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Palladium(II)-Catalyzed Three-Component Coupling Reaction Initiated by Acetoxypalladation of Alkynes: An Efficient Route to γ,δ-Unsaturated Carbonyls

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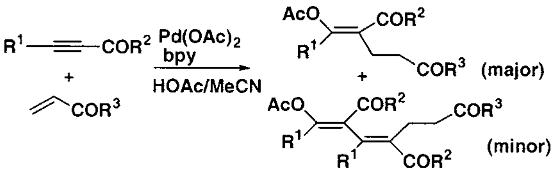
ABSTRACT



A divalent palladium-catalyzed coupling reaction of electron-deficient alkynes and acrolein or MVK (methyl vinyl ketone) was developed. The reaction provides an efficient method to synthesize γ,δ-unsaturated carbonyls. A mechanism involving acetoxypalladation of alkyne, followed by insertion of alkene and protonolysis of the C–Pd bond, is proposed. The protonolysis of the carbon–palladium bond with the assistance of bidentate nitrogen containing ligands is the key step in this tandem reaction.

Constructing polyfunctionalized molecules by linking several organic moieties through carbon−carbon coupling in one step is a very attractive strategy for synthetic chemists.[1] During recent years, transition metal-catalyzed processes toward this end have grown at an exponential rate, in particular to the construction of polyfunctionalized molecules.[2] A tremendous amount of attention has been paid to various types of Pd(0)-catalyzed reactions starting from vinylic halides (or triflates) with vinylpalladium species as the intermediate.[3] However, the reactions of vinylpalladium species which can also easily be obtained from nucleopalladation of alkynes under Pd(II) catalysis have received only limited attention.[3b,4] The main reason is that methods of quenching the carbon−palladium bond to regenerate the divalent palladium species are rarely reported, thus an excess amount of oxidants is often required to regenerate the Pd(II) species from Pd(0) species.[5]

During our ongoing study on the Pd(II)-catalyzed reactions, we studied the different kinds of nucleopalladation

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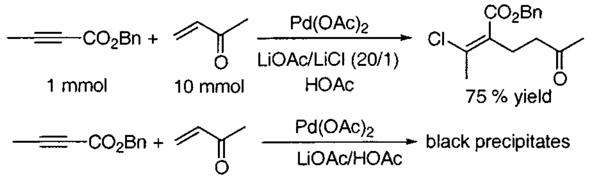
initiated tandem reactions[4h,i] and developed methods of quenching the carbon−palladium bond to regenerate Pd(II) species.[4i,7] In the previous report, we developed a Pd(II)-catalyzed tandem addition of lithium halides to alkynes and α,β-unsaturated carbonyl compounds.[6a] The halide ions act not only as a nucleophile but also as a ligand that plays the key role in inhibiting the usual β-hydride elimination making the catalytic cycle proceed smoothly,[7] thus the halide ion is necessary in the halopalladation initiated reaction as a ligand. To extend this tandem process to other nucleophiles and develop the asymmetric version of this reaction, a suitable nucleophile and ligand must be found in place of the halide ion. Hydroacetoxylation of alkynoates was developed in early work where acetate ion attacked the triple bond under palladium catalyst via *trans*-acetoxypalladation followed by protonolysis,[8] implying that acetate might be a good nucleophile to replace the halide ion. If we can trap the vinylpalladium species generated from acetoxypalladation with an olefin, the pure geometrical isomer of an enol ester derivative, which is the important precursor in stereoselective synthesis,[9] will be synthesized. However, much effort failed when we used acetate as the nucleophile and halide ion as the ligand in the coupling reaction of alkynoates with alkenes. The reaction gave only halopalladation products because the rate of halopalladation is much faster than that of acetoxypalladation (Scheme 1), indicating that the acetoxypalladation initiated coupling reaction can occur only in the absence of halide ions. However, when the acetoxypalladation initiated reaction was carried out in the absence of halide ions, it gave no coupling products but the black precipitates of palladium. Recently, we found that some bidendate nitrogen-containing ligands can play the similar important role as halide ions in inhibiting β-H elimination and regenerating Pd(II) species via β-heteroatom elimination.[10] These results prompted us to explore the possibility of a Pd(II)-catalyzed tandem reaction via acetoxypalladation of alkynes and regeneration of Pd(II) species via protonolysis of the C−Pd bond in the presence of nitrogen-containing ligands. Herein, we report the preliminary results of this novel Pd(II)-catalyzed tandem addition reaction of alkynes to acrolein or MVK by applying this supposition.

Scheme 1



We first investigated the reaction of methyl 2-butynoate **1a** with acrolein in the presence of $Pd(OAc)_2$ and bpy in HOAc (Scheme 2). The reaction was complete within 4 h at 80 °C and gave the expected coupling products **4a** (yield: 17%) and **5a** (yield: 23%), as well as the protonolysis product **3a** (yield: 18%) (entry 1, Table 1).

