Palladacycle-Catalyzed Cascade Reaction of Bicyclic Alkenes with Alkynyl Imines: Synthesis of Polycyclic 5H-Benzo[b]azepines

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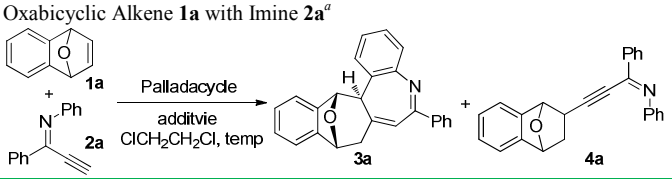
A new methodology to prepare the unique six-seven membered [4,5,0] heterocyclic ring system, an important structure in natural products and medicine chemistry, has been developed via a palladacycle-catalyzed cascade reaction of bicyclic alkenes and alkynyl imines. The unique catalytic activity of palladacycle as well as C-H activation under palladacycle–catalysis, a new catalytic pattern of palladacycle, has been revealed.

Palladacycle as one of the palladium species features easier availability, extra stability toward air and moisture, versatile frameworks as well as high catalytic activity. Many applications have been found in a wide range of fields, such as biological chemistry, material science, organic synthesis, and ligand resolution.[1] More importantly, they have been used as catalyst in carbon-carbon and carbon-hetero atom bond formation[2] as well as asymmetric reactions.[3] Moreover, many studies have revealed that palladacycle have been recognized as reaction intermediate presented in many C-H functionalization reactions.[4] In many cases palladacycles are considered as pre-catalyst and Lewis acid in the reactions, nevertheless, recent achievements show the possibility as real catalyst.[5] However, only a limited type of the reactions could be catalyzed by palladacycles, and the understanding regarding the influence of palladacycles on the reaction is also limited. To have more knowledge of palladacycle in catalysis and to explore more reactions using palladacycle is highly demanded. During the studies on the applications of palladacycles in organic synthesis,[6] we developed a reaction of in situ prepared organozinc halides with oxabicyclic alkenes in the presence of palladacycle as catalyst and revealed that in that reaction palladacycle performed as the real catalyst.[6a] We also realized asymmetric synthesis using chiral palladacycle as catalysis[6b,c] as well as switched the chemoselectivity of the reaction under palladacycle-catalysis and provided plausible explanation why different palladacycle led to different reaction selectivity.[6e] Further studies revealed that palladacycle could also serve as catalyst in C-H activation reaction. In this paper, we would disclose our preliminary results of palladacycle-catalyzed domino reaction of alkynyl imines with oxabicyclic alkenes to afford benzo[*b*]azepines via addition-cyclization-C-H activation sequences.

Recently, we reported a facile and regioselective synthesis of polysubstituted furans via the palladacycle-catalyzed reaction of bicyclic alkenes with terminal ynones.[6d] Based upon these results, alkynyl imine was adopted as a reactant to see if pyrrole was afforded. The reaction of bicyclic alkene **1a** and alkynyl imine **2a** proceeded smoothly in the presence of palladacycle **P1** (entry 1, table 1). However, expected product pyrrole was not obtained, instead, polycyclic product **3a** bearing a nitrogen-containing seven membered ring system, an important subunit in natural products and medicines,[7] was afforded.

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



entry	palladacycle (mol %)	additive (equiv)	temp (°C)	**3a** (%)[b]	**4a** (%)[b]
1	**P1** (10)	*p*-$BrC_6H_4CO_2H$ (0.5)	rt	20	17
2	**P2** (10)	*p*-$BrC_6H_4CO_2H$ (0.5)	rt	12	29
3	**P3** (10)	*p*-$BrC_6H_4CO_2H$ (0.5)	rt	72	--
4	**P4** (10)	*p*-$BrC_6H_4CO_2H$ (0.5)	rt	70	--
5	**P5** (10)	*p*-$BrC_6H_4CO_2H$ (0.5)	rt	trace	93

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6	**P6** (10)	*p*-$BrC_6H_4CO_2H$ (0.5)	rt	trace	--
7	**P3** (5)	*p*-$BrC_6H_4CO_2H$ (0.5)	rt	54	--
8	**P3** (10)	*p*-$BrC_6H_4CO_2H$ (0.5)	0	37	--
9	**P3** (10)	*p*-$BrC_6H_4CO_2H$ (0.5)	50	66	--
10	**P3** (10)	--	rt	51	--
11	**P3** (10)	Et_3N (0.5)	rt	--	--
12	**P3** (10)	Cs_2CO_3 (0.5)	rt	--	--

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.1 mmol), $ClCH_2CH_2Cl$ (2.0 mL). [b]Isolated yield.

