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SHORT COMMUNICATION

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Palladium-Catalyzed Alkynylative Lactonization of Unsaturated Bicyclic Carboxylic Acids: Synthesis of Fused Polycyclic γ-Lactone Compounds

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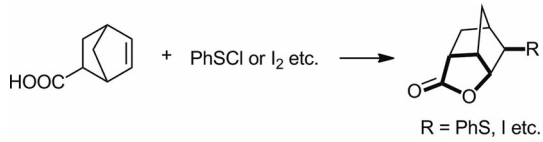
Unsaturated bicyclic carboxylic acids undergo palladium-catalyzed coupling with bromoalkynes to produce γ-alkynyl lactones in moderate to good yields with excellent chemo- and regioselectivity. The reaction conditions were extremely mild, and functional groups such as methyl, methoxy, chloro, and bromo were tolerated under the optimized reaction conditions. Moreover, γ-chloroalkenyl lactones were facilely synthesized through chloropalladation/carboesterification of electron-deficient C≡C bonds by using molecular oxygen as the sole oxidant.

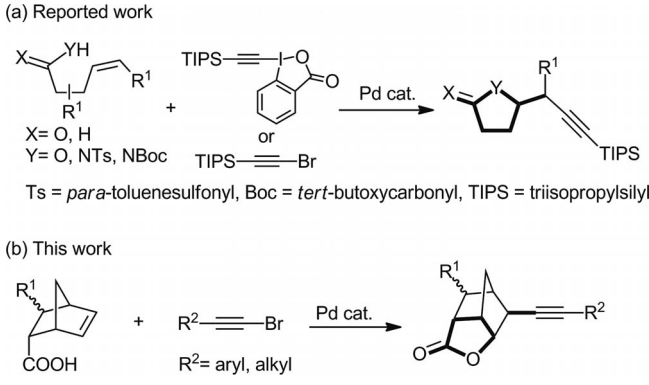
Introduction

The lactone unit is one of the most abundant and relevant esters in natural products and pharmaceuticals. Despite the existence of numerous methods for the synthesis and derivatization of lactone rings, the development of new, more efficient methods is of great importance.[1] Haloalkynes represent an attractive alternative to aryl halides or terminal alkyne derivatives because of their higher reactivity, tolerance under milder conditions, their availability from inexpensive acetylides, and because additional oxidant and base are not required in several applications.[2] Moreover, highly functionalized alkenynes have been prepared through the bromoalkynylation of internal alkynes.[3] Further research on haloalkynes has revealed other possibilities for the synthesis of complex molecules. Norbornene derivatives are an appealing group of organic molecules because of their strained structure and high reactivity. They tend to coordinate to transition metals and have potential applications in various areas of industry; as such, they have attracted considerable research interest from organic chemists.[4] To date, various synthetic methods have been developed for the synthesis phenylsulfenyl lactones and halolactones through intramolecular lactonization of unsaturated carboxylic acids (Scheme 1).[5]



Scheme 1. Usual lactonization procedure for bicyclic carboxylic acids.

Recent research into the transition-metal-catalyzed reactions of norbornenes by the group of Jiang[6] and others[7] led us to investigate the intermolecular alkynylation and carboesterification of this class of molecules. The Pd-catalyzed intramolecular oxy- and aminoalkynylation of nonactivated olefins with the use of a benziodoxolone-derived hypervalent iodine reagent or (2-bromoethynyl)triiospropylsilane as an alkyne transfer reagent was reported by Waser and co-workers for the preparation of tetrahydrofurans and pyrrolidines (Scheme 2, a).[8] Unfortunately, when using phenylethynyl bromides or phenylethylethynyl bromides as substrates, complex mixtures of products were obtained.



Scheme 2. Pd-catalyzed oxyalkynylation of olefins with haloalkynes.

