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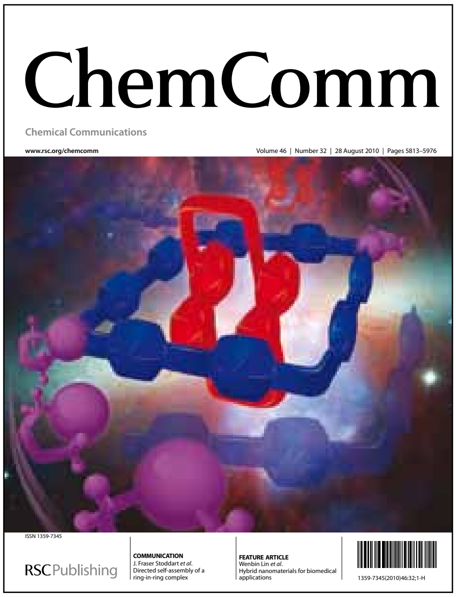

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Novel Palladium-Catalyzed Cascade Carboxylative Annulation to Construct Functionalized γ-Lactones in Ionic Liquids

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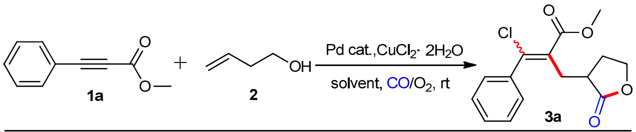
A novel palladium-catalyzed, one-pot, four-step cascade method has been developed to afford functionalized γ-lactones in moderate to good yields. This novel and general methodology represents a rare instance of carbonylation of C(sp^3)-palladium bond.

Motived by the increasing requirements for sustainable chemistry, green and atom-economic synthesis has attracted great attention.[1] Toward this end, carbonylation processes using carbon monoxide (CO) as a C1 building block have been studied extensively, because of the direct formation of complicated molecules from readily accessible starting materials.[2] In particular, transition metal-catalyzed carbonylation of aromatic halides with CO in the presence of various nucleophiles has undergone rapid development,[3] since the pioneering work of Heck and co-workers in 1974.[4] During the past decade, Pd-catalyzed aromatic C-H functionalization/carbonylation simultaneously has attracted more and more interest.[5] However, carbonylation of C(sp^3)-palladium bond remains an outstanding challenge. [6]

On the other hand, the saturated γ-lactones are important moiety in organic synthesis because of their ability to serve as building blocks in a wide variety of functional group transformations.[7] They have also been found as a substructure in numerous bioactive natural products and potential pharmaceutically interesting compounds.[8] Transition metal-catalyzed reactions have emerged as a powerful tool for the construction of saturated γ-lactones and have become one of the most attractive methodologies in the last decade. [9] However, all these elegant developments suffer from certain limitations such as multiple steps, troublesome operation, harsh reaction conditions or low yields, making them less attractive in organic synthesis. Thus, the development of methods that can construct these classes of compounds in an efficient and practical manner from readily accessible substrates continues to attract broad interest. More recently, some representative strategies have been exploited to the preparation of this type of compounds as well.[10] Moreover, we reported an intermolecular carboesterification to construct saturated γ-lactones through copper-catalyzed oxidative [3+2] cycloaddition reactions between alkenes and anhydrides.[11] Despite the significant progress that has been achieved along this line, there are only a few methods that exist for the effective synthesis of functionalized saturated γ-lactone in an efficient, safer and green way. As our part of research program in nucleopalladation[12] and Pd-catalyzed cross-coupling reactions in ionic liquids (ILs),[13] herein, we wish to present the first example of palladium-catalyzed intermolecular carbonylation of alkynes with homoallylic alcohols in [C_2O_2mim]X to selectively construct saturated γ-lactones with high regio- and stereoselectivity.

