Synthetic Methods

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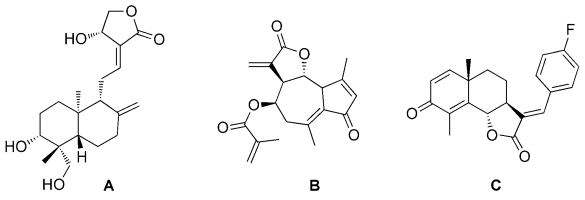
Switch of Selectivity in the Synthesis of α-Methylene-γ-Lactones: Palladium-Catalyzed Intermolecular Carboesterification of Alkenes with Alkynes**

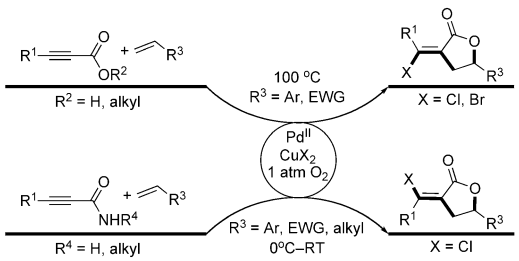
*Liangbin Huang, Qian Wang, Xiaohang Liu, and Huanfeng Jiang**

The development of transition-metal-mediated transformations for the construction of highly functional products in a convenient and concise manner continues to attract broad interest.[1] In particular, cross-coupling reactions of alkynes and alkenes catalyzed by palladium complexes have been studied extensively, because of the accessibility of reactants and the diversity of products.[2–4] One of the major challenges that remain in the nucleopalladation of alkynes is to improve the stereo- and regioselectivities of the nucleopalladation to C–C triple bonds. Three strategies are typically employed: 1) the concentration of the nucleophiles is increased;[5] 2) one palladated isomer is dominant if it leads to the formation of kinetically more stable structures, that is, aromatic rings;[6] 3) a directing group determines the selectivity.[7]

The α-methylene-γ-lactone skeleton is an important moiety in natural products and exhibits potential biological activities. For example, andrographolide and some sesquiterpene lactones, which contain an α-methylene-γ-lactone moiety in the molecule, are used extensively in anti-inflammatory drugs, and have antipyretic, cytotoxic, antitumoral, and often bactericidal properties (Scheme 1).[8] Very recently, we reported an intermolecular carboesterification to construct γ lactones through copper-catalyzed oxidative [3+2] cycloaddition reactions between alkenes and anhydrides.[9] To the best of our knowledge, only one report focuses on the intramolecular [3+2] cycloaddition of alkenes with alkynes to construct a fused ring system that contains an α-methylene-γ-lactone skeleton.[10] Moreover, the products have a *Z*-type configuration. Herein, we present a novel palladium-catalyzed intermolecular carboesterification of alkenes with alkynoates to selectively construct (*E*)-α-methylene-γ-lactone. Interestingly, the stereoselectivities can be switched by a simple modification, the carboesterification of alkenes with alkynamides at room temperature (Scheme 2).



Scheme 1. Chemical structures of andrographolide (**A**) and sesquiterpene lactones (**B** and **C**).



Scheme 2. Switch of stereoselectivity in Pd-catalyzed alkyne–alkene coupling reaction. EWG = electron-withdrawing group.

Our initial investigations of Pd-catalyzed intermolecular carboesterification reactions focused on the cyclization of ethyl 3-phenylpropiolate **1a** with styrene **2a**. No reaction occurred and **1a** was recovered when **1a** and **2a** were treated with 5 mol% $PdCl_2$ and four equivalents of LiCl at 100 °C under 8 atm O_2 in benzene/acetonitrile (v/v = 1:1). α-Methylene-γ-lactone **3a** was produced in low yield with two equivalents of PIDA or DDQ as oxidants (Table 1, entries 2 and 4). The reaction at 40 °C with PIDA as oxidant gave the product in 23% yield (Table 1, entry 3). To our delight, product **3a** was obtained in 92% yield when 1 atm O_2 and two equivalents of $CuCl_2{\cdot}2H_2O$ were used as co-oxidants[11] (Table 1, entry 5). $PdCl_2$ was the best catalyst (Table 1, entries 5, 7, and 8), and a mixture of benzene and acetonitrile (v/v = 1:1) was the best solvent for this reaction (see the Supporting Information for details).[12] In addition, only a trace amount of product was formed when the reaction was performed under anhydrous conditions (Table 1, entry 6). Further studies showed that one oxygen atom of the product came from water [Eq. (1)].[13]

Subsequently, we explored the scope of the reaction between various alkynoates and alkenes under the optimized

