Synthetic Methods

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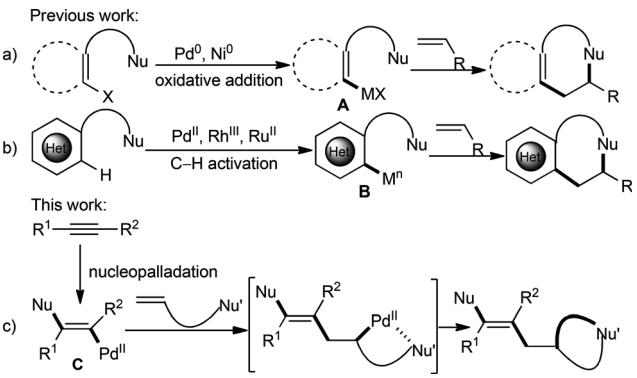
Palladium-Catalyzed Cascade Annulation To Construct Functionalized β- and γ-Lactones in Ionic Liquids**

Jianxiao Li, Wanfei Yang, Shaorong Yang, Liangbin Huang, Wanqing Wu, Yadong Sun, and Huanfeng Jiang**

Abstract: *A highly efficient and mild palladium-catalyzed, one-pot, four-step cascade annulation has been developed to afford functionalized β- and γ-lactones in moderate to good yields with high regio- and diastereoselectivities in ionic liquids. The employment of ionic liquids under mild reaction conditions makes this transformation green and practical. Especially, this reaction provided a novel and convenient methodology for the construction of naturally occurring biologically active β- and γ-lactones.*

Transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond formations have attracted considerable attention over the past decades owing to its easy access to highly functionalized and complex molecules in a rather efficient, atom- and step-economical way.[1] Prominently, carbometalation of carbon–carbon multiple bonds is a crucial process in organometallic chemistry from both theoretical and practical standpoints.[2] Among numerous successful representative strategies, the carbometalation of alkenes provides an efficient and versatile method to realize carbo- and heterofunctionalization of alkenes.[3] Traditionally, the crucial intermediate **A** of the carbometalation process is formed mainly through the oxidative addition of C(sp^2)–X using low-valent transition metals (Scheme 1 a).[4] In recent years, impressive achievements have been made in enhancing the efficiency of transition-metal-catalyzed C–H bond activation for the construction of the indispensable intermediate **B** of the carbometalation process (Scheme 1 b).[5] Despite the significant progress that has been achieved along these lines, the main restrictive limitation is that the olefins are usually limited to allenes, 1,3-dienes, and activated alkenes. Other polyfunctionalized alkenes, such as an enoic acid, are highly desirable.

In addition, saturated lactones are found in a vast array of synthetically challenging[6,7] and biologically significant natural products,[8,9] many of which exhibit extraordinary biological and pharmaceutical properties. Representative saturated lactones are found in natural products and biologically active molecules such as (+)-eldanolide,[10] (+)-harzialactone A,[11] antimycinone,[12] salinosporamide A,[13] and an antibiotic agent[14] as shown in Figure 1.



Scheme 1. Alkene difunctionalization through carbometalation.

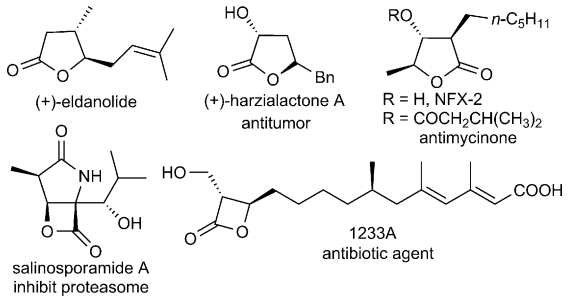


Figure 1. Representative examples containing saturated lactone motifs.