Table 1 Optimization of the reaction conditions[a]

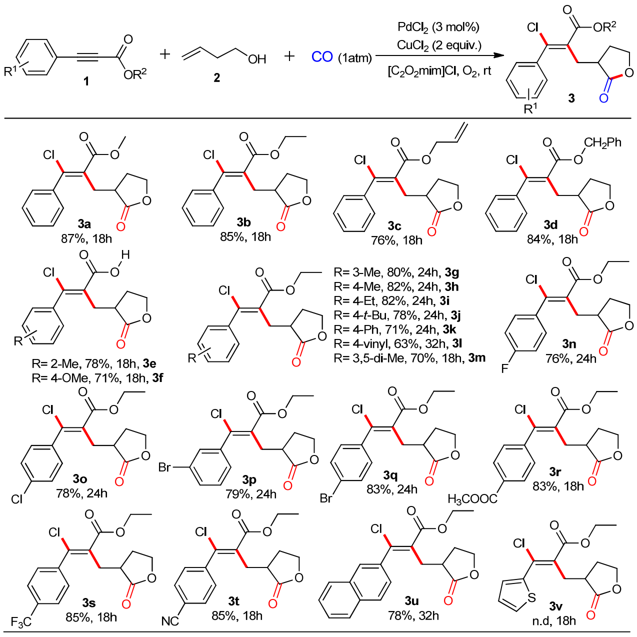


Entry	Catalyst	Solvent	Yield[b]	Z/E
1	$PdCl_2$	[Bmim]Cl	-	-
2	$PdCl_2$	[C_2OHmim]Cl	-	-
3	$PdCl_2$	[C_2O_2mim]Cl	81	>98/2
4[c]	$PdCl_2$	[C_2O_2mim]Cl	37	98/2
5[d]	$PdCl_2$	[C_2O_2mim]Cl	31	94/6
6[e]	$PdCl_2$	[C_2O_2mim]Cl	24	94/6
7[f]	$PdCl_2$	[C_2O_2mim]Cl	93(86)	>98/2
8	$Pd(OAc)_2$	[C_2O_2mim]Cl	47	98/2
9	$PdCl_2(PPh_3)_2$	[C_2O_2mim]Cl	26	98/2
10	$Pd(PhCN)_2Cl_2$	[C_2O_2mim]Cl	43	98/2
11	$Pd(MeCN)_2Cl_2$	[C_2O_2mim]Cl	35	98/2
12	$PdBr_2$	[C_2O_2mim]Cl	61	98/2
13	$PdCl_2$	CH_3CN	80	78/22
14	$PdCl_2$	1,4-dioxane	83	70/30
15	$PdCl_2$	DMF	18	54/46
16	$PdCl_2$	THF	74	79/21

[a] Unless otherwise noted, all reactions were performed with **1a** (0.25 mmol), **2** (0.3 mmol), Pd catalyst (0.03 mol) and $CuCl_2$•$2H_2O$ (2 equiv) under CO/O_2 = 1:1 (1 atm) in the indicated solvent (1.0 mL) at room temperature for 12 h. [Bmim]Cl: 1-butyl-3-methylimidazolium chloride; [C_2OHmim]Cl: 1-hydroxyethyl-3-methylimidazolium chloride; [C_2O_2mim]Cl: 1-carboxymethyl-3-methylimidazolium chloride. [b] Determined by GC using dodecane as the internal standard. Data in parentheses are the isolated yield. [c] Without O_2. [d] Instead of O_2, 2 equiv $K_2S_2O_8$ was used. [e] Instead of O_2, 2 equiv DDQ was used. [f] CO/O_2 = 3:1.

