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Palladacycle-Catalyzed Reaction of Bicyclic Alkenes with Terminal Ynones: Regiospecific Synthesis of Polysubstituted Furans

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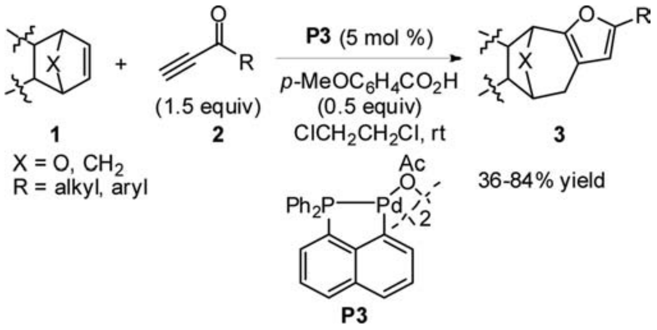
ABSTRACT



A new synthetic strategy to access polysubstituted furans regiospecifically has been developed using simple bicyclic alkenes and terminal ynones as starting materials with palladacycles as unique active catalysts. A rational mechanism has also been proposed. This reaction features mild reaction conditions, easily available starting materials and palladacycle catalysts, a wide substrate scope, and high regiospecificity.

The furan ring as a key structural unit has been found in a variety of natural products and important pharmaceuticals.[1] Polysubstituted furans have also served as versatile building blocks in organic synthesis. A variety of inter- and intramolecular strategies have been developed to synthesize furan rings.[2] Among them, alkyne- or allene-containing derivatives with other functional groups are the most used starting materials in the metal-catalyzed furan synthesis.[2,3] However, their preparation requires multistep syntheses and/or possesses troublesome operations. Development of new and efficient synthetic protocols of furans using readily available and cheap chemicals as reactants is a great challenge. On the other hand, palladacycles are

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easily available organometallics with extra stability toward air and moisture, versatile frameworks, and high catalytic activity and represent an important class of catalysts in organic synthesis.[4] Many advantages have been shown by using palladacycles as catalysts, and high turnover numbers have been achieved. Mechanistic studies showed, however, that they served as catalyst precursors very often, producing nanoparticles as the real catalyst. Only a few reports have appeared to date that used palladacycles as transition metal catalysts.[5,6] Exploration of the applications of palladacycles as real transition metal catalysts, especially in C−C bond formation, is still in high demand. As part of a program aimed at developing palladacycles as real transition-metal catalysts, we have studied the reaction of oxabicyclic alkenes with different reagents by using palladacycles as catalysts.[6] In this communication, we report the reaction of bicyclic alkenes with terminal ynones[7,8] to afford trisubstituted furans regiospecifically, in which a palladacycle serves as a unique and efficient catalyst. Mechanistic investigations to rationalize the experimental observations are also demonstrated.

We observed the formation of the furan ring in the reaction of 7-oxabenzonorbornadiene (**1a**) with a terminal ynone (**2a**) in the presence of palladacycle **P1** as a catalyst when we studied the reaction of alkynes with oxabicyclic alkenes[6b,c] (entry 1, Table 1). Control experiments revealed that the presence of a palladacycle is crucial because no reaction took place or very low yields (< 10%) were achieved if some common palladium species, such as $Pd(OAc)_2$, $Pd(OAc)_2/PPh_3$, $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$, and $Pd(OAc)_2$/diphenylphosphine oxide,[8f] were used as catalysts.

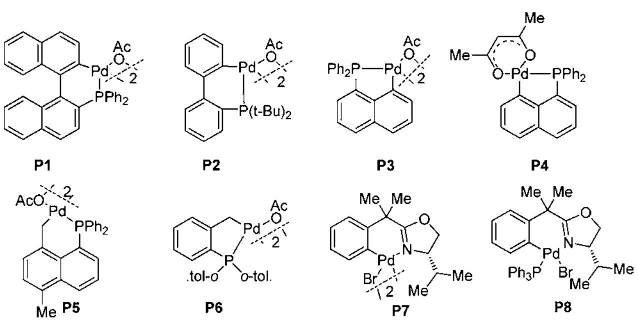

Figure 1. Palladacycles with different scaffolds and donor atoms.