Consequently, the development of concise routes to the construction of saturated lactones continues to be an active area of research. However, these known pioneering methods may, in some cases, suffer from certain limitations such as multiple steps, troublesome operations, harsh reaction conditions, or low yields. Recently, Smith and co-workers discovered an elegant method for the stereoselective synthesis of stereodefined β-lactones based on a [2+2] cycloaddition of alkylarylketenes with electron-deficient benzaldehydes or pyridinecarboxaldehydes.[15] However, complex substrates and harsh reaction conditions are required in these reactions. Very recently, we reported an intermolecular

[*] J. Li, W. Yang, Dr. S. Yang, L. Huang, Dr. W. Wu, Y. Sun, Prof. Dr. H. Jiang
School of Chemistry and Chemical Engineering, South China University of Technology
Guangzhou 510640 (P. R. China)
E-mail: lisryang@scut.edu.cn
jianghf@scut.edu.cn

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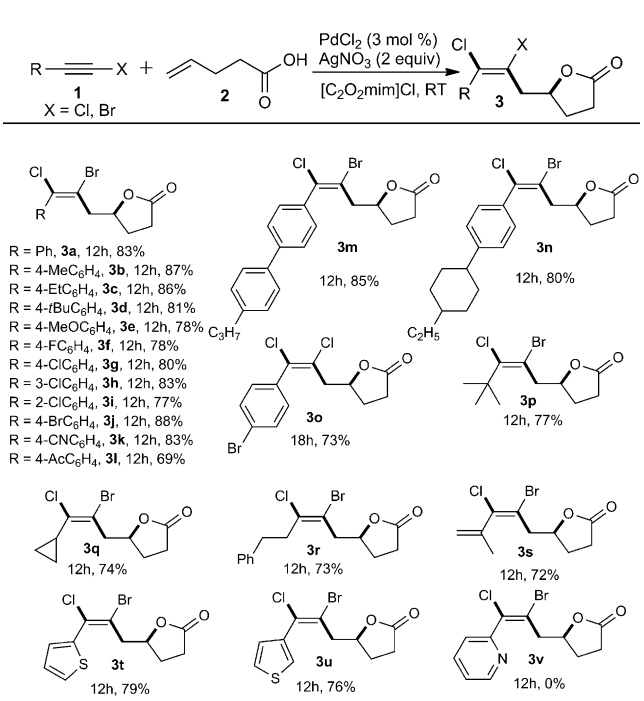
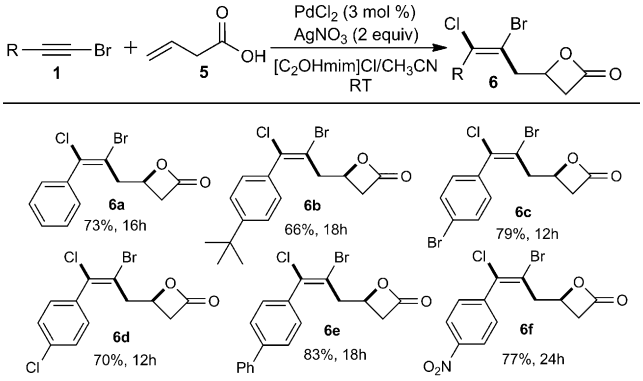
carboxylative annulation cascade to construct saturated functionalized γ-lactones in ionic liquids (ILs) through palladium-catalyzed, one-pot, four-step cascade methods.[16] As part of our research program in nucleopalladation[17] and palladium-catalyzed cross-coupling reactions in ILs,[18] herein, we present the first example of a palladium-catalyzed intermolecular cascade annulation for the synthesis of functionalized β- and γ-lactones with high regio- and stereoselectivity in ILs (Scheme 1c).

We optimized the reaction as follows: the haloalkyne (0.25 mmol), enoic acid (0.30 mmol), $PdCl_2$ (3 mol%), $AgNO_3$ (0.5 mmol), and $[C_2O_2mim]Cl$ (0.5 mL) at room temperature (see the Supporting Information for details). Representative results are summarized in Scheme 2. Gratifyingly, a series of *para*-substituted bromoalkynes, including some with electron-donating groups (Me, Et, *t*Bu, OMe, ethylcyclohexyl, 4-propylphenyl) and some with electron-withdrawing groups (F, Cl, Br, CN, Ac), were converted into the corresponding γ-lactones in excellent yields (**3a**–**n**). Furthermore, the reaction was found to be applicable to a chloroalkyne (**1o**), although the reaction was relatively sluggish. As for the sterically hindered bromoalkynes **1g**, **1h**, and **1i**, the reaction furnished the corresponding products (*Z*)-**3g**, (*Z*)-**3h**, and (*Z*)-**3i** in similar yields. Satisfied with the above results, we then tried more challenging aliphatic bromoalkynes. Delightfully, the γ-lactones **3p**, **3q**, and **3r** were smoothly obtained in a highly stereoselective fashion and with good yields. Besides the wide substrate scope, another impressive feature of the current cascade annulation reaction is its high tolerance for functional groups. For instance, the bromoalkynes containing vinyl or thienyl groups underwent the cascade reaction to give corresponding products in good yields with high stereoselectivities (**3s**–**u**). Unfortunately, 2-(bromoethynyl)pyridine (**1v**) failed to afford the desired products. In terms of the stereoselectivity, all of the products obtained in the presence of an excess of chloride ions and acid in a polar solvent resulted from *trans* addition.[19] The site of halogen addition to asymmetrical acetylenes is controlled by the electronic factors.[20]

