16.7, 14.1, 13.9, 11.5 and 11.1. IR (neat): 2962, 2936, 2876, 1717, 1634 and 1549 cm^{-1}. GC-MS: *m/z* (% relative intensity) 194 (M^+, 10), 152 (11), 124 (100), 109 (40), 95 (25), 79 (16), 67 (24) and 57 (34). Calc. for C_6H_9O: C, 74.23; H, 9.28. Found: C, 73.95; H, 9.44%.

4-Hexyl-5,6-dipropyl-2*H*-pyran-2-one 2d. Chromatography on alumina first with hexane and then with a 5 : 95 (v/v) mixture of ethyl acetate and hexane gave a pale yellow oil (81.0 mg, 0.31 mmol, 62%), which was distilled over Kugelrohr to furnish an analytically pure colorless oil; bath temperature 130 °C/0.8 Torr. ^1H NMR (C_6D_6): δ 5.95 (s, 1H, olefinic CH), 2.12 (t, 2H, $J = 7.6$), 1.95 (m, 4H), 1.50 (m, 2H), 1.22–1.08 (m, 10H), 0.87 (t, 3H, $J = 7.0$), 0.75 (t, 3H, $J = 7.3$) and 0.74 (t, 3H, $J = 7.4$ Hz). ^{13}C NMR (C_6D_6): δ 161.6, 160.9, 159.3, 114.6, 111.5, 32.8, 32.3, 31.8, 29.3, 28.6, 28.1, 24.1, 22.8, 21.1, 14.2, 14.1 and 13.8. IR (neat): 2962, 2934, 2874, 1729, 1632 and 1547 cm^{-1}. GC-MS: *m/z* (% relative intensity) 264 (M^+, 16), 235 (4), 207 (18), 194 (52), 179 (23), 166 (100), 151 (75), 137 (31), 123 (31) and 71 (74). Calc. for $C_{17}H_{28}O_2$: C, 77.27; H, 10.61. Found: C, 77.00; H, 10.85%.

4-(3-Cyanopropyl)-5,6-dipropyl-2*H*-pyran-2-one 2e. Chromatography on alumina first with hexane and then with a 15 : 85 (v/v) mixture of ethyl acetate and hexane gave an orange oil (69.2 mg, 0.28 mmol, 56%), which was distilled over Kugelrohr to furnish an analytically pure colorless oil; bath temperature 125–130 °C/1.0 Torr. ^1H NMR (C_6D_6): δ 5.64 (s, 1H, olefinic CH), 2.08 (t, 2H, $J = 7.5$), 1.79 (m, 4H), 1.49 (m, 2H), 1.25 (t, 2H, $J = 6.8$), 1.11 (m, 2H), 0.89 (m, 2H), 0.77 (t, 3H, $J = 7.3$) and 0.73 (t, 3H, $J = 7.4$ Hz). ^{13}C NMR (C_6D_6): δ 161.4, 161.2, 156.9, 118.6, 114.3, 111.6, 32.8, 30.4, 27.9, 24.1, 23.8, 21.1, 16.1, 14.0 and 13.8. IR (neat): 2960, 2932, 2876, 2248, 1721, 1630 and 1545 cm^{-1}. GC-MS: *m/z* (% relative intensity) 247 (M^+, 20), 218 (30), 207 (17), 190 (100), 166 (22), 148 (19), 91 (22), 77 (31), 71 (60) and 55 (20). Calc. for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 72.39; H, 8.66; N, 5.72%.

4-Phenyl-5,6-dipropyl-2*H*-pyran-2-one 2f. Chromatography on alumina with hexane followed by crystallization from pentane (−40 °C) gave colorless crystals (72.3 mg, 0.28 mmol, 57%); mp 96.0–97.5 °C. ^1H NMR ($CDCl_3$): δ 7.42–7.22 (m, 5H), 6.03 (s, 1H, olefinic CH), 2.54 (t, 2H, $J = 7.6$), 2.22 (t, 2H, $J = 7.8$), 1.74 (m, 2H), 1.16 (m, 2H), 1.01 (t, 3H, $J = 7.3$) and

0.69 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$): δ 162.6, 162.1, 160.3, 137.6, 128.6, 128.4, 127.4, 115.2, 112.9, 32.1, 28.6, 23.5, 21.2, 13.9 and 13.8. IR (KBr): 2968, 2936, 2876, 1711, 1628, 1539, 1390, 940, 899, 768 and 706 cm^{-1}. GC-MS: *m/z* (% relative intensity) 256 (M^+, 23), 228 (32), 199 (100), 157 (28), 128 (20) and 71 (50). Calc. for $C_{17}H_{20}O_2$: C, 79.69; H, 7.81. Found: C, 79.57; H, 7.89%.

