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Palladium-Catalyzed Nucleophile−Alkyne−α,β-Unsaturated Carbonyl Coupling through Tandem Nucleopalladation and Conjugate Addition

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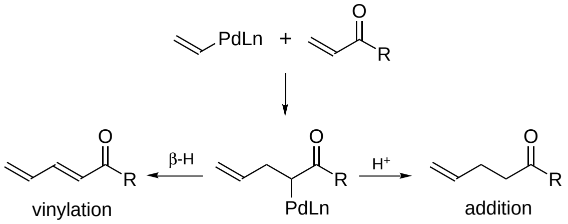
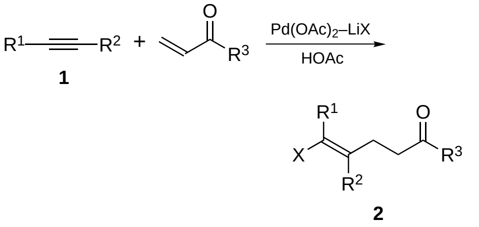
There are only sporadic reports on successful 1,4-additions of organometallic reagent to α,β-unsaturated aldehydes.[1,2] In a catalytic precedent, transmetalated organopalladium species mediated the 1,4-addition of organomercurials to α,β-unsaturated carbonyls.[3] Alkenylpalladium intermediates are easily obtained from halopalladation and oxypalladation of alkynes.[4] Our recent studies revealed that alkenylpalladium species so generated readily undergo conjugate additions to α,β-unsaturated aldehydes and ketones in the presence of metal halides and thus effect a nucleophile−alkyne−alkene three-component addition. Herein, we report these results and the synthesis of γ,δ-unsaturated carbonyl compounds and lactonic aldehydes or ketones applying such chemistry.

Vinylpalladium species usually react with α,β-unsaturated carbonyls to give vinylation products through β-hydride elimination of the insertion intermediate rather than addition products through protonolysis (Scheme 1).[5] Inhibition of the normal β-hydride elimination pathway was achieved by addition of excess phosphine,[6] but this inhibited the insertion step as well when we attempted the reaction of acrolein with the vinylpalladium generated by halopalladation of an alkyne. With the thought that an increase in electron density at the palladium center might also diminish *cis*-hydride elimination[7] and that excess halide ligand might serve this purpose, we conducted the palladium-catalyzed reaction of methyl propynoate (**1a**) with acrolein in the presence of excess LiBr in HOAc. Addition of the vinylpalladium intermediate to acrolein did occur, and (*Z*)-**2a** was obtained in good yield and stereoselectivity (*Z*:*E* > 97:3) (eq 1).[8]

Scheme 1



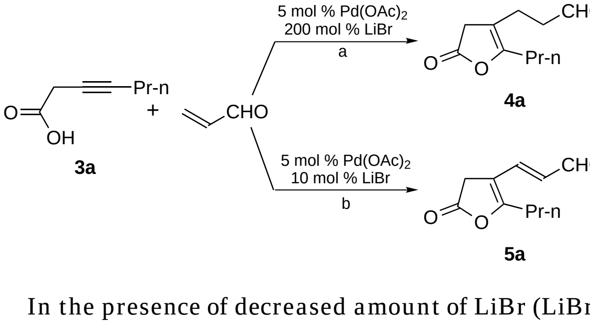


(1)

2a: R^1, R^3 = H, R^2 = COOMe, X = Br 79%
2b: R^1, R^3 = H, R^2 = COOBn, X = Cl 85%
2c: R^1= Me, R^2 = COOBn, R^3 = Me, X = Cl 75%

Similar conditions were applied to other alkynes, α,β-unsaturated carbonyl compounds, and lithium chloride, and through various combinations of the three components efficient syntheses of γ,δ-unsaturated aldehydes and ketones were achieved.

Oxypalladation of triple bonds is a process analogous to halopalladation. With the hope that oxypalladation of alkynes followed by insertion of α,β-unsaturated carbonyls may lead to 1,5-dicarbonyl compounds, we examined the carboxylate−alkyne−acrolein coupling using lithium acetate and methyl propynoate. Only halogen-incorporated product **2a** was formed in the presence of lithium bromide,[9] and the reaction without LiBr resulted in fast decomposition of Pd(OAc)$_2$ to Pd metal with no identifiable products from the reaction of **1a**. However, an intramolecular carboxyl did effect this oxypalladation−acrolein coupling sequence. Using Pd(OAc)$_2$ as the catalyst, 3-heptynoic acid (**3a**) and 5 equiv of acrolein in the presence of excess LiBr (2 equiv) in HOAc gave the cyclized coupling product **4a** in 85% yield (eq 2, a).