Based on the results obtained, we were interested in extending the method to bromoalkynes and but-3-enoic acid (**5**) to prepare a variety of substituted β-lactones under similar reaction conditions (Scheme 3).[21] To our delight, the chloropalladation of bromoalkynes could also initiate this domino-type reaction with but-3-enoic acid (**5**) to give functionalized β-lactone products. Similarly, the bromoalkynes substituted with electron-donating groups and electron-withdrawing groups proceeded smoothly to give the products in moderate to good yields.



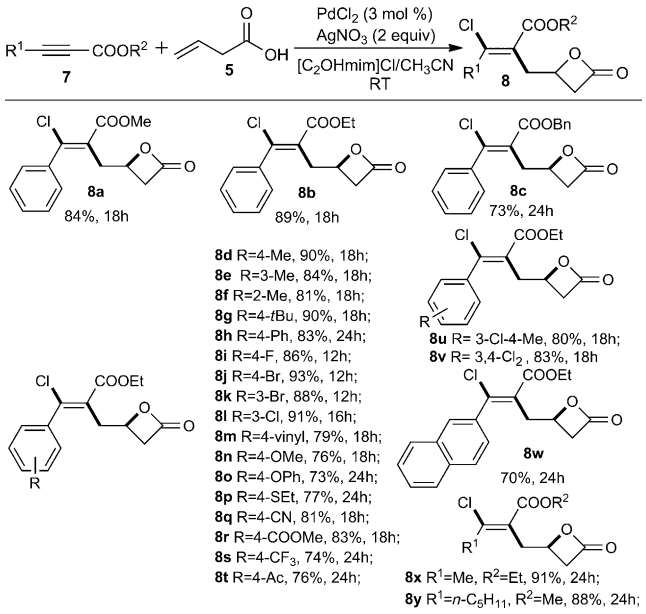
Scheme 2. Substrate scope of the cascade annulation of haloalkynes with **2** in $[C_2O_2mim]Cl$. Reaction conditions: **1** (0.25 mmol), **2** (0.30 mmol), $PdCl_2$ (3 mol%), $AgNO_3$ (0.5 mmol), and $[C_2O_2mim]Cl$ (0.5 mL) at room temperature.



Scheme 3. Cascade annulation of bromoalkynes with **5** in $[C_2OHmim]Cl$. Reaction conditions: **1** (0.25 mmol), **5** (0.30 mmol), $PdCl_2$ (3 mol%), $AgNO_3$ (0.5 mmol), $[C_2OHmim]Cl$ (0.5 mL), and CH_3CN (0.1 mL) at room temperature.