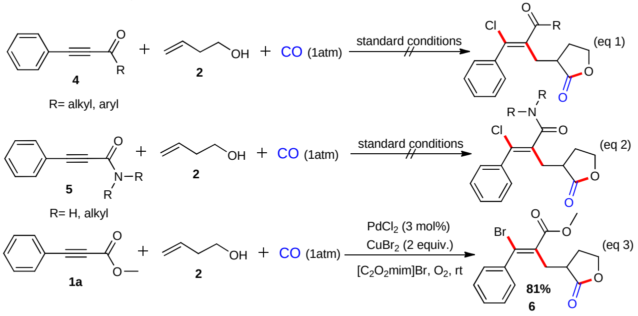
Our experiment was initiated by treating ethyl 3-phenylpropiolate (**1a**) with homoallyl alcohol (**2**) in the presence of 1 atm CO/O_2 (Table 1). Firstly, when **1a** and **2** were treated with $PdCl_2$ (3 mol%) and $CuCl_2$•$2H_2O$ (2 equiv.) in [Bmim]Cl, no desired product **3a** was obtained. Subsequently, the reaction was further investigated by replacing [Bmim]Cl with other ionic liquids, such as [C_2O_2mim]Cl and [C_2OHmim]Cl, and [C_2O_2mim]Cl was found to be the most suitable medium for this process (entries 2 and 3). Optimization of the reaction conditions showed that the O_2 played a crucial role in the success of this transformation (entries 4-6). Gratifyingly, when the carbonylation was conducted under mixed gas outside the CO/O_2 explosion limits (CO/O_2 = 3:1), 93% yield of desired (Z)-**3a** was obtained (entry 7). The configuration was elucidated by interpret NOSEY spectra.[14] Furthermore, other palladium catalysts were also examined. Except for $PdCl_2$, other Pd sources, including $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(MeCN)_2Cl_2$, $Pd(PhCN)_2Cl_2$ and $PdBr_2$, showed low efficiencies (entries 8-12). Finally, various conventional solvents were examined, such as CH_3CN, THF, 1,4-dioxane and DMF, significantly decreased the yields and stereoselectivities (entries 13-16).

Table 2 Substrate scope of the carbonylation of alkynoates with **2** in $[C_2O_2mim]Cl$[a]

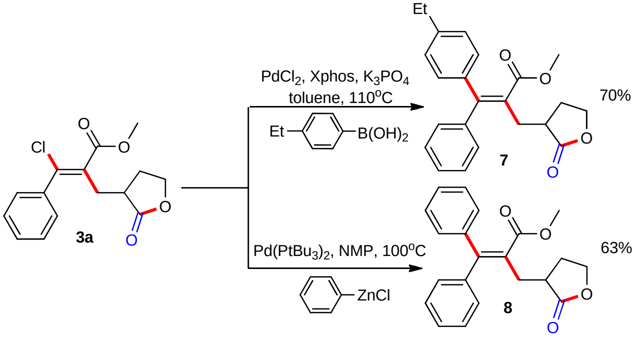


[a] Reaction conditions: **1** (0.25 mmol), **2** (0.30 mmol), $PdCl_2$ (3 mol%), O_2 (1 atm) and $[C_2O_2mim]Cl$ (1 mL) at room temperature. Reaction was monitored by TLC for the completion of the reaction. Yields referred to isolated yields.

With the optimal conditions in hand, we further investigated the scope and limits of this reaction. Representative results are summarized in Table 2. As expected, ethyl, allyl and phenyl alkynoates and substituted phenylpropiolic acid were allowed to react under the optimal conditions, and good to excellent yields of the desired products were obtained (**3b**-**3f**). Pleasingly, all the reaction exhibited high functional-group tolerance and smoothly and cleanly occurred with both electron-withdrawing and electron-donating substituents on the aromatic ring. When **2** reacted with alkynoates with electron-donating groups, the corresponding products **3g**-**3m** were obtained in moderate yields (63%-80%). Notably, vinyl group was tolerated under the standard reaction conditions, providing **3l** in 63% yield with high stereoselectivity. Substitution at the 4-position or 3-position of the aromatic ring had a slight impact (**3e**, **3g** and **3f**). Moreover, the di-electron-donating group substituted substrate also gave moderate yield (**3m**). Thus, this result indicated that these reactions were not considerably inhibited by the steric hindrance of alkynoates. Alkynoates with halide substituents remained intact in these coupling reactions. For example, alkynoates with -Cl, -F, or -Br substituent at the 4-position reacted with **2** to give **3n**, **3o**, and **3q** in 76%, 78%, and 83% yields, respectively. Alkynoates with a strong electron-withdrawing group at the 4-position, such as -COOMe, -CN, or $-CF_3$, gave products **3r**, **3s**, and **3t** in 83%, 83%, and 85% yields, respectively. In addition, naphthalene alkynoate exhibited excellent reactivity under the standard reaction conditions and gave the desired products **3u** in 78% yield. Disappointingly, heterocyclic alkynoate, such as ethyl 3-(thiophen-2-yl)propiolate (**1v**), failed to react with **2** to afford the desired products. In terms of the stereoselectivity, all the products obtained in the presence of an excess of chloride ions and acid in a polar solvent, resulted from *trans* additions.[15] The site of the halogen addition to asymmetric acetylenes was controlled by electronic factors.[16]



