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Intramolecular Pauson–Khand reaction catalyzed by oxime-derived palladacycles

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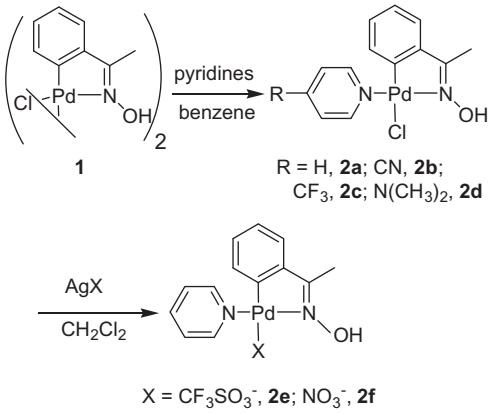
ABSTRACT

Oxime-derived palladacycles were successfully applied as a novel class of catalysts in the intramolecular Pauson–Khand reactions. Allylpropargyl ethers and allylpropargyl amines can be efficiently converted to the cyclopentenone products with good to excellent yields.

The construction of complex polycyclic systems using transition metal-catalyzed annulation reactions provides an effective method for the synthesis of many complex molecules. A very attractive example is the Pauson–Khand reaction (PKR),[1,2] a formal [2+2+1] cycloaddition of an alkene, an alkyne, and carbon monoxide leading to cyclopentenones which are useful synthetic intermediates in natural product synthesis.[3] Catalytic and catalytic asymmetric PKR using Co,[4] Ti,[5] Ni,[6] Ru,[7] Rh,[8] Ir[9], and Pd[10] complexes have been reported in the past two decades. As a class of intensively investigated organometallic compounds of great importance, palladacycles have been successfully exploited in catalytic reactions ranging from classical hydrogenation to asymmetric aldol-type condensations.[11] Due to their important contributions in the catalytic cross-coupling reactions with palladacycle compounds, Heck, Suzuki, and Negishi have been awarded the 2010 Nobel Prize in chemistry. Furthermore, the structures of palladacycles can be easily modified for their high catalytic activity and selectivity. However, to the best of our knowledge, palladacycles have not been used in catalytic PKR. Thus, exploring the application of palladacycles to PKR will be of great value.

At the same time, we have realized that palladium(II)–thiourea complexes were successfully applied in PKR by the Yang group.[10] Also some palladacycles were used for the carbonylation reactions.[12] Based on the above considerations and our experience in palladacycle chemistry,[13] we investigated the possibility of using palladacycles as a new type of catalysts in the PKR. We report herein the preliminary results from our work.

Oxime-derived palladacycles are described as being very stable and showing high efficiency in catalytic processes.[14] So we first checked the possibility of using oxime palladacycles **2** (shown in Scheme 1) in PKR. The syntheses of these palladacycles began from oxime-derived chloro-bridged dimer **1**, which was prepared following the literature method reported by Baleizao and Corma.[15] Addition of pyridine or its derivatives to dimer **1** in benzene at room temperature afforded palladacycles **2a–d**. Counter ions exchange by treating **2a** with silver nitrate or silver triflate resulted in palladacycles **2e** and **2f**, respectively. The characterization of these palladacycles has been deposited in Supplementary data.



Scheme 1. Synthesis of palladacycles **2a–f**.

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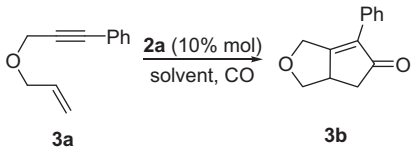
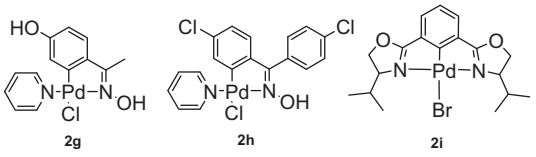


Scheme 2. The intramolecular Pauson–Khand reaction with catalyst **2a**.

Table 1
Optimization of reaction conditions in the palladacycle **2a** catalyzed Pauson–Khand reaction of **3a**[a]

Entry	Solvent	Temp (°C) (oil bath)	pCO[b] (atm)	Time (h)	Yield[c] (%)
1	THF	60	1	48	32
2	THF	100	1	24	50
3	THF	120	1	24	56
4	THF	110	2	24	55
5	THF	110	2	12	75
6	DME	130	2	4	64
7	DME	130	2	10	94
8	DME	130	2	14	85
9	DME	130	2	10	69[d]
10	DME	130	2	10	59[e]
11	Toluene	130	2	2.5	54
12	Toluene	130	2	4	66
13	Toluene	130	2	10	69

[a] Reagents and conditions: enyne **3a** (0.5 mmol) in 10 mL of solvent.
[b] CO pressure in the reaction vessel at room temperature.
[c] Yield of isolated product.
[d] In the presence of 7 mol % **2a**.
[e] In the presence of 5 mol % **2a**.