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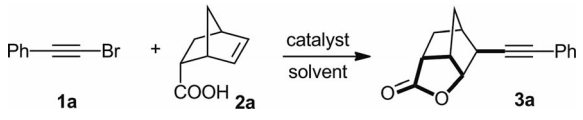
Herein, we report a general protocol for the alkynylation and carboesterification of unsaturated bicycle carboxylic acids to give functional γ-alkynyl lactone derivatives (Scheme 2, b). This approach is another utilization of alkyl or aryl bromoalkynes for the formation of lactone rings under palladium catalysis. As such, bicycle alkynyl lactones may be readily converted into alkynyl hydrins, γ-oxocarboxylic acids, and epoxides.[9] Furthermore, we extended this methodology to other internal electron-deficient alkynes and successfully obtained the corresponding chloropalladation/carboesterification products in good yields.

Results and Discussion

At the onset, through the screening of a variety of conditions, we found that several palladium salts could effect the alkynylative lactonization of phenylethynyl bromide (**1a**) with *endo*-norborn-5-ene-2-carboxylic acid (**2a**, Table 1). In experiments to optimize the reaction, we found that the solvent played a very important role in the process (Table 1, entries 1–3). The best results were obtained with a catalytic amount of $Pd(OAc)_2$ in CH_3CN. Under these conditions, conversion was complete within 8 h at 50 °C without the addition of base or ligand (Table 1, entry 3). The alkynylative lactonization of **2a** with **1a** under $Pd(PPh_3)_4$ catalysis led to low conversion and the starting material was recovered (Table 1, entry 5). The use of $Pd_2(dba)_3$ as the catalyst gave good results (Table 1, entry 6). The addition of a base such as K_2CO_3 did not disturb the reaction (Table 1, entry 7). We next focused on PPh_3 and 1,10-phenanthroline (phen) as ligands, and both hampered the oxyalkynylation process (Table 1, entries 8 and 9). Notably, the reaction was sluggish when CuI was employed instead of a palladium salt (Table 1, entry 10). The reaction did not occur without a palladium catalyst (Table 1, entry 11).

Table 1. Optimization of the reaction conditions.[a]



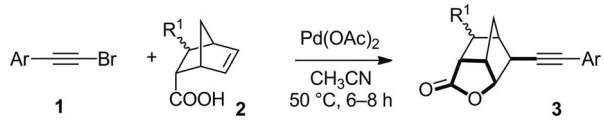
1a 2a 3a

Entry	Catalyst	Solvent	Additive	Yield [%][b]
1	$Pd(OAc)_2$	DMSO	–	35
2	$Pd(OAc)_2$	NEt_3	–	–
3	$Pd(OAc)_2$	CH_3CN	–	93
4	$PdCl_2$	CH_3CN	–	83
5	$Pd(PPh_3)_4$	CH_3CN	–	42
6	$Pd_2(dba)_3$	CH_3CN	–	91
7	$Pd(OAc)_2$	CH_3CN	K_2CO_3	85
8	$Pd(OAc)_2$	CH_3CN	PPh_3	45
9	$Pd(OAc)_2$	CH_3CN	phen	28
10[c]	CuI	CH_3CN	–	–
11[d]	–	CH_3CN	–	–

[a] Reaction conditions: phenylethynyl bromide (1.0 mmol), norbornene (1.5 mmol), catalyst (5 mol-%), and additive (10 mol-%) in solvent (3 mL) at 50 °C for 8 h. [b] Isolated yield. [c] 1,4-Diphenylbuta-1,3-diyne was obtained as the major product. [d] Starting material was recovered.