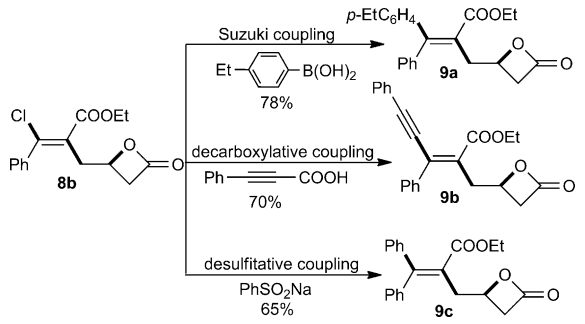
The scope of the reaction at room temperature was further expanded to a range of alkynoates (Scheme 4). Gratifyingly, methyl, ethyl, and phenyl alkynoates were reacted under the optimal reaction conditions, and good to excellent yields of the desired products were obtained (**8a**–**c**). Various functional groups, including alkyl, fluoro, chloro, bromo, cyano, ester, acetyl, alkoxyl, thiol, and trifluoromethyl groups, were compatible with the reaction conditions (**8d**–**t**). Notably, a vinyl group was tolerated under the standard reaction conditions, thus providing **8m** in 79% yield with high Z stereoselectivity. Substitution at the 4-, or 3-, or 2-position of the aromatic ring had a slight impact (**8d**,**f** and **8j**,**k**). Moreover, the more bulky fused aryl alkynoate, such as 2-naphthyl alkynoate (**7w**), could be converted into the corresponding products **8w** in moderate yield as well. Furthermore, besides the aryl alkynoates, alkyl alkynoates (**7x** and **7y**) were also found to be suitable substrates under the standard reaction conditions.

To demonstrate the synthetic utility of this protocol, the newly formed chlorinated acrylates were employed for



Scheme 4. Cascade annulation of alkynoates with **5** in $[C_2OHmim]Cl$. Reaction conditions: **7** (0.25 mmol), **5** (0.30 mmol), $PdCl_2$ (3 mol%), $AgNO_3$ (0.5 mmol), $[C_2OHmim]Cl$ (0.5 mL), and CH_3CN (0.1 mL) at room temperature.

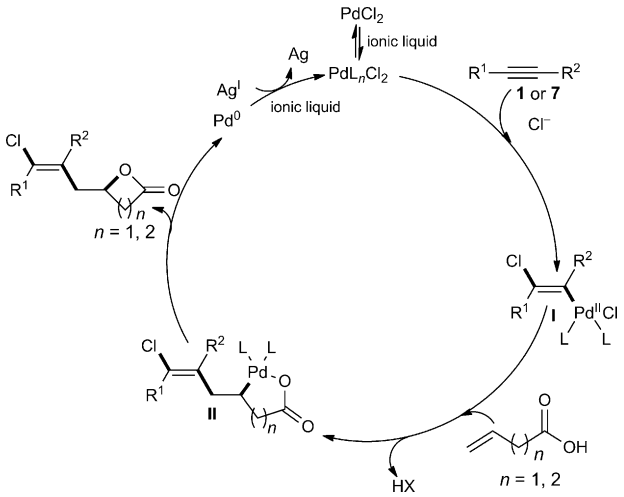
further transformations to prepare a series of functionalized products (Scheme 5). For instance, the Suzuki–Miyaura cross-coupling reactions of **8b** with phenylboronic acid delivered the arylated compound **9a** in moderate yield.[22] Furthermore,



Scheme 5. Synthetic transformations of **8b**.

8b underwent the decarboxylative coupling to produce the highly functionalized β-lactone **9b** in 70% yield.[23] To our satisfaction, the desulfitative coupling of **8b** occurred uneventfully as well, thus providing the stereodefined tetra-substituted alkene **9c** in 65% yield.[24]

Based on the current results and previous literature,[17,18,25] the postulated mechanism is depicted in Scheme 6. A palladium complex is initially formed in situ in ILs,[17,18] and the vinylpalladium intermediate **I** is formed by *trans*-chloropalladation of the alkyne in a polar solvent system[19] in the presence of excess chloride ions.[26] Subsequently, **I** could undergo alkene insertion. Simultaneously, the vinylpalladium species coordinates to the oxygen atoms of the hydroxy group to generate the palladium/alkyl intermediate **II**. Finally,



Scheme 6. Plausible reaction mechanism.

a reductive elimination gives the target product. Worthy of note, a silver mirror reaction was observed after the reaction was finished.[27] Hence, the resulting palladium(0) is additionally oxidized to palladium(II) to complete this catalytic cycle.

In conclusion, we have successfully accomplished an attractive strategy for the synthesis of functionalized β- and γ-lactones with high regio- and diastereoselectivities by a palladium-catalyzed cascade annulation of alkynes with olefins in ionic liquids. This cascade annulation process, is a one-pot, four-step reaction which proceeds smoothly with good functional-group tolerance. Most importantly, this methodology provides a new tool for the construction of diversely substituted β- and γ-lactone derivatives from inexpensive starting materials.

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