Scheme 3. Palladacycles **2g–i**.

Table 2
Palladacycles **2a–i** catalyzed Pauson–Khand reactions of **3a**[a]

Entry	Palladacycles	Additives	Yield[b] (%)
1	**2a**	—	75
2	**2b**	—	91
3	**2c**	—	77
4	**2d**	—	30
5	**2g**	—	74
6	**2h**	—	72
7	**2i**	—	N.R.
8	**2e**	—	11
9	**2e**	LiCl (1.0)	57
10	**2f**	—	Traces
11	**2f**	LiCl (1.0)	32
12	**2a**	LiCl (0.5)	48
13	**2a**	LiCl (1.0)	42
14	**2a**	LiCl(5.0)	37
15	**2a**	LiCl (10)	19
16	**2a**	PPh_3 (1)	Trace
17	**1**	—	41
18	**1**	Pyridine	70

[a] Reagent and conditions: THF, 12 h, 110 °C, 2 atom of CO pressure in the reaction vessel at room temperature, 10 mol % palladacycle **2a** was applied.
[b] Yield of isolated product after column chromatography (silica gel, petroleum/EtOAc, 10:1–2:1).

Enyne **3a** was selected as a substrate for the optimization of other reaction conditions (Scheme 2). The reactions were carried out in parallel in ampules sealed under carbon monoxide. The effects of solvents, temperature, pressure of CO, and reaction time were screened, results from which are summarized in Table 1.

The obtained results demonstrate that reaction temperature is an important factor, as the yields of the desired product increase as the reaction temperature was raised (entries 1–4). Among the solvents used, DME seems to lead to the best results (entries 7 and 8). THF is also a good solvent but its lower boiling point translates into a longer reaction time for achieving higher yields. The higher boiling point of toluene is beneficial for reducing reaction time. However the limited solubility of the catalysts in this solvent compromises the outcome of the reaction. The results also demonstrate that higher pressure of CO resulted in higher yields. Thus, extending reaction time improves the yields of product, although the efficiency of a reaction is also dependent on other factors such as solvent, temperature, and pressure of CO.

As a short summary, an optimal conversion to the desired cyclization product **3b** was achieved with a yield of 94% in the presence of 10 mol % palladacycle **2a** in DME at 130 °C (oil bath) and 2 atm of carbon monoxide for 10 h.

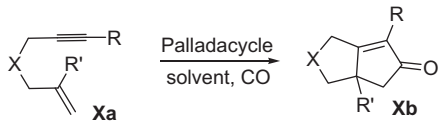
A series of analogous palladacycles **2b–h** and a pincer palladacycle **2i** (Scheme 3), along with the effects of the additives were then tested in the PKR of **3a**. The results are summarized in Table 2. To make a clear comparison of catalytic activities in the presence of different palladacycles and additives, THF, in which substrate **3a** was converted into **3b** in moderate yields was used as solvent for the PK reactions. The results suggested that the structures of the palladacycles played very important roles in catalytic performances. Regarding the effect of coligand, palladacycles containing weakly coordinating co-ligands including 4-cyanopyridine (**2b**) and 4-trifluoromethylpyridine (**2c**) gave good to excellent conversion with the yields of 91% and 77%, respectively, (entries 2 and 3 in Table 2). Meanwhile palladacycle containing strongly coordinating 4-*N*,*N*-dimethylaminopyridine (**2d**) showed a very poor catalytic efficiency with a yield of only 30% (entry 4 in Table 2). The observed effect of co-ligand on the catalytic activity is consistent with their catalytic performance in the transesterification of neutral thiophosphates.[13a] At the same time, the readily available oxime-derived palladacycles **2g** and **2h** also showed good catalytic activities (entrries 5 and 6 in Table 2). However, the pincer palladacycle **2i** showed no catalytic activity for the same reaction (entry 7 in Table 2).

Changing counter ions from chloride to weakly coordinating triflate (**2e**) or nitrate (**2f**) resulted in poor catalytic efficacy, and the

Table 3
Palladacycles catalyzed intramolecular PKR[a,b]

No.	Sub.	Prd.	Yield[c] (%) **2a**
1	**3a**	**3b**	94 (75)
2	**4a**	**4b**	97
3	**5a**	**5b**	86
4	**6a**	**6b**	51
5	**7a**	**7b**	85
6	**8a**	**8b**	92
7	**9a**	**9b**	51
8	**10a**	**10b**	31
9	**11a**	**11b**	50
10	**12a**	**12b**	41

[a] Conditions: DME, 10 h, 130 °C (oil bath), 2 atom CO pressure in the reaction vessel at room temperature, 10 mol % palladacycle.
[b] For the yield in the parenthesis the condition is the same as 'a' except that: THF, 12 h, 110 °C (oil bath).
[c] Yield of isolated product after column chromatography (silica gel, petroleum/EtOAc, 10:1–2:1).



