Acetoxypalladation of unactivated alkynes and capture with alkenes to give 1-acetoxy-1,3-dienes taking dioxygen as terminal oxidant[†]

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A new and general protocol for the synthesis of 1-acetoxy-1,3-dienes by an acetoxypalladation/Heck cross-coupling/ β -H elimination tandem process is described in which dioxygen is the terminal oxidant. Electron-rich and electron-deficient alkynes are both effective substrates in this system. It is the first example of acetoxypalladation of diarylalkynes.

Transition-metal-catalyzed tandem coupling is now recognized to be a useful tool for constructing new carbon-carbon and carbon-hetero bonds from simple starting materials in a one-pot style which has undergone great development during the past decades.¹ And acetoxypalladation of alkynes has been proven to be a very important and convenient method for the construction of both carbon-carbon and carbon-oxygen bonds in a single step.² Acetoxypalladation of alkynes generates a reactive σ-vinylpalladium intermediate A (Scheme 1). However, how to capture A and how to quench carbon-palladium bond still remain challenging. the Moreover, in the reported systems, the initial alkynes were often limited to alkynes and alkenes with electron-withdrawing groups and the methods to quench the carbon-palladium bond were often protonolysis (Scheme 1, path a) or deacetoxypalladation (Scheme 1, path b). However, another familiar route to quench the carbon-palladium bond of chloropalladation-\beta-hydride elimination has received limited attention in the field of acetoxypalladation because it requires the existence of oxidants. As for oxidant, dioxygen is no doubt the best choice regardless of the source and environmental considerations and recently has attracted more and more attention.³ Based on our interest in oxygen and carbon-carbon bond formation from triple bonds,⁴ we herein wish to report an intermolecular acetoxypalladation of unactivated alkynes which were captured



Scheme 1 Acetoxypalladation of alkynes and a tandem crosscoupling with carbon–carbon double bond.

by alkenes and quenched by β -hydride elimination to 1-acetoxy-1,3-diene taking dioxygen as the oxidant.

Diphenylethyne (1a) and butyl acrylate (2a) were chosen as the starting materials and the catalyst, additive, oxidants and solvent were investigated in detail (Table 1). Initially, the reaction was carried out according to Lu's conditions^{2a} in which no designed product 3aa was detected (entry 1). When taking 2 mL mixed CH₃CN-AcOH (4:1) as solvent, a trace amount of 3aa could be detected by GC-MS with the presence of 1 equiv. $Cu(OAc)_2$ as the oxidant (entry 2). Interestingly, the yields of 3aa could be enhanced greatly by adding 0.5 equiv. LiCl or LiBr as the additives (entries 3, 4); the yield in the case of LiBr is 69%. Further experiments showed that different amounts of LiBr will give quite different results (entries 4–7); the best results were obtained by using 0.4 equiv. LiBr. Running the reaction with other bromide salts showed KBr led to a 77% yield but no desired product 3aa was detected with KI (entries 8 and 9). Importantly, up to 89% yield of 3aa was obtained using Cu(OAc)₂ (0.4 equiv.) and dioxygen (1 atm) as co-oxidants (entry 10).⁵ However, air can't play the same role as dioxygen (entry 11). When taking dioxygen as sole oxidant, the pressure played a crucial role (entries 12 and 13). Obviously, Pd salts could affect the yield of the reaction (entries 14 and 15). Subsequently a set of solvents were examined, but other cosolvents did not improve the yield and isomers of 3aa were detected when dioxane, DMF and toluene were used (entries 16-17).

With best conditions in hand (Table 1, entry 10), we examined the scope of the acetoxypalladation/Heck crosscoupling process with respect to a variety of alkynes and alkenes (Table 2). To our knowledge, the regiochemistries of chloropalladation and acetoxypalladation were controlled by the electron-withdrawing properties of the substituents on the triple bond. However, in our systems, the electron-rich alkynes gave good yields of acetoxy-substituted 1,3-dienes in excellent stereoselectivities with *trans*-acetoxypalladation providing the expected products. Obviously, acrylates in common use within other acetoxypalladation systems were also provided with good activation (3aa, 3ab, 3ac, 3ad). To our delight, styrene (2e) which is usually inert in acetoxypalladation was also efficient in this system (3ae). As for other diarylalkynes, different substituents on the benzene ring could not affect the yield obviously such as 4-F, 4-Cl, 4-Me, 4-t-Bu and 3-Me (3ed, 3dd, 3fd, 3ca, 3cf, 3gd). Interestingly, 4-octyne, easily trimerized with Pd/Cu, also exhibited excellent activation and selectivity (3ba, 3bf). At lower temperature, the method also could be applied to methyl oct-2-ynoate (1h) and 2a which means the methodology is useful for both electron-rich alkynes and electron-deficient alkynes. When terminal alkynes like ethynylbenzene, acetylene and propargylic alcohols were

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou City, Guangdong Province 510640, China. E-mail: jianghf@scut.edu.cn; Fax: +8620-87112906 † Electronic supplementary information (ESI) available: Experimental procedure and spectral data. See DOI: 10.1039/c0cc03723k

Table 1 Optimization of the reaction conditions for the intermolecular acetoxypalladation of 1,2-diphenylethyne (1a) with butyl acrylate $(2a)^a$
 Table 2
 Acetoxypalladation of unactivated alkynes and capture with alkenes to 1-acetoxy-1,3-diene^{ab}