[*] L. B. Huang, Q. Wang, X. H. Liu, Prof. Dr. H. F. Jiang
School of Chemistry and Chemical Engineering
South China University of Technology (China)
E-mail: jianghf@scut.edu.cn
Homepage: http://www2.scut.edu.cn/ce/lshxyjzx/links.html

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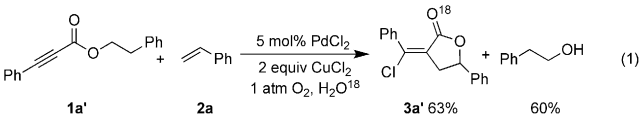
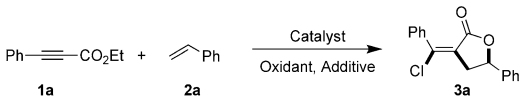
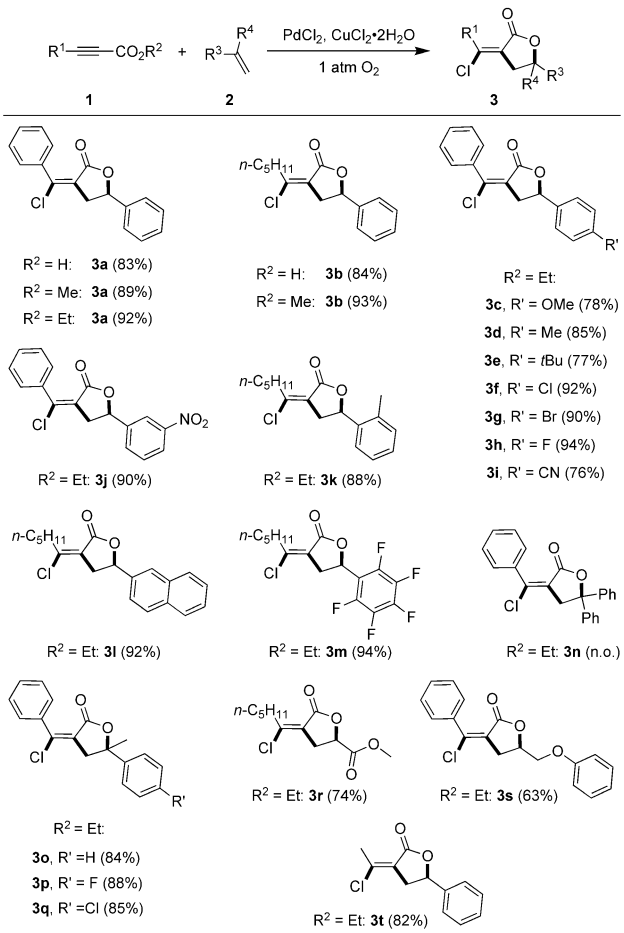


Table 1: Impact of reaction parameters on the carboesterification of alkenes.[a]



Entry	Catalyst	Oxidant	Additive	Yield [%][b]
1	$PdCl_2$	8 atm O_2	LiCl	n.o.
2	$PdCl_2$	PIDA	LiCl	28
3[c]	$PdCl_2$	PIDA	LiCl	23
4	$PdCl_2$	DDQ	LiCl	18
5	$PdCl_2$	$CuCl_2{\cdot}2H_2O$/1 atm O_2	–	95(92)
6[d]	$PdCl_2$	$CuCl_2$/1 atm O_2	–	trace
7	$Pd(OAc)_2$	$CuCl_2{\cdot}2H_2O$/1 atm O_2	–	83
8	$[Pd(dba)_2]$	$CuCl_2{\cdot}2H_2O$/1 atm O_2	–	54

[a] Reaction conditions: Unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.6 mmol) and Pd catalyst (5 mol%) in 1 mL of benzene/acetonitrile (v/v = 1:1) at 100°C for 12 h. [b] Determined by GC using dodecane as the internal standard. Data in parentheses is the yield of isolated product. [c] 40°C. [d] 1 mL of anhydrous benzene/anhydrous acetonitrile (v/v = 1:1). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, n.o. = not obtained, PIDA = phenyliodonium diacetate.