The reaction of methyl 3,6-dichloro-2-hexenoate with 4-octyne. The reaction formed two products, **2g** and **2g′**, approximately in a 1 : 2.7 ratio. Chromatography on alumina first with hexane and then with a 5 : 95 (v/v) mixture of ethyl acetate and hexane gave analytically pure samples of **2g** (11.0 mg, 0.043 mmol, 9%) and **2g′** (38.1 mg, 17.3 mmol, 35%) both as a pale yellow oil and a mixture of these.

4-(3-Chloropropyl)-5,6-dipropyl-2H-pyran-2-one **2g**. ^1H NMR (C_6D_6): δ 5.77 (s, 1H, olefinic CH), 2.91 (t, 2H, $J = 6.1$), 2.08 (t, 2H, $J = 7.3$), 1.96 (t, 2H, $J = 7.7$), 1.86 (t, 2H, $J = 8.1$), 1.54–1.06 (m, 6H), 0.74 (t, 3H, $J = 7.3$) and 0.73 (t, 3H, $J = 7.4$ Hz). ^{13}C NMR (C_6D_6): δ 161.4, 161.3, 157.7, 114.4, 111.7, 44.0, 32.8, 31.0, 29.1, 27.9, 24.1, 21.1, 14.0 and 13.8. IR (neat): 2966, 2936, 2876, 1725, 1632 and 1545 cm^{-1}. GC-MS: *m/z* (% relative intensity) 256 (M^+ for ^{35}Cl isotope, 18), 228 (15), 199 (89), 166 (100), 151 (26), 123 (20), 107 (13), 91 (37), 71 (82) and 55 (57). Calc. for $C_{14}H_{21}ClO_2$: C, 65.50; H, 8.19. Found: C, 65.03; H, 8.35%.

4-(Cyclopropyl)-5,6-dipropyl-2H-pyran-2-one **2g′**. ^1H NMR (C_6D_6): δ 5.61 (s, 1H, olefinic CH), 2.15–2.04 (m, 4H), 1.50 (m, 2H), 1.29–1.07 (m, 3H), 0.77 (t, 3H, J = 7.4), 0.74 (t, 3H, J = 7.4 Hz), 0.42 (m, 2H) and 0.25 (m, 2H). ^{13}C NMR (C_6D_6): δ 161.9, 160.8, 160.4, 115.2, 106.9, 33.8, 28.4, 23.7, 21.1, 14.1, 13.8, 12.7 and 9.1 (2C). IR (neat): 2964, 2936, 2876, 1721, 1632 and 1545 cm^{-1}. GC-MS m/z (% relative intensity) 220 (M^+ for ^{35}Cl isotope, 35), 192 (28), 163 (100), 149 (24), 121 (30), 91 (48), 71 (79) and 55 (23).

Reaction of compound 1a with 1-phenyl-1-butyne forming isomeric 2h. The reaction formed two regioisomers **2h-A** and **2h-B** in a 1.2 : 1 ratio. Chromatography on alumina first with hexane and then with a 5 : 95 (v/v) mixture of ethyl acetate and hexane allowed isolation of analytically pure **2h-A** (15.4 mg, 0.06 mmol, 12%) and **2h-B** (20.5 mg, 0.08 mmol, 16%) as a pale yellow oil in addition to mixture fractions.

