Catalytic tandem addition route to γ,δ-unsaturated carbonyls

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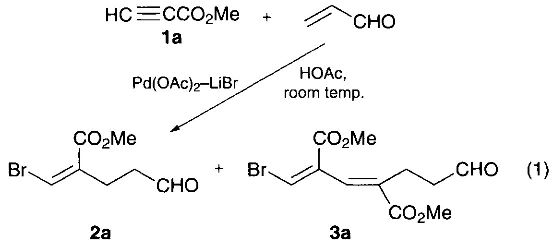
Divalent palladium catalysed tandem addition of lithium halides to alkynes and α,β-unsaturated carbonyl compounds gives δ-halo-γ,δ-unsaturated carbonyls in high yield and good stereoselectivity, the key step being the halide assisted protonolysis of the carbon–palladium bond following halopalladation and carbon–carbon double bond insertion.

Constructing polyfunctionalized molecules by linking two organic moieties through carbon–carbon bond formation is a very attractive strategy for synthetic chemists.[1] The preparations of ω-functionalized aldehydes and ketones, important intermediates in both laboratory synthesis[2] and industrial manufacture,[3] have attracted a great deal of interest.[2,4] However, most routes involved the stoichiometric use of special reagents or protection and deprotection.[4] Recently, coupling of alkynes and allylic alcohols catalysed by a ruthenium complex was reported to give γ,δ-enones and enals,[5] but harsh conditions were required and the regioselectivity was only moderate. Here we present a highly efficient palladium-catalysed synthesis of γ,δ-unsaturated aldehydes and ketones from simple alkynes and α,β-unsaturated carbonyl compounds. By the halopalladation of alkynes we and Kaneda *et al.* have developed a number of useful reactions leading to halofunctionalized 1,4-dienes[6] and α-alkylidene-γ-butyrolactone derivatives.[7] The halopalladation of electron-deficient alkynes was found to be fast and stereoselective.[7] To further explore the potential application of this reaction in synthesis we studied the reaction of electron-deficient alkynes with other unsaturated compounds.



When methyl propynoate **1a** (1.0 mmol) was treated with acrolein (5.0 mmol) in the presence of Pd(OAc)$_2$ (0.02 mmol) and LiBr (4.0 mmol) in acetic acid, two products **2a** and **3a** were isolated [eqn.(1)].

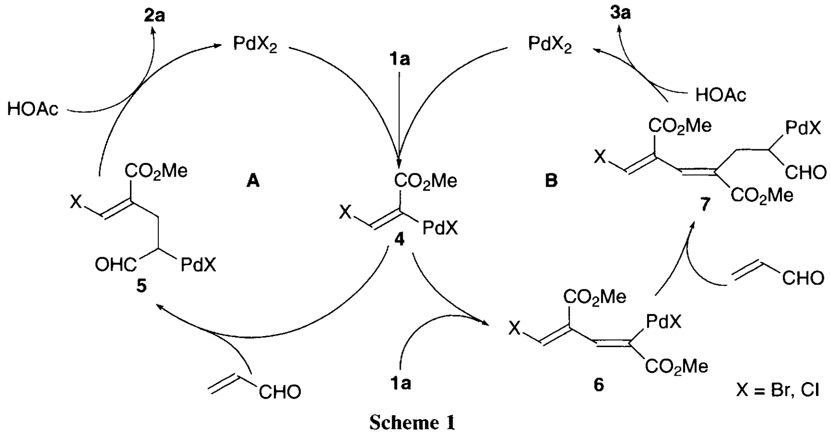
Compound **2a** was the 1 : 1 codimerization product and **3a** was the 2 : 1 cotrimerization product. The formation of these two products was rationalized by the mechanism shown in Scheme 1.

Vinylpalladium intermediate **4** was first formed by *trans*-halopalladation of **1a** in HOAc, followed by acrolein insertion (path A) or subsequent alkyne and acrolein insertion (path B). The competing alkyne insertion may be ascribed to the higher reactivity of acetylenes than olefins. Both reaction paths involved the protonolysis of the carbon–palladium bond to regenerate the catalytic Pd^{II} species, giving **2a** and **3a** respectively. In principle, protonolysis is also an important basic reaction of organopalladium compounds but its study and application are far less reported in the literature than β-hydride elimination and other elementary reactions.[8] In our case, the protonolysis of (2-oxoalkyl)palladium intermediates effectively recycles the catalytic species. The high efficiency of this process against the possible β-hydride elimination might be due to the presence of high concentration bromides.[9]

Different conditions were examined to control the selectivity of the reaction. When **1** (1.0 mmol) in HOAc (5 cm^3) was slowly added to a solution of the other reactants including acrolein (5.0 mmol), LiBr (4.0 mmol) and Pd(OAc)$_2$ (0.02 mmol) in HOAc (5 cm^3), a clean reaction was observed and only **2a** was isolated in 79% yield. The tandem addition reaction of other acetylenes and α,β-unsaturated carbonyl compounds were conducted under these standard conditions. Other halides, *e.g.* lithium chloride were also used. The results are listed in Table. 1†

Electron-deficient alkynes and phenyl acetylene all gave good yields of the 1 : 1 codimerization product with acrolein and methylvinyl ketone. The regiochemistry was affected by the electronic properties of the substituent on the triple bond, in accordance with the results reported by Kaneda *et al.*:[6] the halide attacks the more electropositive carbon atom.