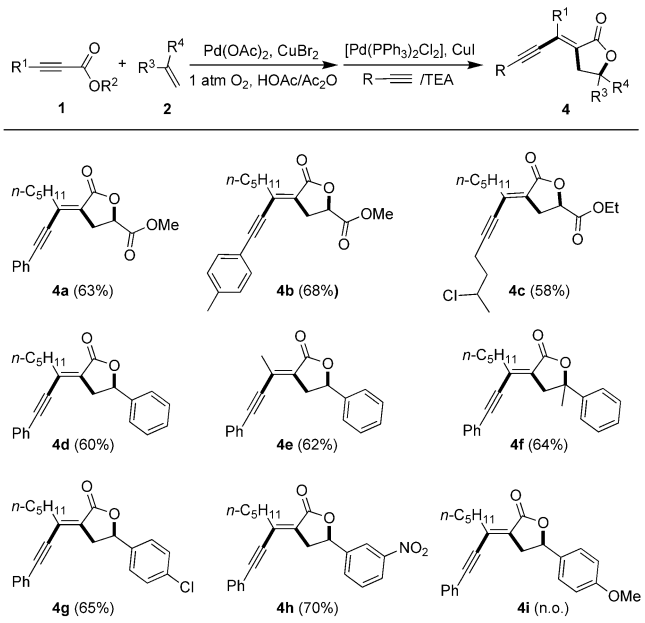
Scheme 3. Substrate scope of the carboesterification of alkenes with alkynoates. The reactions were carried out at 100°C and 1 atm of O_2 using alkynes (0.5 mmol), alkenes (0.6 mmol), $PdCl_2$ (5 mol%), $CuCl_2{\cdot}2H_2O$ (1 mmol), and 1 mL of benzene/acetonitrile (v/v = 1:1) for 12 h.

conditions. Propiolic acids and propiolic acid esters reacted with styrene to afford carboesterification products **3a** and **3b** in good yields (Scheme 3). Both styrene derivatives and simple, electronically deficient alkenes afforded the desired products in good to excellent yields (Scheme 3, **3a**–**k** and **3r**). A series of *para*-substituted styrenes, including some with electron-donating groups (R′ = OMe, Me, *t*Bu) and some with electron-withdrawing groups (R′ = F, CN, NO_2), were converted into the corresponding α-methylene-γ-lactones in excellent yields (Scheme 3, **3c**–**j**).

This transformation was compatible with alkenes that contain Cl- and Br-substituted aryl rings, which could undergo a Heck-type reaction with themselves under Pd catalysis, but in this case do not (Scheme 3, **3f** and **3g**). The structure of **3f** was confirmed by X-ray crystallographic analysis (see the Supporting Information for details), and the configuration of the α-methylene-γ-lactone moiety is different from that of the products of Pd-catalyzed intramolecular carboesterifications of alkenes.[5,10] Other substituted styrenes were also good substrates for this transformation and afforded the corresponding products **3k**–**m** in high yields. These results showed that this new transformation was tolerant toward electronic and steric effects of the aromatic ring. In contrast to 1,1-diphenylethene, which was unreactive (Scheme 3, product **3n**), sterically less hindered 1,1-disubstituted olefins gave products **3o**–**3q** in high yields. When ethyl but-2-ynoate was employed as substrate, the desired product **3t** was isolated in 82% yield (Scheme 3 **3t**). Unfortunately, internal olefins failed to afford the desired products.

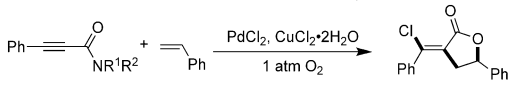
To our delight, the bromopalladation of alkynoates under similar reaction conditions in $AcOH/Ac_2O = 1:1$ (v/v, see the Supporting Information) as solvent and with $CuBr_2$ as co-oxidant could also initiate this domino-type reaction with various alkenes to give α-bromo-α-methylene-γ-lactones (Scheme 4). Upon completion of the carboesterification of alkenes and extraction with diethyl ether, crude products **3** were directly subjected to the palladium-catalyzed Sonogashira coupling without additional purification. Similarly, reactions with both electron-deficient alkenes and styrene derivatives proceeded smoothly to give the products in moderate to good yields. Electron-deficient olefins proved to be the better substrates (**4g**, **4h**).

To our surprise, the major products had a reversed configuration when alkynamides were used as substrates (Table 2; X-ray crystallographic analysis in the Supporting Information). Inspired by these results, we decided to attempt increasing the selectivity toward the (*Z*)-α-methylene-γ-lactone skeleton. When the temperature was decreased to room temperature, a selectivity of $Z/E = 97:3$ could be achieved (Table 2, entries 1–3). At least one N–H bond was necessary for this transformation to occur; disubstituted



Scheme 4. Conversion of vinylbromides to multifunctional lactones. The carboesterification reactions were carried out at 100 °C under 1 atm of O_2 with alkynoates (0.5 mmol), alkenes (0.6 mmol), $Pd(OAc)_2$ (5 mol %), $CuBr_2$ (1 mmol), and $AcOH/Ac_2O = 1:1$ (v/v, 1 mL) for 12 h. The crude products were extracted with diethyl ether. Terminal alkynes (0.6 mmol), $[Pd(PPh_3)_2Cl_2]$ (5 mol %), CuI (5 mol %), TEA (0.1 mL), and DMF (1.5 mL) were added and the Sonogashira coupling was carried out at 80 °C for 8 h. TEA = triethylamine.