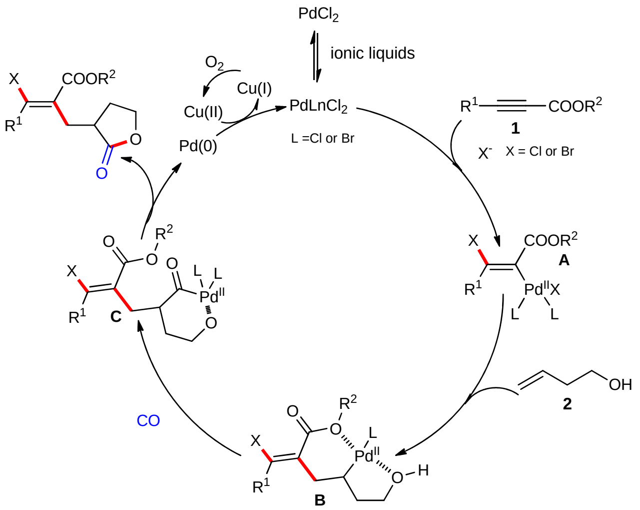
Inspired by these results, we further examined other types of alkynes for this transformation under the standard reaction conditions. Unfortunately, alkynone (**4**) and alkynamides (**5**), failed to afford the desired products (eq 1 and eq 2). It is noteworthy that the reaction of **1a** with **2** in $[C_2O_2mim]Br$ (1-carboxymethyl-3-methylimidazolium bromide) under the similar reaction conditions provided **6** in 81% yield (eq 3).



Scheme 1 Synthetic transformations of **3a**

To further demonstrate the utility of the present reaction in synthesizing various saturated γ-lactone derivatives, the transformations of the resultant **3a** were investigated (Scheme 1). For instance, **3a** underwent the Suzuki-Miyaura coupling to produce the highly functionalized γ-lactone **7** in the yield of 70%.[17] To our satisfaction, the Negishi coupling of **3a** occurred uneventfully as well, providing the stereodefined tetrasubstituted alkene **8** in 63% yield.[17]

Based on the current results and previous literature,[12, 13, 18] the postulated mechanism is depicted in Scheme 2. Pd complex is initially formed *in situ* in ILs,[13] and vinylpalladium intermediate **A** is formed by *trans*-chloropalladation of the alkyne in a polar solvent system[15] in the presence of excess chloride ions.[19] Then, intermediate **A** could undergo alkene insertion. Simultaneously, the vinylpalladium species coordinates to both the oxygen atoms of OR^2 and the hydroxyl group to generate a Pd-alkyl intermediate **B**. Subsequently, migratory insertion of CO into the palladium-carbon σ bond to produce intermediate **C**.[18] Finally, a reductive elimination gives the target product and Pd(II) was regenerated in the presence of oxidant for the next cycle.



Scheme 2 Proposed mechanism

In conclusion, we have developed a practical, efficient, and versatile method for the synthesis of functionalized saturated γ-lactones. This novel and general methodology may open up a new viewpoint to the carbonylation of $C(sp^3)$-palladium bond. Further investigation of the reaction mechanism, as well as the synthetic applications of this protocol for the construction of functionalized γ-lactones are currently in progress.

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† Electronic Supplementary Information (ESI) available: Experimentalsection, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for isolated compounds. See DOI: 10.1039/b000000x/

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