Scheme 2

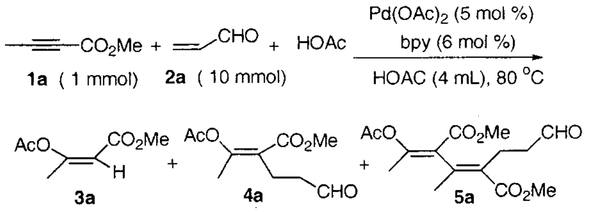


Table 1. The Solvent Effect on the Distribution of Products of the Tandem Reactions[a]

entry	solvent[b]	yield (%)[c]	*t* (h)	**3a** (%)	**4a**:**5a**
1	HOAc	40	4	18	43:57
2	HOAc:DMF	[d]	12	–	
3	HOAc:PhH	38	5	trace	94:6
4	HOAc:DCE	66	5	trace	72:28
5	HOAc:acetone	30	24	trace	87:13
6	HOAc:THF	17	24	–	97:3
7	HOAc:MeCN	72	12	–	97:3

[a] Reaction conditions: $Pd(OAc)_2$ (0.05 mol), bpy (0.06 mol), **1a** (1 mmol), **2a** (10 mmol), solvent (4 mL), at 80 °C. The ratio of **4a** and **5a** was determined by ^1H NMR (300 MHz). [b] The volume ratio of mixed solvent is 1:3. [c] Isolated total yield of **4a** and **5a**. [d] A black precipitate appeared within several minutes.

The formation of compound **4a** (codimerization product) and **5a** (cotrimerization product) was rationalized by the mechanism shown in Scheme 3. Vinylpalladium intermediate **I** was first formed by *trans*-acetoxypalladation of **1a** in

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(7) In the Pd(II)-catalyzed coupling reactions, the halide ion can block the β-H elimination of a carbon−palladium bond, giving preferentially the protonolysis or β-heteroatom elimination product, see: (a) Wang, Z.; Zhang, Z.; Lu, X. *Organometallics* **2000**, *19*, 775. (b) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724.

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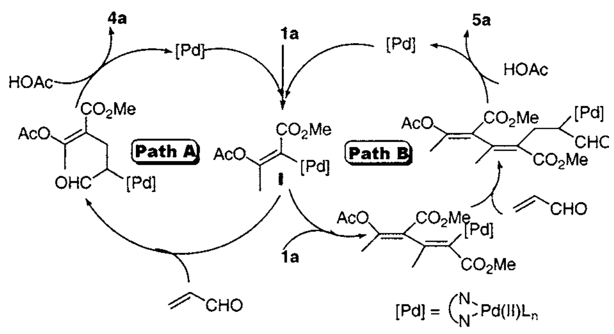
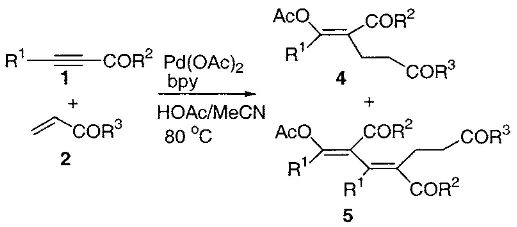
Scheme 3



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 alkynes than olefins.[6a] Both reaction paths involved the protonolysis of the carbon−palladium bond to regenerate the catalytic Pd(II) species, giving **4a** and **5a**, respectively. It is noteworthy that bidentate nitrogen-containing ligands are important in stabilizing vinylpalladium intermediates and assisting the protonolysis of the carbon−palladium bond.[10]

Further experiments confirmed the solvent effect played a significant role in the distribution of products (Table 1). In most cases, mixed solvents can inhibit the formation of product **3a**, implying that low solvent acidity can inhibit the protonolysis of the vinylpalladium bond. When HOAc (entry 1) or HOAc/1,2-dichloroethane (entry 4) was used, the reaction gave moderate total yield but with poor chemoselectivity. However, the reaction gave low yield but high chemoselectivity on using HOAc/benzene (entry 3) or HOAc/THF (entry 6) as solvent. The best result was acquired when HOAc and MeCN were used as mixed solvent.