Highest stereoselectivity was obtained for the propynoates: only *Z*-isomers were produced from methyl and benzyl propynoates (entries 1, 4 and 6, Table 1). Benzyl but-2-ynoate



Scheme 1

gave a 60:40 Z:E-mixture of coupled products with acrolein and this ratio increased to 95:5 when the olefin was changed to vinyl ketone (entry 2 *vs.* entry 8, Table 1); these Z-isomers were formed *via trans*-halopalladation. For phenyl acetylene, Z-isomers predominated in the products, generated *via cis*-halopalladation. These results showed that the stereoselectivity controlling factors still needed investigation.

Aliphatic acetylenes did not give satisfactory results under the standard conditions. However, using acrolein as the solvent at 0 °C, the reaction did give the codimerization product in 55% yield. A trace amount of **8** was also detected, which might be formed through β-hydride elimination from the acrolein-inserted intermediate [eqn.(2)].

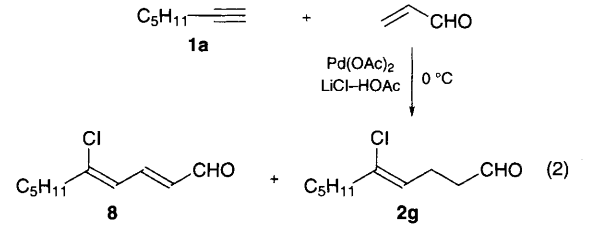
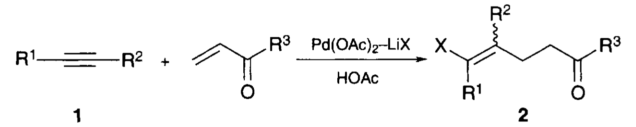


Table 1 Palladium(II) catalysed tandem addition of lithium halides to alkynes and α,β-unsaturated carbonyls[a]



	Substrate					Product		
	R^1	R^2	**1**	R^3	X	**2**	Yield (%)	Z:E[b]
1	H	CO_2Me	**a**	H	Br	**a**	79	>97:3
2	Me	CO_2Bn	**b**	H	Br	**b**	76	60:40
3	Ph	H	**c**	H	Br	**c**	75	93:7
4	H	CO_2Me	**a**	H	Cl	**d**	82	>97:3
5	Ph	H	**c**	H	Cl	**e**	77	95:5
6	H	CO_2Bn	**d**	H	Cl	**f**	85	>97:3
7	C_5H_{11}	H	**e**	H	Cl	**g**	55[c]	90:10
8	Me	CO_2Bn	**b**	Me	Cl	**h**	75	95:5
9	Ph	H	**c**	Me	Cl	**i**	73	95:5

[a] Reaction conditions: **1** (1.0 mmol) in HOAc (5 cm^3) was slowly added to a solution of $Pd(OAc)_2$ (0.02 mmol), LiBr (4.0 mmol) and carbonyl compound (5.0 mmol) at room temp. [b] Z:E was determined by ^1H NMR. [c] Acrolein was used as solvent with 1 equiv. of HOAc.

Another feature of the present reaction is the economic employment of the Pd^{II} catalyst: palladium salt and lithium halide could be reused simply by drying the aqueous solution after workup.

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Footnote

† All the new compounds are fully characterized by spectral and HRMS data. *Selected data* for (Z)-**2b**: ^1H NMR (300 MHz), $CDCl_3$) δ 9.72 (s, 1 H), 7.45–7.30 (m, 5 H), 5.22 (s, 2 H), 2.70–2.55 (m, 4 H) and 2.39 (s, 3 H); IR (neat) cm^{-1} 2900, 2700, 1725, 1380, 1270, 1140, 795, 750 and 700; MS m/z(%): 313[M^+ + 1(^{81}Br)](0.44), 311[M^+ + 1(^{79}Br)](0.44), 231(14.80), 203(5.66), 125(11.81), 91(100.00), 77(4.85) and 65(13.71); HRMS Calcd. for $C_{14}H_{15}O_3$(M^+ − Br): 231.1021; found: 231.1043. For (Z)-**2d**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1 H), 6.51 (s, 1 H), 3.80 (s, 3 H) and 2.75–2.60 (m, 4 H); IR (neat) cm^{-1} 2940, 2700, 1720, 1605, 1440, 1120 and 815; MS m/z(%): 179[M^+ + 1(^{37}Cl)](13.98), 177[M^+ + 1(^{35}Cl)](38.90), 147(42.84), 145(100.00), 141(48.53), 113(78.23), 109(65.61), 81(58.97) and 53(84.06); HRMS Calcd. for $C_7H_9O_3$ (M^+ − Cl): 141.0552; found: 141.0504.

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