Using the $Pd(OAc)_2$-catalyzed system (Table 1, entry 3), we examined the generality of the synthesis of substituted fused polycyclic γ-lactone compounds. Varying the aryl substituent of bromoalkynes **2** (Table 2) showed that substrates bearing electron-donating (Table 2, **3b**–**g**) and electron-withdrawing groups (Table 2, **3h**–**l**) were well tolerated. Notably, the C–Br bond remained intact when a bromine substituent was introduced on the aryl ring, and therefore the product may undergo additional functionalization at the C–Br bond (Table 2, **3k** and **3p**). Next, the effects of the unsaturated carboxylic acid moiety in the synthesis of γ-alkynyl lactones were examined. The reaction of 3-(methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid under the standard reaction conditions afforded the corresponding γ-alkynyl lactones in good yields (Table 2, **3n**–**p**). In addition to aryl bromoalkynes, aliphatic bromoalkynes were also found to be suitable substrates for the alkynylative lactonization reaction (Scheme 3). When 2-(6-bromohex-5-ynyl)isoindoline-1,3-dione, 1-(2-bromoethynyl)cyclohex-1-ene, 1-bromooct-1-yne, and 1-(3-bromoprop-2-ynyl)benzene were employed, the desired products were formed and isolated in excellent yields (Scheme 3, **3r**–**u**).

Table 2. Scope of the alkynylative lactonization reaction.[a]

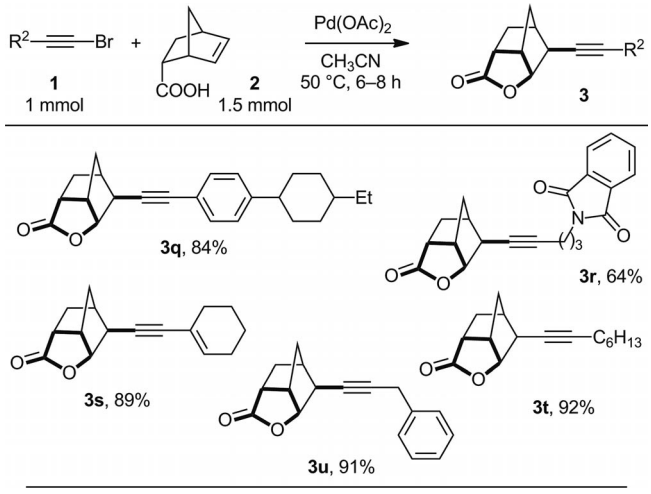


1 2 3

Entry	Ar	R^1 (**2**)	Product	Yield [%][b]
1	C_6H_5	H (**2a**)	**3a**	93
2	4-MeC_6H_4	H (**2a**)	**3b**	95
3	3-MeC_6H_4	H (**2a**)	**3c**	92
4	2,4-$Me_2C_6H_3$	H (**2a**)	**3d**	83
5	4-EtC_6H_4	H (**2a**)	**3e**	87
6	4-*t*BuC_6H_4	H (**2a**)	**3f**	95
7	4-$EtOC_6H_4$	H (**2a**)	**3g**	90
8	2-ClC_6H_4	H (**2a**)	**3h**	83
9	3-ClC_6H_4	H (**2a**)	**3i**	87
10	4-ClC_6H_4	H (**2a**)	**3j**	88
11	4-BrC_6H_4	H (**2a**)	**3k**	87
12	4-FC_6H_4	H (**2a**)	**3l**	86
13	4-PhC_6H_4	H (**2a**)	**3m**	92
14	4-EtC_6H_4	COOMe (**2b**)	**3n**	85
15	2-ClC_6H_4	COOMe (**2b**)	**3o**	81
16	4-BrC_6H_4	COOMe (**2b**)	**3p**	83

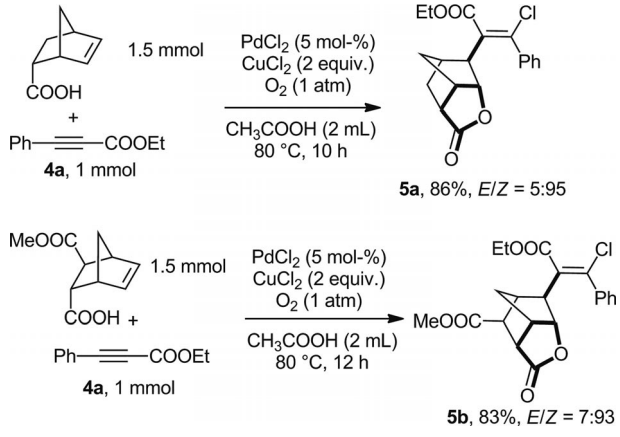
[a] Reaction conditions: $Pd(OAc)_2$ (5 mol-%), norbornene (1.5 mmol), bromoalkyne (1.0 mmol), and CH_3CN (3 mL) at 50 °C for 6–8 h. [b] Isolated yield.