		X
X = O	R = 4-ClC$_6$H$_4$, R' = H:	4
	R = 4-EtOC$_6$H$_4$, R' = H:	5
	R = C$_6$H$_5$, R' = Me:	6
X = NTs	R = C$_6$H$_5$, R' = H:	7
	R = 4-ClC$_6$H$_4$, R' = H:	8
	R = 4-MeOC$_6$H$_4$, R' = H:	9
X = C(COOEt)$_2$	R = C$_6$H$_5$, R' = H:	10
	R = H, R' = H:	11
	R = 4-ClC$_6$H$_4$, R' = H:	12

Scheme 4. The intramolecular Pauson–Khand reactions of various substrates with palladacycle **2a**.

yield dropped to 11% or even 0 (entries 8 and 10 in Table 2). The observed behavior is quite different from that of the catalysis in the degradation of neutral thiophosphates, where palladacycles containing triflate counter anion showed better reactivity.[13a] In contract to the observation made on Pd(II)–tetramethylurea complex catalyzed PKR,[10a] adding LiCl did not facilitate the reaction, but instead reduced the yield of the product (see entries 12–15 in Table 2). Addition of the strongly coordinating PPh_3 poisoned the catalyst (entry 16 in Table 2). However, the presence of chloride in a palladacycle is essential for maintaining the catalytic activity as addition of LiCl to the palladacycles with nitrate or triflate counter ions greatly improved the reaction yields (entries 9 and 11 in Table 2). Palladacycle dimer **1** can also catalyzed PKR. Addition of pyridine to the reaction mixture clearly improved the catalytic activity (entries 17 and 18 in Table 2).

To explore the scope of the palladacycle catalyzed PKR, a broad range of substrates were tested in the presence of **2a**. Along this line, allylpropargyl-ethers **4a**–**6a** (entries 2–4 in Table 3), allylpropargyl-amines **7a**–**9a** (entries 5–7 in Table 3), and allylpropargyl-malonates **10a**–**12a** (entries 8–10 in Table 3) were prepared and examined in different solvents (Scheme 4). The results including that of **3a** at the optimized conditions are listed in Table 3.

At first, three allylpropargyl ethers **4a**–**6a** were investigated. Interestingly, the enyne with electron-withdrawing substituent (chloro-) **4a** gave a higher yield while the enyne with electrondonating substituent (ethoxy-) **5a** afforded a relatively lower yield (entries 3 and 4 in Table 3). The additional methyl group attached to the C=C bond of **6a** reduced the reactivity significantly in comparison to the analogous substrate **3a**, thus only low yields were obtained with the palladacycles tested (entry 4 in Table 3). Such results are consistent with the reported PKR catalyzed by other catalysts.[9d,16] Among allylpropargylamines **7a**–**9a**, compounds **8a**, with an alkyne moiety bearing electron-withdrawing group (4-chloro, entry 6 in Table 3), gave an excellent yield (92%), while **9a**, with an alkyne moiety bearing an electron-rich group (4-methoxyl, entry 7 in Table 3), afforded a lower yield (51%). Whereas with allylpropargyl malonates **10a**–**12a**, it was found that these substrates were not as reactive, for which only lower yields (31–50%) were obtained.

For allylpropargyl-amines and allylpropargyl malonates, the results of the palladacycles are in good agreement with those of thiourea–Pd complex. Apparently it can be seen that the catalytic activity of the oxime derived palladacycles are better than Pd(II)–thiourea complex for the PKR reaction of allylpropargyl ethers.

The active species of oxime palladacycles catalyzed cross-coupling reactions is mostly believed to be palladium nanoparticles.[14a] However, considering Pd(0) particles are not able to form the metallocycles for yielding the products by coordinating with the substrates, cationic Pd species are usually needed.[10b] Furthermore, the obtained results showed that the presence of both a weakly coordinated co-ligand and chloride in the palladacycles plays a critical role for the catalysis of PKR. The role of chloride is consistent with the study by Yang et al. in which a halometalation of the alkyne is involved in their catalysis.[10b] Thus a Pd(II)–Pd(IV) catalytic cycle would be more reasonable for the present catalysis. Further work is needed to prove the actual reactive species for the oxime-palladacycle catalyzed PKRs.

In summary, we have shown that oxime-derived palladacycles with pyridine co-ligand are a novel class of catalysts for the PKR. Good to excellent conversions for allylpropargyl ethers and allylpropargylamines have been achieved. Considering the wide applications of oxime palladacycles in the cross-coupling reactions, this work has provided an avenue for developing new catalysts for PKR to cascade other catalytic reactions. Further study to examine the reactive species in the catalytic cycle and the application of palladacycles in the cascade PKR is currently undergoing in our laboratory.

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Supplementary data

Supplementary data (experimental procedures and NMR spectra of the substrates and products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.106.

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