To have a better understanding of the reaction, the influence of the parameters on the reaction was investigated. It showed that both the structure scaffold and donor atom of the palladacycles have a great impact on the reaction (Figure 1, Table 1). The palladacycle **P2**,[9] an analogue of palladacycle **P1**,[10] gave furan **3a** in 10% yield, while a 62% yield of **3a** was provided using palladacycle **P1** (entry 2 vs 1). The palladacycle **P3** based on a naphthalene scaffold gave a slightly higher yield than **P1** (entry 3 vs 1). The change of OAc in palladacycle **P3**[11] to acac in palladacycle **P4**[11] resulted in a similar yield of furan **3a** (entry 4 vs 3), while the use of palladacycles **P5** and **P6**[12] containing *sp*3 carbon−palladium bonds provided furan **3a** in 34% yield (entries 5 and 6). Palladacycles **P7**[10] and **P8**[10] with a nitrogen donor atom showed low catalytic activity in the reaction, with a trace amount of product **3a** being observed (entries 7 and 8). With palladacycle **P3** as the catalyst, the effect of temperature on the reaction was evaluated. Raising the temperature did not change the yield of furan **3a** (entry 9 vs 3). In contrast, an increase of the yield of furan **3a** to 76% was observed by lowering the temperature to rt (entry 10 vs 3). Lowering the temperature to 0 °C did not improve the yield further (entry 11).

It was observed that the reaction gave furan **3a** only in 54% yield in the absence of acid using palladacycle **P3** as the catalyst at rt. The addition of bases such as Et_3N and Cs_2CO_3 made the reaction sluggish, providing a trace amount of furan **3a**, although ynone **2a** was consumed completely. These results indicate the importance of the presence of acid. Thus, the effect of acid as additives on the reaction was investigated (Table 2). Stronger acids such as CF_3CO_2H and 2,4,6-$F_3C_6H_2CO_2H$ have a deleterious impact on the reaction, with only a trace amount of furan **3a** being observed (entries 1 and 2), while the other

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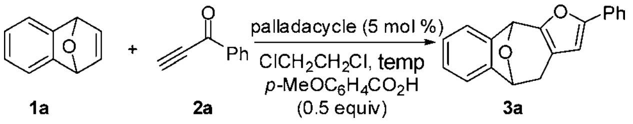
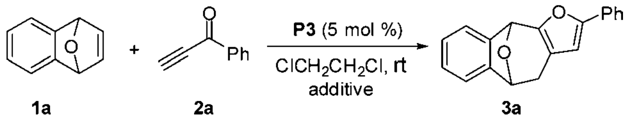
Table 1. Screening of Palladacycles and Temperature for the Reaction of Oxabicyclic Alkene **1a** with Terminal Ynone **2a**[a]



entry	palladacycle	temp (°C)	**3a** (%)[b]
1	**P1**	50	62
2	**P2**	50	10[c]
3	**P3**	50	64
4	**P4**	50	61
5	**P5**	50	34
6	**P6**	50	34
7	**P7**	50	trace[c]
8	**P8**	50	trace[c]
9	**P3**	80	66
10	**P3**	rt	76
11	**P3**	0	71

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $ClCH_2CH_2Cl$ (3.0 mL). [b] Isolated yields. [c] ^1H NMR yields using mesitylene as internal standard.

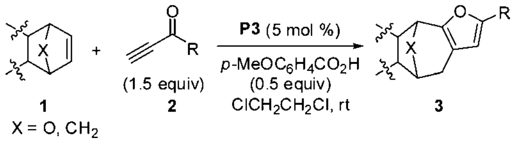
Table 2. Evaluation of Acid Additive for the Reaction of Oxabicyclic Alkene **1a** with Terminal Ynone **2a**[a]