The above studies dealt only with bromoalkynes as the reactive point in the substrates. To extend the substrate scope, we used other electronic-deficient compounds, such as ethyl 3-phenylpropiolate, to investigate the possibility of this transformation (Scheme 4). The reaction of *endo*-norborn-5-ene-2-carboxylic acid with ethyl 3-phenylpropiolate afforded chloropalladation/carboesterification product **5a** with high *Z*/*E* selectivity. In addition, 3-(methoxycarbonyl)-

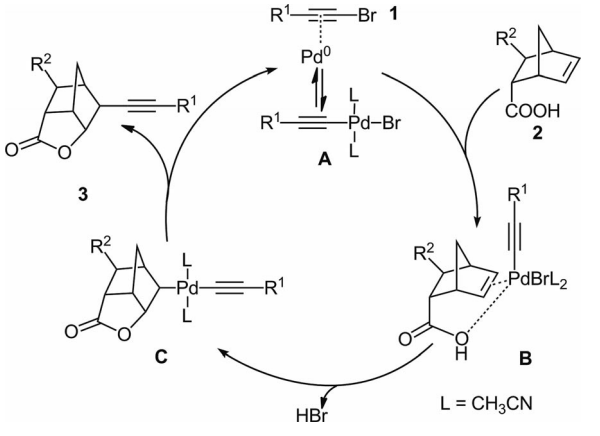


Scheme 3. Pd-catalyzed oxyalkynylation of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid with bromoalkynes.

bicyclo[2.2.1]hept-5-ene-2-carboxylic acid was equally adaptable to the applied reaction conditions and formed corresponding product **5b** in good yield.



Scheme 4. Synthesis of γ-chloroalkenyllactone products.



Scheme 5. Proposed mechanism for the alkynylative lactonization process.

The basic mechanistic features of the alkynylative lactonization reaction are reasonably well established and are shown in Scheme 5.[6,8] Bromoalkyne **1** first undergoes oxidative addition with the low-valent palladium to give alkynyl palladium(II) intermediate **A**. Intermediate **A** coordinates to norbornene **2** to generate intermediate **B**, which is followed by *trans* oxypalladation to give alkynyl alkyl palladium intermediate **C** with well-defined stereochemistry. Subsequent reductive elimination of **C** generates γ-alkynyl lactone product **3** and the active catalyst species.

Conclusions

In conclusion, we have developed the Pd-catalyzed alkynylative lactonization of unsaturated bicyclic carboxylic acids by using common bromoalkynes as substrates. This protocol is compatible with a large variety of bromoalkynes, and fused polycyclic γ-alkynyl lactones and γ-chloroalkenyl lactones were obtained in good yields. Further synthetic application of these fused polycyclic γ-alkynyl lactones and direct alkynylative lactonization of straight-chain unsaturated carboxylic acids is ongoing. The results will be reported in due course.

Experimental Section

Typical Procedure for the Reaction of Bromoalkynes with Unsaturated Bicyclic Carboxylic Acids: $Pd(OAc)_2$, (12 mg, 0.05 mmol), CH_3CN (3 mL), *endo*-norborn-5-ene-2-carboxylic acid (208 mg, 1.5 mmol), and phenylethynyl bromide (180 mg, 1.0 mmol) were added successively to a Schlenk tube. After stirring for 8 h at 50 °C, the solution was filtered though a small amount of silica gel. The residue was purified by silica gel preparative TLC (*n*-hexane/ethyl acetate = 10:1), which furnished **3a** (221 mg, 93%) as a pale-yellow oil.

Supporting Information (see footnote on the first page of this article): Full experimental procedures, characterization data, ^1H NMR and ^{13}C NMR spectra, MS data, and IR spectra.

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