Table 2. Reactions of **1** with α,*β*-Unsaturated Carbonyls Catalyzed by Pd(II) Species[a]

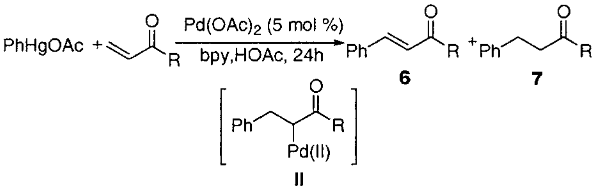


entry	1	R¹	R²	R³	*t* (h)	yield, % (**4**:**5**)[b]
1	**1a**	Me	OMe	H	12	72 (**4a**:**5a** > 97:3)
2	**1b**	Me	OBn	H	24	78 (**4b**:**5b** > 97:3)
3	**1c**	Ph	OMe	H	30	91 (**4c**:**5c** = 81:19)
4	**1d**	*n*-Pr	OMe	H	26	76 (**4d**:**5d** = 93:7)
5	**1e**	Me	*n*-Pr	H	12	78 (**4e**:**5e** = 88:12)
6	**1f**	Me	Ph	H	24	70[c] (**4f**:**5f** = 94:6)
7	**1g**	Me	O^{t}Bu	H	24	58 (**4g**:**5g** > 97:3)
8	**1h**	*n*-C_7H_{15}	OMe	H	27	78 (**4h**:**5h** = 94:6)
9	**1i**	$MeOCH_2$	OMe	H	48	60 (**4i**:**5i** = 92:8)
10	**1a**	Me	OMe	Me	7	63[d] (only **4k**)
11	**1j**	H	OMe	H	24	*e*

[a] Reaction conditions: A mixture of **1** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), bpy (0.06 mmol), and unsaturated carbonyl compound (10 mmol) in a mixed solution of HOAc (1 mL) and MeCN (3 mL) at 80 °C. [b] The ratio of product **4** and **5** was determined by ^1H NMR, and new compounds were characterized by ^1H NMR, IR, MS, and HRMS. [c] Substrate **1f** was recovered in 28%. [d] Another product: 1-acetoxylacetone (97 mg) was also obtained. [e] The reaction system turned to black after half an hour, and no obvious product can be found.

The scope and generality of the present reaction was studied as shown in Table 2. Most of the electron-deficient alkynes gave good yields of the 1:1 codimerization product with acrolein or methylvinyl ketone (entries 1−10). However, in the present catalytic system, the terminal propiolate cannot afford the tandem coupling product (entry 11), which might be attributed to the possible formation of alkynylpalladium species.[11] In addition, when the above reaction was performed *in the absence of* $Pd(OAc)_2$ *or bpy*, no coupling products were obtained at all. The regiochemistry was controlled by the electron-withdrawing properties of the substituents on the triple bond,[4c] The stereochemistry of the double bond in **4** was assigned as the *Z*-configuration based on ^1H NMR[10] and that of **4a** was confirmed by NOESY spectra, which indicated the *trans*-acetoxypalladation involved in this reaction. The stereochemistry of acetoxypalladation seems different from that of chloropalladation reported by Bäckvall, where the alkynes undergo both cis and trans chloropalladation according to the concentration of halide ion.[4g]

Table 3. Pd(II)-Catalyzed Reactions of Phenylmercuric Acetate with Acrolein or MVK[a]



entry	R	bpy (mol %)	*t* (°C)	yield (%)[b]	**6**:**7**[c]
1	H	0	70	6	86:14
2	H	10	70	48	15:85
3	H	25	70	78	<3:97
4	Me	0	50	7	>97:3
5	Me	10	50	47	27:73
6	Me	25	50	47	15:85

[a] Reaction conditions: PhHgOAc (1 mmol), acrolein or MVK (5 mmol), and $Pd(OAc)_2$ (0.05 mol). [b] Isolated total yield of **6** and **7**. [c] The ratio of **6** and **7** was determined by ^1H NMR spectra.

To probe the role of nitrogen-containing ligands, we investigated a catalytic process incorporating Pd(II)-mediated transmetalation.[3b] The reaction of phenylmercuric acetate with acrolein or MVK in the presence of 5 mol % of $Pd(OAc)_2$ in HOAc was conducted by different loading of bpy as shown in Table 3. With an increase in the amount of bpy, the total yield increased obviously and the protonolysis product **7** was dominant as compared to the *β*-H elimination product **6**. Employment of phenanthroline as the ligand gave a similar result to that of bpy. The results strongly supported the fact that these nitrogen-containing ligands play a crucial role in inhibiting the β-H elimination of alkylpalladium(II) species and assisting the protonolysis of the carbon−palladium bond, making the catalytic cycles possible.

The products obtained by palladium(II)-induced three-component coupling can be used in further synthetic transformation. Vinyl acetates not only are important precursors in the synthesis of functionalized molecules but also can be conveniently converted into the 1,5-diketones.[12]

In summary, a Pd(II)-catalyzed three-component tandem coupling reaction of acetate ion, alkyne, and α,β-unsaturated carbonyls initiated by acetoxypalladation of alkynes was developed with high atom economy. The present catalytic system provides not only an efficient route to γ,δ-unsaturated carbonyl compounds but also a method of quenching the carbon−palladium bond via protonolysis with assistance from nitrogen-containing ligands. Further application of the present catalytic system is underway.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds **4a−k** and NOESY spectra of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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