Table 2: Carboesterification of alkenes with alkynamides.[a]

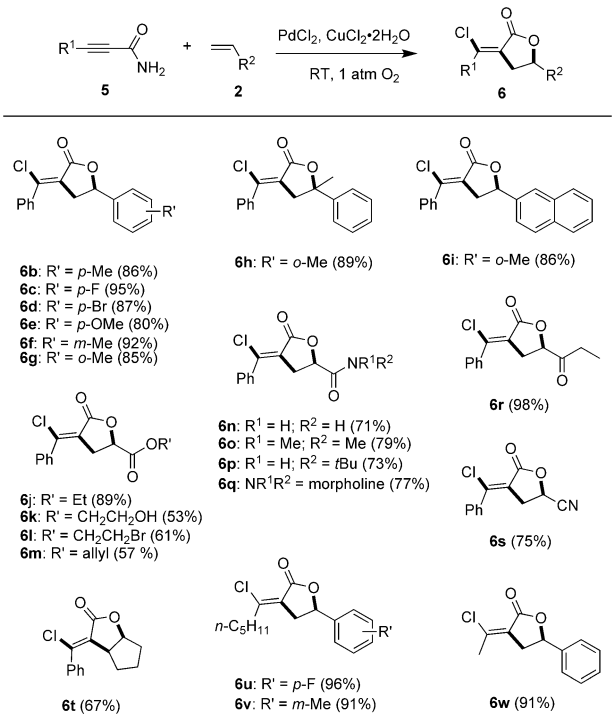


Entry	R^1	R^2	T [°C]	Z/E	Yield [%][b]
1	H	H	100	91:9	73
2	H	H	50	95:5	89
3	H	H	RT	97:3	93
4	H	Me	RT	97:3	89
5	H	*t*Bu	RT	98:2	78
6	Me	Me	RT	–	–

[a] The reactions were carried out under 1 atm of O_2, with alkynes (0.5 mmol), alkenes (0.6 mmol), $PdCl_2$ (5 mol %), and $CuCl_2 \cdot 2H_2O$ (1 mmol) in acetonitrile (0.5 mL) for 12 h. [b] Yields of isolated products.

alkynyl carboxamides did not give the desired product (Table 2, entry 6).[14]

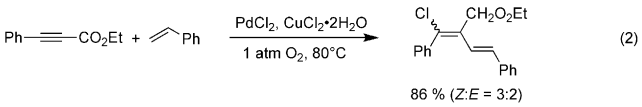
The scope of the reaction at room temperature was further expanded to a range of alkynamides and alkenes (Scheme 5). Styrene derivatives could be smoothly transformed into the desired products in good yields. Ethyl acrylate reacted efficiently to produce **6j** in 89 % yield, whereas OH- or Br-substituted ethyl acrylate was converted into the corresponding products in lower yields (53 % and 61 %, respectively). The reaction was compatible with OH and Br substituents when substituted allyl acrylates were used as the substrates. Acryl amide derivatives also worked well for this transformation. When vinyl ketone and acrylonitrile were used for this reaction, carboesterification products **6r** (98 %)



Scheme 5. Carboesterification of alkenes with alkynamides: The reactions were carried out under 1 atm of O_2, with alkynes (0.5 mmol), alkenes (0.6 mmol), $PdCl_2$ (5 mol %), and $CuCl_2 \cdot 2H_2O$ (1 mmol) in acetonitrile (0.5 mL) for 12 h.

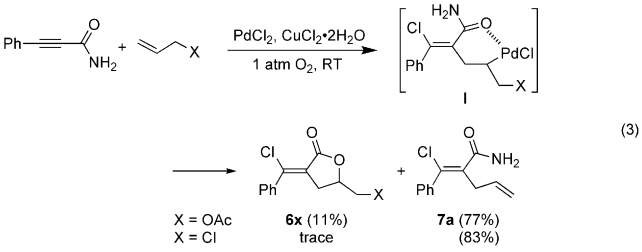
and **6s** (75 %), respectively, were obtained. Interestingly, when cyclopentene was used as the terminating coupling reagent, product **6t** (67 %) was obtained. When the initial coupling reagent was but-2-ynamide or oct-2-ynamide, the corresponding (*Z*)-α-methylene-γ-lactones were obtained in high yields.