Ph 1a	Ph + //	^℃00n-Bu 2a	[Pd] catalyst AcO Additives Oxidants Solvent 80°C	Ph CO Ph 3aa	On-Bu
Entry	Pd (10 mol%)	Additive	Solvent	Oxidant	Yield $(\%)^b$
1	Pd(OAc) ₂	0.1 equiv.	AcOH		0
2	Pd(OAc) ₂		$CH_3CN/AcOH$	1 equiv. Cu(OAc)	<5
3	$Pd(OAc)_2$	0.5 equiv.	$CH_3CN/AcOH$	1 equiv.	37
4	$Pd(OAc)_2$	0.5 equiv.	$CH_3CN/AcOH$	1 equiv.	69
5	$Pd(OAc)_2$	l equiv.	$CH_3CN/AcOH$	1 equiv.	65
6	$Pd(OAc)_2$	0.2 equiv.	$CH_3CN/AcOH$	1 equiv.	43
7	Pd(OAc) ₂	0.4 equiv. LiBr	$CH_3CN/AcOH$ (4 · 1)	1 equiv.	71
8	Pd(OAc) ₂	0.4 equiv. KBr	$CH_3CN/AcOH$ (4 · 1)	2 equiv. Cu(QAc)	77
9	Pd(OAc) ₂	0.4 equiv.	$CH_3CN/AcOH$	1 equiv.	0
10	Pd(OAc) ₂	0.4 equiv. KBr	(4:1) CH ₃ CN/AcOH (4:1)	0.4 equiv. Cu(OAc) ₂	89
11	Pd(OAc) ₂	0.4 equiv. KBr	CH ₃ CN/AcOH (4:1)	$1 \text{ atm } O_2$ 0.4 equiv. $Cu(OAc)_2$ air	47
12	Pd(OAc) ₂	0.4 equiv. KBr	$CH_3CN/AcOH$ (4:1)	1 atm O ₂	<5
13	Pd(OAc) ₂	0.4 equiv. KBr	$CH_3CN/AcOH$ (4 · 1)	8 atm O_2	87 ^c
14	PdCl ₂	0.4 equiv. KBr	CH ₃ CN/AcOH (4:1)	0.4 equiv. Cu(OAc) ₂ $1 \text{ atm } O_2$	23
15	_	0.4 equiv. KBr	CH ₃ CN/AcOH (4:1)	0.4 equiv. $Cu(OAc)_2$ $1 \text{ atm } O_2$	0
16	Pd(OAc) ₂	0.4 equiv. KBr	Dioxane/ AcOH (4:1)	0.4 equiv. $Cu(OAc)_2$ $1 \text{ atm } O_2$	68 ^{<i>d</i>}
17	Pd(OAc) ₂	0.4 equiv. KBr	THF/AcOH (4:1)	0.4 equiv. $Cu(OAc)_2$ $1 \text{ atm } O_2$	76

^{*a*} Reactions were carried out using **1a** (0.5 mmol), **2a** (1 mmol), [Pd] catalyst (10 mol%), additives, oxidants and 2 mL solutions in a capped tube, heating at 80 °C for 24 h. ^{*b*} Determined by GC. ^{*c*} The reaction was carried out in a 15 mL autoclave. ^{*d*} With isomers.

treated with this reaction, the systems got complicated without any desired products.

A potential mechanism for this acetoxypalladation/Heck cross-coupling reaction is proposed for the present reaction on the basis of the previously reported mechanism (Scheme 2). This transformation should come about by the unique combination of several steps below: (1) *trans*-acetoxypalladation and (*E*)-vinylpalladium intermediate **B** was formed, followed by (2) a Heck cross-coupling with alkenes and intermediate **C** was produced in this step; (3) a β -H elimination produced the target product **3aa**. Pd(II) was regenerated in the presence of Cu(OAc)₂ for the next cycle and the resulting Cu(I) was



^{*a*} Reaction conditions: alkynes (0.5 mmol), alkenes (1 mmol), Pd(OAc)₂ (10 mol%), KBr (40 mol%), Cu(OAc)₂ (40 mol%) and 2 mL CH₃CN/AcOH (4:1) in a capped tube with 1 atm of dioxygen, heating at 80 °C for 24 h. ^{*b*} Isolated yield. ^{*c*} 50 °C for 24 h.

oxidized to Cu(II) by O₂. According to Lu's researches, the halide ion played a role as ligand.^{2b,g-,j}





Scheme 3 Synthesis of 3ag from 1a and 2g under standard conditions.

The reaction of **1a** and methyl methacrylate (**2g**) was also tested under the standard conditions. Interestingly and surprisingly, an unexpected product **3ag** was obtained in good yield. It's easy to understand if we write down the intermediate **B1**, as there exist two β -H in the structure **B1**, and β -H elimination happens selectively towards the sterically less bulky methyl C–H giving the product **3ag** (Scheme 3). This result provided an additional proof for the proposed mechanism in Scheme 2.

In conclusion, we have developed a new and general protocol for the synthesis of 1-acetoxy-1,3-dienes by an acetoxy-palladation/Heck cross-coupling/ β -H elimination tandem process. A series of 1-acetoxy-1,3-dienes were synthesized from electron-rich and electron-deficient alkynes in high regioand stereoselectivity with high atom efficiency. Importantly, the reaction used dioxygen as the terminal oxidant and H₂O is the only byproduct. Work to expand the scope and apply the method to the field of natural products is currently underway. The authors are grateful to the National Natural Science Foundation of China (Nos. 20625205, 20772034 and 20932002), National Basic Research Program of China (973 Program) (No. 2011CB808603) and Doctoral Fund of Ministry of Education of China (20090172110014) for financial support.

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