(2)

In the presence of decreased amount of LiBr (LiBr:Pd(OAc)$_2$ = 2:1), **5a**, produced by β-hydride elimination, was obtained in 94% yield (based on Pd) together with precipitated palladium black (eq 2, b). This, again, demonstrated the significant role of halide in the present reaction. Lithium chloride also works here, but bromide seems to be effective at lower concentrations.[10]

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[7] The β-hydride elimination of an alkylmetal is a process in which the metal center accepts electron density from the β-hydride; see ref 6b.

[8] Polar solvent and high concentration halides favor *trans*-halopalladation which gives β-(*Z*)-halopropenoate derivatives; see ref 4b and: Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120. Bäckvall, J.-E.; Nilsson, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242.

[9] In our previous work on palladium(II)-catalyzed cyclization of 4′-acetoxy-2′-butenyl 2-alkynoates, we found that even in the presence of a large amount of lithium acetate, chloropalladation products are formed in preference to acetoxypalladation products.

[10] A preliminary study showed that at a Pd(OAc)$_2$:LiX:**3a** =1:5:20 ratio, LiBr gave a clean reaction producing **4a** while LiCl resulted in the formation of **5a** and Pd metal.

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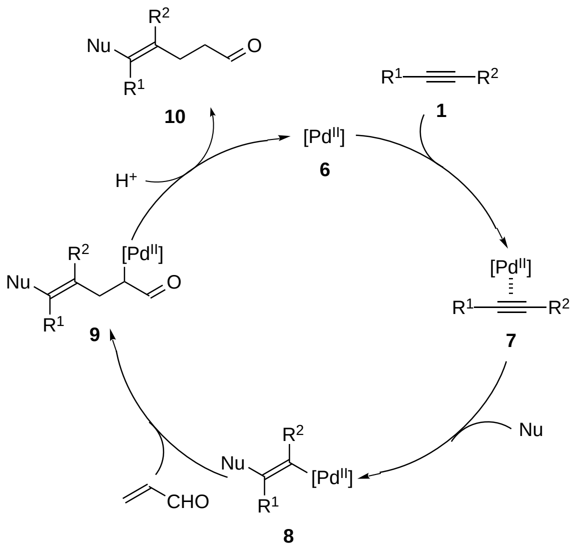
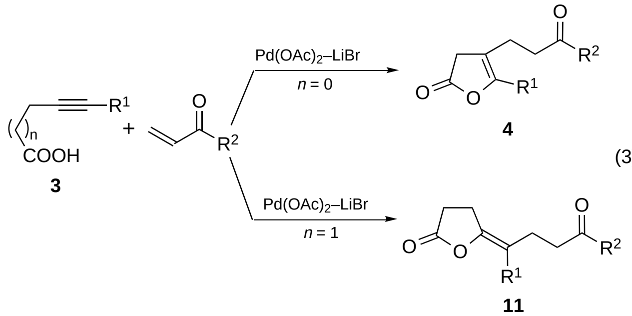
Scheme 2



$[Pd^{II}]$ = palladium(II) with coordinating ligands

So far, we have succeeded in achieving nucleophile–alkyne–acrolein coupling from both halide and carboxylate nucleophiles. A general mechanism is proposed as follows (Scheme 2): nucleopalladation of the coordinated triple bond gives the vinylpalladium intermediate **8** which on acrolein insertion forms the (2-oxoalkyl)palladium intermediate **9**. The key step to form the product **10** and regenerate the Pd(II) catalytic species is the protonolysis of the carbon–palladium bond in **9**. Although protonolysis of the carbon–palladium bond is, in principle, also an important reaction of organopalladium compounds, its study and application are far less reported in the literature than the β-hydride elimination and other elementary reactions.[11] The ease of this process in our case might be due to several factors. First, the large excess of halide may make the β-H elimination less feasible through electron donation to palladium and occupancy of the coordination site needed for a *cis*-hydride elimination. Second, intermediate **9**, which is actually a mesomeric palladium enolate, may readily undergo a heterolytic Pd–O fission by nucleophilic attack by halide on the palladium center.[3]



(3)