Isomer ***2h-A***. ^1H NMR ($CDCl_3$): δ 7.44–7.37 (m, 3H), 7.15–7.12 (m, 2H), 6.06 (s, 1H, olefinic CH), 2.27–2.07 (m, 4H), 1.34–1.08 (m, 7H) and 0.74 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 163.1, 163.0, 160.8, 134.4, 130.1, 128.7, 128.0, 118.8, 110.1, 33.2, 30.1, 25.3, 22.1, 13.8 and 12.2. IR (neat): 2962, 2934, 2874, 1727, 1632, 1545, 768 and 704 cm^{-1}. GC-MS: m/z (% relative intensity) 256 (M^+, 13), 214 (30), 186 (100), 171 (23), 128 (24) and 57 (68). Calc. for $C_{17}H_{20}O_2$: C, 79.69; H, 7.81. Found: C, 79.55; H, 7.90%.

Isomer ***2h-B***. ^1H NMR ($CDCl_3$): δ 7.49–7.40 (m, 5H), 6.15 (s, 1H, olefinic CH), 2.49 (t, 2H, J = 7.2), 2.40 (t, 2H, J = 7.4), 1.64–1.37 (m, 4H), 1.07 (t, 3H, J = 7.4) and 0.96 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 162.4, 161.1, 157.7, 133.1, 129.6, 128.7, 128.3, 118.2, 112.3, 31.8, 30.8, 22.5, 19.8, 15.3 and 13.8. IR (neat): 2962, 2934, 2876, 1727, 1630, 1543, 1062 and 698 cm^{-1}. GC-MS: m/z (% relative intensity) 256 (M^+, 24), 214 (49), 185 (91), 171 (23), 129 (12), 105 (84) and 77 (100).

Reaction of compound 1a with 2,7-dimethyl-1-octen-3-yne forming 2i. The reaction formed two regioisomers **2i-A** and **2i-B** in a 1 : 1 ratio. Chromatography on alumina first with hexane and then with a 2 : 98 (v/v) mixture of ethyl acetate and hexane allowed isolation of analytically pure **2i-A** (12.0 mg, 0.046 mmol, 9%) and **2i-B** (22.2 mg, 0.085 mmol, 17%) as a pale yellow oil in addition to mixture fractions.

Isomer 2i-A. ^1H NMR (C_6D_6): δ 5.95 (s, 1H, olefinic CH), 4.96 (q, 1H, J = 1.6, olefinic CH), 4.60 (q, 1H, J = 0.9 Hz, olefinic CH), 2.23–1.86 (m, 4H), 1.56 (m, 3H), 1.41–1.31 (m, 7H) and 0.78–0.74 (m, 9H). ^{13}C NMR (C_6D_6): δ 161.5, 160.7, 158.4, 139.5, 119.1, 118.6, 110.9, 37.2, 32.1, 30.8, 30.2, 29.8, 28.1, 24.4, 22.6, 22.3 and 13.9. IR (neat): 2962, 2936, 2876, 1734 and 1456 cm^{-1}. GC-MS: m/z (% relative intensity) 262 (M^+, 16), 205 (4), 191 (73), 177 (18), 163 (25), 149 (28), 105 (27), 91 (83), 77 (75), 69 (22) and 55 (100).

Isomer ***2i-B***. ^1H NMR (C_6D_6): δ 5.98 (s, 1H, olefinic CH), 4.98–4.95 (m, 2H, olefinic CH_2), 2.15–1.95 (m, 4H), 1.79 (s, 3H), 1.16–1.04 (m, 7H) and 0.81–0.75 (m, 9H). ^{13}C NMR (C_6D_6): δ 161.0, 159.6, 159.5, 138.1, 118.6, 115.1, 112.9, 40.5, 31.9, 30.9, 28.6, 24.8, 22.7, 22.4, 21.5 and 13.9. IR (neat): 2960, 2932, 2874, 1734, 1543 and 1075 cm^{-1}. GC-MS: m/z (% relative intensity) 262 (M^+, 10), 205 (14), 191 (24), 177 (27), 163 (34), 150 (28), 107 (24), 91 (59), 79 (47), 69 (100) and 55 (69). HRMS: calc. for $C_{17}H_{26}O_2$ m/z 262.1931, found 262.1925.