This unusual result intrigued us to clarify what affected the generation of compound **3a** (Table 1). Firstly, the effect of palladium catalysts on the reaction was investigated. The common palladium catalysts, such as $Pd(OAc)_2$, $Pd(PPh_3)Cl_2$, $Pd(OAc)_2/PPh_3$ and $Pd_2(dba)_3$, did not work in this reaction (not shown in table), implying the unique catalytic activity of palladacycle. The further studies revealed that the different structure of palladacycles, including the coordination atoms, the framework as well as hybridization of carbon connected with Pd, has great impact on the reaction (Figure 1). Palladacycles **P1-5** with phosphine donor atom is proved to be suitable catalyst for the transformation (entries 1-5), while that with nitrogen as coordination atom **P6** could not catalyze the reaction (entry 6). Importantly, palladacycles **P3** and **P4** with sp^2 C-Pd bond as catalysts led to the desired product **3a** in 72% and 70% yield respectively (entries 3 and 4), sharply in contrast, palladacycle **P5** containing sp^3 C-Pd bond afforded the addition product **4a** in 93% yield (entry 5), which is in accordance with our findings before.[6e] It is rather surprised that much bigger different results were provided using palladacycles **P1** and **P2** or **P3** and **P4** as catalyst (entries 1 and 2 *vs* entries 3 and 4), though all of these four palladacycles have sp^2 C-Pd bond with phosphorus as coordination atom. It can be seen that the differences between palladacycles **P1**, **P2** and **P3**, **P4** are that **P3** and **P4** should have planar structures while **P1** and **P2** should be non-planar, also the bond length of Pd-P in **P1** and **P2** and in **P3** and **P4** should not be same. These results reflect some worthwhile to be studied characteristics of palladacycles as the catalyst. The effect of acid additive on the reaction was evaluated, which revealed the importance of the presence of acid as additives in the reaction (entry 3 *vs* entry 10), meanwhile, the addition of base such as Cs_2CO_3 or Et_3N suppressed the reaction completely (entries 11 and 12). It was found that *p*-BrC_6H_4COOH is the best choice (for evaluation of other acid additive, see SI). The influence of temperature on the reaction was investigated with palladacycle **P3** as the catalyst. Raising or lowering the reaction temperature did not improve the yield of product **3a** (entries 8 and 9). The reaction is sensitive to the loading of catalyst because the use of 5 mol% of **P3** resulted in the decreased of the yield (entries 7 *vs* entry 3).

We also investigated the influence of solvents (not shown in table). The reaction did not proceeded in polar solvents such as *N*,*N*-dimethylformamide and dimethyl sulfoxide while that in non-polar solvents like dichloromethane and toluene gave the target compound **3a** in 53% yield and 63% yield respectively, which was lower than that of using 1,2-dichloroethane as solvent. When the ratio of **1a** to **2a** was reduced from 2/1 to 1.3/1, the product **3a** was still obtained in 72% yield.

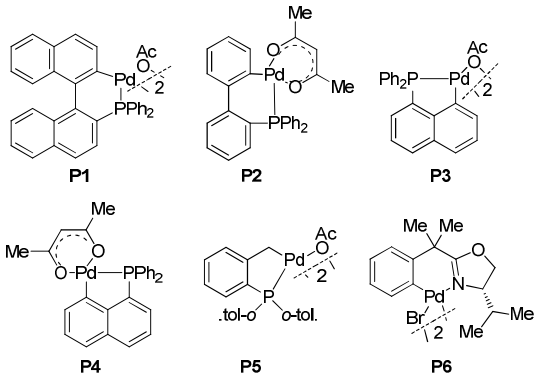
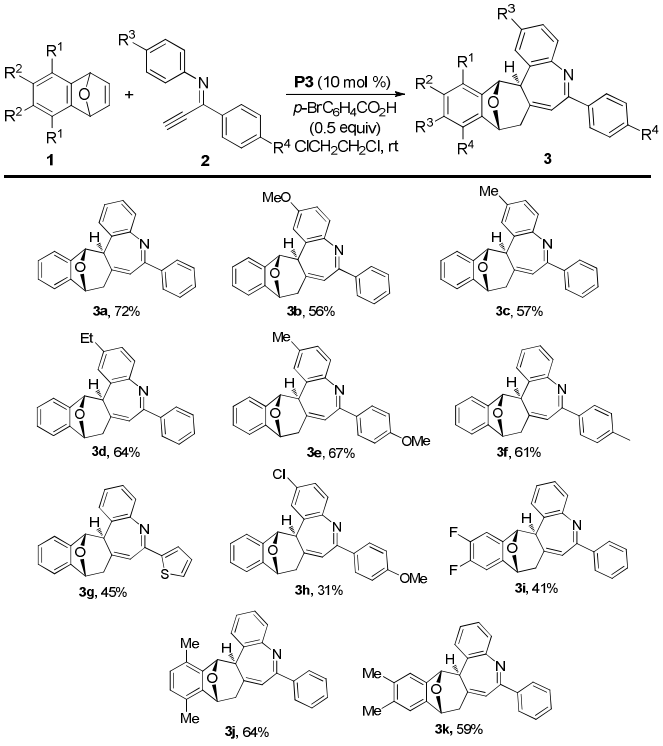