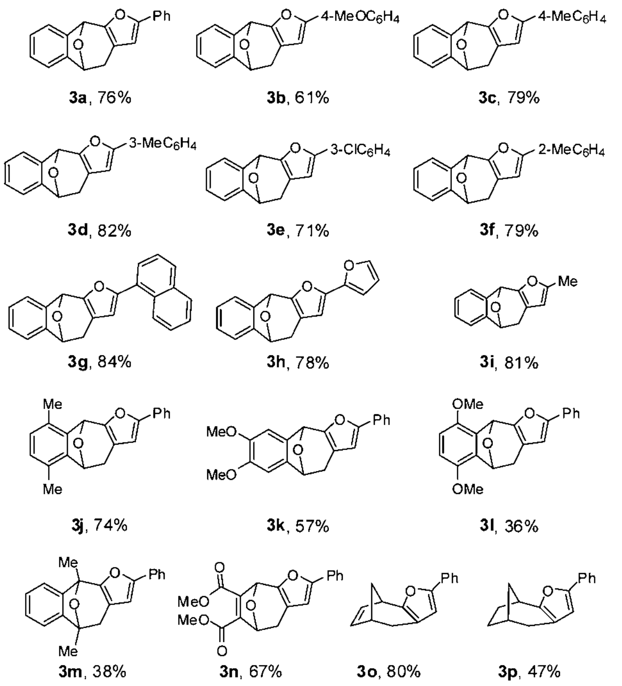


entry	additive (equiv)	solvent	**3a**(%)[b]
1	CF_3CO_2H (0.5)	$ClCH_2CH_2Cl$	trace[c]
2	2,4,6-$F_3C_6H_2CO_2H$ (0.5)	$ClCH_2CH_2Cl$	trace[c]
3	AcOH (0.5)	$ClCH_2CH_2Cl$	52
4	$PhCO_2H$ (0.5)	$ClCH_2CH_2Cl$	46
5	m-$NO_2C_6H_4CO_2H$ (0.5)	$ClCH_2CH_2Cl$	52
6	p-$MeOC_6H_4CO_2H$ (0.5)	$ClCH_2CH_2Cl$	76
7	–	$ClCH_2CH_2Cl$	54
8	p-$MeOC_6H_4CO_2H$ (1.0)	$ClCH_2CH_2Cl$	74
9	p-$MeOC_6H_4CO_2H$ (0.25)	$ClCH_2CH_2Cl$	69
10	p-$MeOC_6H_4CO_2H$ (0.5)	CH_2Cl_2	64
11	p-$MeOC_6H_4CO_2H$ (0.5)	$CHCl_3$	67
12	p-$MeOC_6H_4CO_2H$ (0.5)	toluene	46
13	p-$MeOC_6H_4CO_2H$ (0.5)	THF	54
14	p-$MeOC_6H_4CO_2H$ (0.5)	EA	63

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $ClCH_2CH_2Cl$ (3.0 mL). [b] Isolated yields. [c] ^1H NMR yields using mesitylene as internal standard.

Table 3. Substrate Scope for Palladacycle **P3**-Catalyzed Reaction of Bicyclic Alkenes **1** with Terminal Ynones **2**[a]



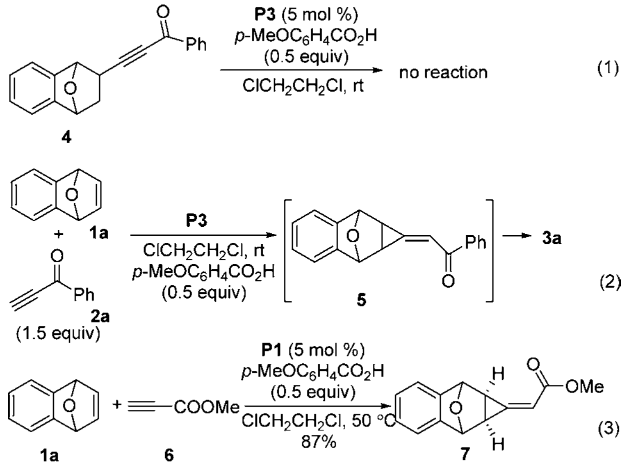


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $ClCH_2CH_2Cl$ (3.0 mL); isolated yields.

acids, for example, AcOH and $PhCO_2H$, did not improve the yield of the reaction compared to that using p-$MeOC_6H_4CO_2H$ (entries 3–5 vs entry 6). The impact of the loading of p-$MeOC_6H_4CO_2H$ was also studied. Increasing or decreasing the amount of p-$MeOC_6H_4CO_2H$ exerted a limited influence on the yield of furan **3a** (entries 7 and 8 vs entry 6). The investigation of the impact of solvent on the reaction revealed that the reaction in CH_2Cl_2 and $CHCl_3$ gave slightly lower yields (entries 9 and 10). Using toluene, THF, or ethyl acetate (EA) as the reaction media also afforded **3a** in low yields (entries 11–13).