Palladium-catalysed cross-coupling of compound 1a with 1-hexyne affording methyl 3-(n-butyl)-(*Z*)-2-nonen-4-ynoate 3. The reaction was carried out under conditions similar to those described for compound **2**. After 5 h of heating, the reaction mixture was similarly worked up. Chromatography on alumina with hexane gave an oil (60.0 mg, 0.27 mmol, 54%), which was distilled over Kugelrohr to furnish a pale yellow oil; bath temperature 110 °C/1.2 Torr. ^1H NMR (C_6D_6): δ 5.98 (s, 1H, C=CH), 3.44 (s, 3H), 2.24 (t, 2H, $J = 6.5$), 2.06 (t, 2H, $J = 7.5$ Hz) and 1.54–0.76 (m, 14H). ^{13}C NMR (C_6D_6): δ 165.1, 140.6, 123.2, 103.3, 79.8, 50.6, 39.2, 30.6, 30.4, 22.2, 22.1, 19.9, 13.9 and 13.7. IR (neat): 2962, 2934, 2866, 2220, 1734, 1615, 1218, 1193 and 1154 cm^{-1}. GC-MS: *m/z* (% relative intensity) 222 (M^+, 1), 193 (38), 180 (26), 165 (100), 151 (46), 138 (20), 105 (24), 91 (35), 77 (28) and 55 (28). HRMS: calc. for $C_{14}H_{22}O_2$ *m/z* 222.1619, found 222.1640.

Complex 4. A solution of compound **1a** (35.2 mg, 0.2 mmol) and $Pd(PPh_3)_4$ (115.4 mg, 0.1 mmol) in toluene (2.0 mL) was stirred at 90 °C for 3 h. Removal of volatiles *in vacuo* followed by recrystallization from a toluene–hexane mixture gave analytically pure complex **4** (67.0 mg, 0.083 mmol, 83.0%) as a white solid, mp 172.5–174.0 °C (decomp.). ^1H NMR ($CDCl_3$): δ 7.78–7.72 (m, 12H), 7.40–7.33 (m, 18H), 4.96 (s, 1H, olefinic CH), 3.43 (s, 3H), 2.00 (t, 2H, $J = 7.3$ Hz), 0.77–0.73 (m, 2H) and 0.55–0.47 (m, 5H). ^{31}P NMR ($CDCl_3$): δ 23.1. Calc. for $C_{44}H_{43}ClO_2P_2Pd$: C, 65.51; H, 5.34; Cl, 4.34. Found: C, 65.41; H, 5.17; Cl, 4.11%.

Acknowledgements

We thank the Japan Science and Technology Corporation (JST) for financial support through the CREST (Core Research for Evolutional Science and Technology) program and for a postdoctoral fellowship to R.H.

References and notes

1 J. V. N. Vara Prasad, K. S. Para, E. A. Lunney, D. F. Ortwine, J. B. Dunbar, Jr., D. Ferguson, P. J. Tummino, D. Hupe, B. D. Tait, J. M. Domagala, C. Humblet, T. N. Bhat, B. Liu, D. M. A. Guerin, E. T. Baldwin, J. W. Erickson and T. K. Sawyer, *J. Am. Chem. Soc.*, 1994, **116**, 6989.

2 For synthesis and chemistry of 2*H*-pyran-2-ones, see: (*a*) L. Staunton, in *Comprehensive Organic Chemistry*, ed. P. G. Sammes, Pergamon Press, Oxford, 1979, vol. 4, p. 629; (*b*) G. P. Ellis and J. D. Hepworth, in *Comprehensive Heterocyclic Chemistry*, ed. A. J. Boulton and A. Mckillop, Pergamon Press, Oxford, 1984, vol. 3, p. 675.; (*c*) Other publications on the synthesis: Y. Inoue, Y. Itoh and H. Hashimoto, *Chem. Lett.*, 1977, 855; (*d*) Y. Inoue, Y. Itoh and H. Hashimoto, *Chem. Lett.*, 1978, 633; (*e*) Y. Inoue, Y. Itoh, H. Kazama and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3329; (*f*) D. Walther, H. Schonberg and E. Dinjus, *J. Organomet. Chem.*, 1987, **334**, 377; (*g*) T. Tsuda, T.