Figure 1. Palladacycles with Different Scaffolds and Donor Atoms

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



[a]Reaction conditions: **1** (0.26 mmol), **2** (0.2 mmol), $ClCH_2CH_2Cl$ (2.0 mL); Isolated yields.

The substrate scope of bicyclic alkenes **1** and imine **2** was explored under the optimized reaction conditions, and the results are compiled in Table 2. It can be seen that many oxabicyclic alkenes **1** and alkynyl imines **2** are suitable substrates for the reaction, affording corresponding *5H*-benzo[*b*]azepines **3** in moderate to good yields.

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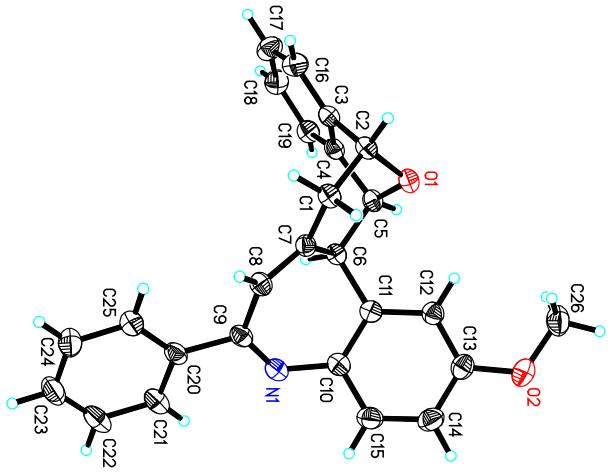
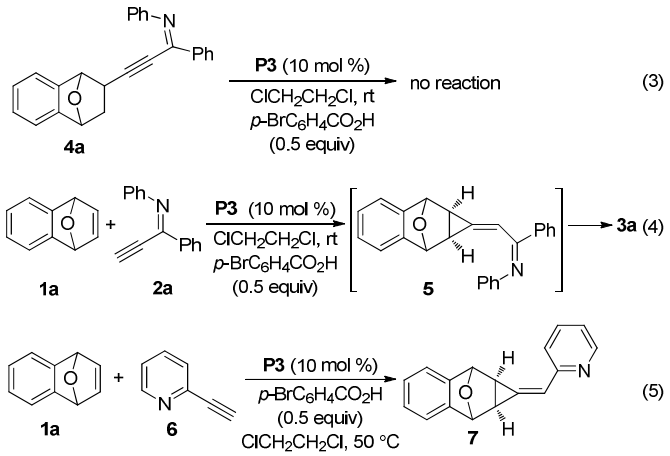
The alkynyl imines **2** with electron-donating substituents located at the 4-positions of the aryl ring are tolerated, providing the corresponding products **3b-3f** in moderate yield. When R^3 was electron-withdrawing group, the yield of corresponding product **3h** became low (31%). If R^3 was a stronger electron-withdrawing group such as CF_3, the reaction was fully retarded with starting reactant being recovered (not shown in table). A thienyl substituted imine is suitable reactant, providing corresponding *5H*-benzo[*b*]azepine **3g** in 45% yield. Substituent on the oxabicyclic alkenes **1** affected reaction to some extent. Oxabicyclic alkenes **1** containing electron-donating groups worked well to give the product **3j** and **3k** in good yield. The incorporation of electron-withdrawing groups into oxabicyclic alkene **1** led to an inferior result (**3i**). Several other bicyclic alkenes, for example, norbornene, 2,5-norbornadiene, and dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate were tested, but corresponding target compounds were not detected by GC-MS. The structure of this unique polycyclic ring system was further determined by X-ray analysis of single crystal of compound **3b**