Under the optimized reaction conditions, the scope of the substrates of this new type of furan synthesis was examined, and the results are compiled in Table 3. In general, treatment of all bicyclic alkenes **1** and terminal ynones **2** under the effect of palladacycle **P3** regiospecifically furnished the corresponding 2,3,4-trisubstituted furans **3** in good yields. The reaction tolerated ynones **2** with various substituents located at the 2-, 3- or 4-positions of the aryl ring, affording the corresponding furans **3b**–**3f** in high yield. The use of furanyl substituted ynone led to a 2,2′-bifuran **3h** in 78% yield. An ynone with an alkyl substituent was also tolerated, providing corresponding furan **3i** in 81% yield. It has also been revealed that not only oxabicyclic alkenes but also norbornene, norbornadiene, and a furan–acetylenedicarboxylate adduct are suitable substrates to produce substituted furans **3n**–**p**. It was found that the reaction of oxabicyclic alkenes with a substituent on the aryl ring also proceeded smoothly to give the substituted furans, though the yields were slightly lower for **3k**, **3l**, and **3m**. No reactions occurred when

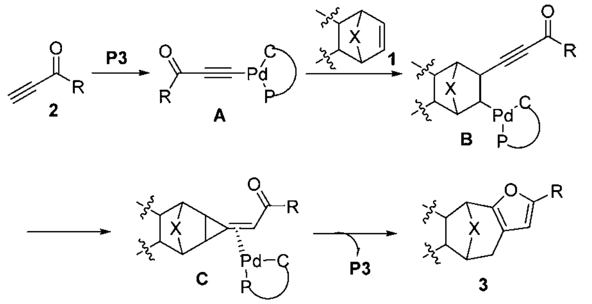
Scheme 1. Experiments for Identifying the Reaction Intermediate



2,3-dihydrofuran, cyclopentene, and cyclohex-2-enone were used. So we thought that the bridged ring was important for this reaction, which could be the result of a release of strain when the reaction occurred.

To gain a greater understanding of the mechanism of this unusual furan formation reaction, some experiments were carried out (Scheme 1). When **4** was treated with palladacycle **P3**, no furan product was found (eq 1). Some clues were provided by monitoring the course of the reaction of oxabicyclic alkene **1a** and ynone **2a** with ^{1}H and ^{13}C NMR spectroscopy (eq 2). When the reaction ran for 5 min, ^{1}H NMR showed two new peaks at δ 2.00 (d, J = 7.2 Hz), 2.10 (d, J = 7.6 Hz). These two peaks could be assigned as two protons on the cyclopropane ring of the intermediate **5** by comparison to that of **7** (δ 1.98 d, J = 7.2 Hz and 2.23 d, J = 7.6 Hz) (eq 3). When the reaction was allowed to proceed for 40 min, these two peaks disappeared, and the peaks of protons of furan **3a** appeared. ^{13}C NMR gave same information for the formation of a cyclopropane ring. When the reaction proceeded for 5 min, two peaks appeared at δ 26.3, 29.4, which have similar chemical shifts with the two carbons of the cyclopropane ring of **7**. These two peaks disappeared after 40 min. These NMR experiments offered evidence for the reaction pathway to furans via alkylidenecyclopropane **5** as the reaction intermediate.[8f,13]

Scheme 2. Proposed Reaction Mechanism of Furan Formation



Based on the above experiments and literature,[5d] we propose a possible reaction mechanism for furan formation via the reaction of bicyclic alkene **1** with terminal ynone **2** (Scheme 2). The terminal ynone **2** reacts with the monomer of palladacycle **P3** to give an alkynylpalladium(II) **A**. Carbopalladation of intermediate **A** to bicyclic alkene **1** affords a species **B**, which undergoes an intramolecular addition and a subsequent tautomerization to furnish an alkylidenecyclopropane **C** coordinated with palladacycle **P3**. Rearrangement of **C** affords furan **3** accompanying the release of the palladacycle **P3**.[13]

In conclusion, we have developed a new synthetic strategy to access polysubstituted furans regiospecifically using bicyclic alkenes and terminal ynones in an intermolecular way. The unique catalytic activity of palladacycles has been demonstrated. A rational mechanism has also been proposed. This reaction features mild reaction conditions, easily available starting materials and palladacycle catalysts, a wide substrate scope, and high regiospecificity. Further studies on the extension of the method as well as the applications of palladacycles as catalysts in organic synthesis are underway in our lab.

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Supporting Information Available. Experimental procedures, the synthesis of palladacycle **P3**–**P5**, and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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