It should be noted that the corresponding (*E*)-γ-lactone could not be obtained when the temperature was decreased to 80 °C [Eq. (2)].[4g] This result indicates that, in this case,

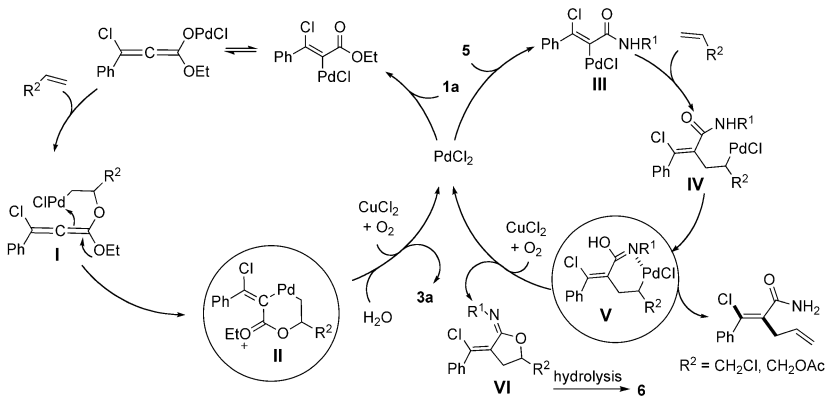


(2)

temperature plays a crucial role in the transformation. A competitive reaction occurred when allyl chloride and allyl acetate were used as the terminating coupling reagents. A tentative explanation for this phenomenon is that the C–Pd bond in the shown intermediate [Eq. (3)] could be quenched by β-X elimination to afford product **7a**, or by $C(sp^3)$–O bond formation[16] to obtain **6x**. In addition, (*Z*)-product **6a**, which

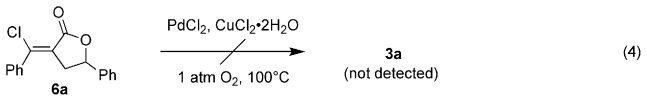


(3)



Scheme 6. Tentative mechanisms that explain the switched selectivity in Pd-catalyzed alkyne–alkene coupling reactions.

was obtained at room temperature, could not be converted into the isomer with *E* configuration [Eq. (4)]. It seems that the two configurations are obtained through two different reaction pathways.



(4)

A tentative mechanism for the switched selectivity in Pd-catalyzed intermolecular carboesterification of alkenes to synthesize α-methylene-γ-lactones is proposed on the basis of the above-mentioned results (Scheme 6). The left pathway is initiated by *trans*-halopalladation of alkynoate and keto–enol equilibria, subsequently, *cis*-oxypalladation gives intermediate **I**,[16] followed by the formation of **II** through the addition of the enol to the Pd^{II} species. The reductive elimination to the $C(sp^2)$–$C(sp^3)$ bond and hydrolysis then afforded the (*E*)-product. For the right pathway, Pd^{II}-catalyzed carboesterification of alkenes with alkynamide was also initiated by the halopalladation of alkynamide, giving vinylpalladium intermediate **III**. Subsequently, **III** is captured by the alkene through a Heck addition to produce intermediate **IV**. Isomerization to form intermediate **V**[14] is followed by β-X elimination if the alkenes were allyl choride and allyl acetate, or by $C(sp^3)$–O bond formation.[15] The hydrolysis of intermediate **VI** affords (*Z*)-lactones. Finally, the active Pd^{II} species is regenerated by oxidation with Cu^{II} and O_2.

In conclusion, we have developed a new and convenient carboesterification method to construct α-methylene-γ-lactone rings. The selectivity can be switched by using either alkynoates or alkynamides as substrates together with alkenes, the temperature also plays an important role in this transformation. Our ongoing studies involve broadening of the scope of the carboesterification to the carboetherification and the carboamination of alkenes. An investigation toward potential applications, for example, in stereoselective synthesis, is currently under way.

Experimental Section

General procedure for the palladium-catalyzed carboesterification of alkenes with alkynoates: Alkynoate (0.5 mmol), alkene (0.6 mmol), $PdCl_2$ (5 mol%), $CuCl_2$ (0.75 mmol), and CH_3CN/benzene = 1:1 (1 mL) were added to a Schlenk tube. The tube was charged with O_2 (1 atm), and the mixture was stirred at 100 °C (oil bath temperature) for the desired reaction time. After the reaction was finished, the mixture was cooled to room temperature and quenched with aqueous NaCl, and the crude product was extracted with ethyl acetate. The organic extracts were concentrated in vacuum, and the resulting residue was purified by column chromatography on silica gel with light petroleum ether/ethyl acetate as eluent to afford the desired product.

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