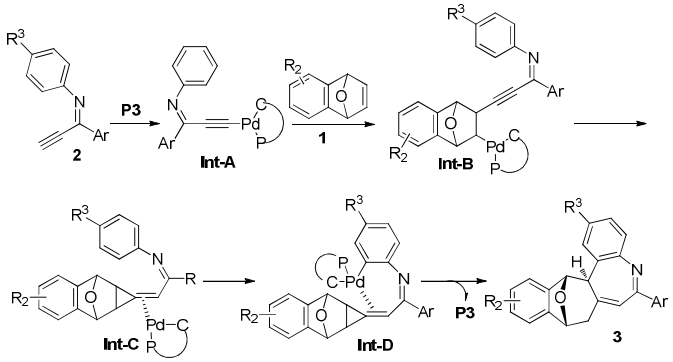




Scheme 1. Experiments of Identifying the Reaction Intermediate **5**

To understand the reaction mechanism and the formation of six-seven membered rings [4,5,0] heterobicyclic system, some experiments were carried out. Initially, addition product **4a** was subjected to the reaction condition of table 2, however, no reaction occurred, which suggested that it was not the reaction intermediate (eq 3). We have found that an alkylidenecyclopropane serves as a possible intermediate in the furan formation reaction.[6d] Thus, we monitored the progress of the reaction of oxabicyclic alkene **1a** and imine **2a** via ^{1}H- and ^{13}C NMR spectroscopies (eq. 4). Two new peaks at δ 1.52 (dd, J = 0.4, 7.2 Hz) and 1.81 (d, J = 7.2 Hz) appeared in ^{1}H NMR when the reaction ran for 6 minutes. These two peaks could be assigned as two protons on the cyclopropane ring of the intermediate **5** by comparison to that of compound **7** (δ 2.00, d, J = 7.2 Hz and 2.24, dd, J = 1.2, 7.2 Hz), which was produced in the controlled experiment, the reaction of bicyclic alkene **1a** with alkynyl pyridine **6** (eq 5). These two peaks weakened, and the protons of compound **3a** appeared when the reaction was allowed to proceed for longer time. ^{13}C NMR experiments gave similar information for the formation of an alkylidenecyclopropane. Two peaks appeared at δ 26.7, 28.9 in 6 minutes, which have similar chemical shifts with the two carbon of cyclopropane ring of compound **7**. These NMR experiments indicated the alkylidenecyclopropane **5** should be a reaction intermediate in the formation of compound **3a**.

Based upon the clues we have and literature report,[4,5a,6d] a plausible reaction mechanism for the formation of compound **3** could be proposed (Scheme 2). An alkynylpalladium(II) **Int-A** was generated via the reaction of the imine **2** with palladacycle, which underwent a carbopalladation with bicyclic alkene **1** to give **Int-B**, which proceeds an intramolecular addition and a subsequent protonation to afford an alkylidenecyclopropane **Int-C**. An intramolecular C-H bond activation of **Int-C** furnishes **Int-D**, which is converted to the compound **3** accompanying the release of the palladacycle catalyst. The further experiments are needed to have real reaction mechanism, especially the transformation of intermediate **C** to the final product **3**.



Scheme 2. Proposed Reaction Mechanism

In conclusion, we have developed a new methodology to prepare the six-seven membered [4,5,0] heterocyclic ring system, an important structure in natural products and medicinal chemistry, via the cascade reaction of bicyclic alkenes and alkynyl imines. The possible reaction mechanism was proposed. Also the unique

catalytic activity of palladacycle as well as C-H activation under palladacycle–catalysis, a new catalytic pattern of palladacycle, has been revealed. Further studies on the understanding the characters of palladacycle as the real catalyst as well as their applications in organic synthesis are onging in our lab.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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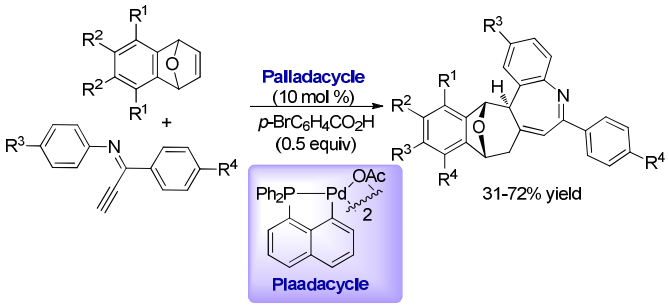
Graphic abstract



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