Kiyoi, N. Hasegawa and T. Saegusa, *Yuki Gosei Kagaku Kyokaishi*, 1990, **48**, 362 and references therein; (*h*) L. S. Liebeskind and J. Wang, *Tetrahedron*, 1993, **49**, 5461; (*i*) S. H. Cho and L. S. Liebeskind, *J. Org. Chem.*, 1987, **52**, 2631; (*j*) R. K. Dieter and J. R. Fishpaugh, *J. Org. Chem.*, 1988, **53**, 2031; (*k*) W. Brady and M. O. Agho, *J. Org. Chem.*, 1983, **48**, 5337; (*l*) V. Kvita and H. Sauter, *Helv. Chim. Acta*, 1990, **73**, 883; (*m*) H. Stetter and H.-J. Kogelnik, *Synthesis*, 1986, 140; (*n*) X. Shi, W. S. Leal, Z. Liu, E. Schrader and J. Meinwald, *Tetrahedron Lett.*, 1995, **36**, 71; (*o*) L. Viallon, O. Reinaud, P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, 1995, **36**, 6669; (*p*) Recent publications on the reactions of *2H*-pyran-2-ones: M. E. Jung, M. Node, R. W. Pfluger, M. A. Lyster and J. A. Lowe, *J. Org. Chem.*, 1982, **47**, 1150; (*q*) F. Effenberger and T. Ziegler, *Chem. Ber.*, 1987, **120**, 1339; (*r*) K. Afarinkia and G. H. Posner, *Tetrahedron Lett.*, 1992, **33**, 7839; (*s*) K. Afarinkia, V. Vinader, T. D. Nelson and G. H. Posner, *Tetrahedron*, 1992, **48**, 9111; (*t*) G. H. Posner, H. Dai, D. S. Bull, J.-K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor and S. Petr, *J. Org. Chem.*, 1996, **61**, 671 and references therein.

3 R. Hua, S. Shimada and M. Tanaka, *J. Am. Chem. Soc.*, 1998, **120**, 12365.

4 M. Tanaka and R. Hua, *Jpn. Appl.*, 1999/061234, March 9, 1999.

5 (*a*) R. C. Larock, M. J. Doty and X. Han, *J. Org. Chem.*, 1999, **64**, 8770; (*b*) Palladium-catalysed annulation of internal alkynes with methyl *o*-iodobenzoate was reported to give isocoumarins: W. Tao, L. J. Silverberg, A. L. Rheingold and R. F. Heck, *Organometallics*, 1989, **8**, 2550; (*c*) R. C. Larock, E. K. Yum, M. J. Doty and K. C. Sham, *J. Org. Chem.*, 1995, **60**, 3270. However, attempted reactions of methyl *o*-chlorobenzoate with 4-octyne under our reaction conditions did not proceed.

6 The reaction run at higher temperatures (160 °C), using 2 mol% of the catalyst, required a longer time (24 h). This procedure formed a by-product (13%), which was found to be methyl 3-diethylamino-2-heptenoate. For N–C bond cleavage in palladium-catalysed reactions, see: T. Kobayashi and M. Tanaka, *J. Organomet. Chem.*, 1982, **231**, C12.

7 Methyl 3-diethylamino-2-heptenoate was formed as undesired side product in small quantities. See ref. 6.

8 Cyclopropane ring formation from γ-haloganoalkanoates and related compounds having a γ-halogenoalkyl group bound to electron-withdrawing groups has been well documented. See: B. Zwanenburg and N. De Kimpe, in *Methods of Organic Chemistry*, ed. A. de Meijere, Georg Thieme Verlag, Stuttgart, 1997, Vol. E17a, p. 45.

9 The reaction also produced dimers and trimers of 1-hexyne as main by-products, along with the recovery of compound **1a** in 12% yield.

10 Carbon–oxygen bond formation *via* reductive elimination from palladium complexes has been reported: (*a*) G. Mann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 13109; (*b*) R. A. Widenhoefer, H. A. Zhong and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 6787.

11 NEt_3 also is likely to hinder the nucleophilic attack of the carbonyl oxygen through its coordination to the palladium center of complex ***Z*-4**. At the same time, however, its presence in the system facilitates the reaction by trapping chloromethane generated. Accordingly the effect of NEt_3 on the reaction rate is ambiguous.