Table 1. Palladium-Catalyzed Cyclizing Coupling of Alkynoic Acids with α,β-Unsaturated Carbonyl Compounds[a]

	substrate				product[b]	
entry	**3**	*n*	R^1	R^2	**4** or **11**	yield[c] (%)
1	**3a**	0	*n*-Pr	H	**4a**	85
2	**3b**	0	*n*-Bu	H	**4b**	82
3	**3c**	0	Ph	H	**4c**	39
4	**3a**	0	*n*-Pr	CH_3	**4d**	79
5	**3d**	1	H	H	**11a**	66
6	**3e**	1	Ph	H	**11b**	85
7	**3d**	1	H	CH_3	**11c**	65

[a] Reaction conditions. A mixture of **3** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), LiBr (2 mmol), and carbonyl compound (5 mmol) in HOAc at rt. [b] New compounds have been characterized by ^1H NMR, ^{13}C NMR, IR, MS, and high-resolution mass spectra. [c] Isolated yield, not optimized.

The scope of the cyclizing coupling reaction was briefly examined (eq 3, Table 1). Other 4-substituted 3-butynoic acids reacted smoothly to give cyclized acrolein coupling products, but 4-phenyl-3-butynoic acid (**3c**) gave a much lower yield (entry 3, Table 1). It was noteworthy that only intramolecular oxypalladation products were obtained although halopalladation was in competition. 3-Butynoic acid itself did not give the cyclized product.[12]

The reaction of 4-alkynoic acids with acrolein afforded γ-alkylidene-γ-butyrolactone derivatives in good yield and stereoselectivity. Only (*E*)-**11a**–**c** are produced from **3d** and **3e**, conforming to *trans*-oxypalladation of the triple bonds (entries 5–7, Table 1). The stereochemistry of the exocyclic double bond in **11a** and **11c** was determined by comparing the chemical shifts of the vinylic protons with analogous compounds,[13] and for **11b**, the (*E*)-configuration was established by NOESY spectra.[14] Methyl vinyl ketone as the olefin partner also gave good yields of lactonic ketones (entries 4 and 7, Table 1), revealing the potential of the present reaction for easy access to a number of polyfunctionalized lactones.

Concerning the environmental and economical aspects, the $Pd(OAc)_2$–LiX system has another feature of merit—the palladium salt and lithium halide could be reused simply by drying the aqueous solution after workup.

In conclusion, we have developed a high-yielding coupling reaction assembling a nucleophile, an alkyne, and an α,β-unsaturated carbonyl in one step.[15] This method permits facile entry to γ,δ-unsaturated carbonyl compounds and lactonic aldehydes (ketones) from halide and carboxyl nucleophiles, respectively, and may well be extended to other nucleophiles giving carbocyclic or different heterocyclic structures. The good regio- and stereoselectivity, the high catalyst efficiency, and mild conditions ensuring compatibility for sensitive functional groups should make the method an attractive tool in synthesis. The steering effect of halides on the reaction has stimulated our interest in a mechanistic study which is now under active investigation.

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Supporting Information Available: Copies of ^1H NMR spectra for compounds **2a**–**c**, **4a**–**d**, **5a**, and **11a**–**c**; ^{13}C NMR spectra for **4b**,**d** and **11a**–**c**; and NOESY spectra for **11b** (18 pages).

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(12) In Utimoto's work on palladium-catalyzed cyclization coupling of alkynoic acids with allyl halides, 3-butynoic acid also failed to give the cyclization product; see ref 4d.

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(14) There is strong NOE between two groups of allylic protons and no NOE between the phenyl group and the protons on lactone ring.

(15) In a typical experiment, a mixture of $Pd(OAc)_2$ (0.02 mmol), LiBr (2 mmol), **3** (1 mmol), and acrolein (5 mmol) in HOAc (5 mL) was stirred at rt. After **3** disappeared, the mixture was fractioned by addition of water (5 mL) and ethyl ether (80 mL). The organic layer was dried and concentrated, and the residue was column chromatographed on silica gel to afford the product. For the Pd(II)-catalyzed halide–alkyne–acrolein coupling, a solution of **1** (1mmol) in HOAc (5 mL) was added to a stirred homogeneous solution of $Pd(OAc)_2$ (0.02 mmol), LiBr (2 mmol), and acrolein (5 mmol) in HOAc (5 mL) in 1 h at rt. Similar workup gave the coupled product.