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Applications of the palladium-catalyzed carbonylative annulation of internal alkynes to the synthesis of medium-sized rings

Dmitry V. Kadnikov† and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, IA 50011-3111, USA. Fax: +1 515 294 0105; e-mail: larock@iastate.edu

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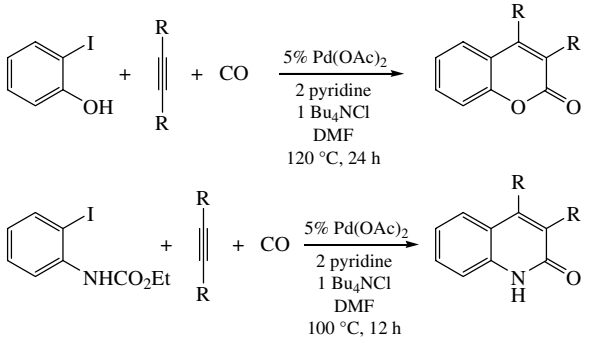
Seven- and eight-membered ring lactones were synthesized by the palladium-catalyzed carbonylative annulation of internal alkynes, and scope and limitations of the process were examined.

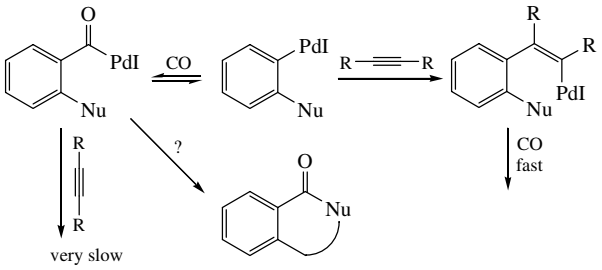
Unsaturated molecules, such as alkenes, alkynes, or carbon monoxide, undergo facile insertion into the carbon–palladium bond, and these insertions have given rise to a wide variety of synthetic transformations now widely used in organic synthesis.[1–3] Our laboratories have been actively involved in exploring the utility of these insertion processes for the synthesis of carbo- and heterocycles.[4,5] We have developed a widely applicable methodology for the synthesis of such rings based on the reactions of aryl and vinylic halides bearing neighbouring nucleophilic substituents with alkenes, dienes and internal or terminal alkynes. Indoles, isoquinolines, benzofurans, benzopyrans, isocoumarins, α-pyrones, indenones, naphthalenes and phenanthrenes can all be efficiently prepared using this methodology. We have also developed processes in which two unsaturated molecules undergo sequential insertion into the carbon–palladium bond. Thus, 2-iodophenols and N-substituted 2-iodoanilines react with an internal alkyne and carbon monoxide in the presence of a palladium catalyst to afford coumarins[6,7] and 2-quinolones[8] in good yields (Scheme 1).



Scheme 1

The remarkable feature of these two reactions is the selectivity of the insertion into the carbon–palladium bond. We have not observed any products arising from initial insertion of carbon monoxide, followed by insertion of an alkyne, which would lead to chromones and 4-quinolones. This fact is noteworthy since it is well-established that the insertion of carbon monoxide into a carbon–palladium bond is faster than the insertion of an internal alkyne.[9–12] To account for these inconsistencies, we have previously proposed the mechanism shown in Scheme 2. Insertion of carbon monoxide is fast but reversible, while

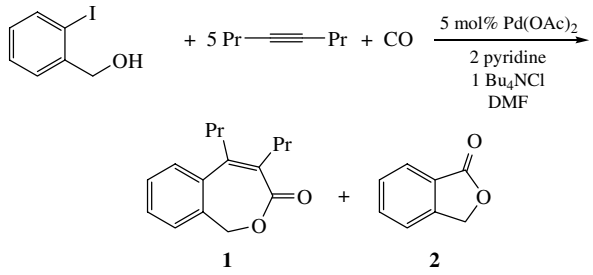
† A former student of the Higher Chemical College of the RAS (1991–1997). Current address: Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL, USA.



Scheme 2

insertion of an internal alkyne is irreversible. We have suggested that the insertion of an internal alkyne into an acylpalladium bond is quite slow, and in the absence of nucleophiles an acylpalladium complex can react only by undergoing decarbonylation back to the arylpalladium complex. Since alkyne insertion is irreversible, eventually all starting material is going to be channeled into the annulation product.

Since six-membered rings are formed very efficiently utilizing our carbonylative annulation methodology, we were interested in investigating whether larger rings can also be synthesized employing the same strategy. The results are presented in this communication.



Scheme 3

We began our studies with the reaction of 2-iodobenzyl alcohol and 4-octyne under one atmosphere of carbon monoxide (Scheme 3). If the reaction proceeds in the same way as the reaction with 2-iodophenol, the formation of seven-membered ring lactone **1** is anticipated. However, in the case of 2-iodobenzyl alcohol, an internal nucleophile capable of capturing an acylpalladium intermediate is now available. Thus, the formation of five-membered ring lactone **2** is expected to compete with the formation of the desired product. Indeed, under our standard reaction conditions developed for the synthesis of

Table 1 Optimization of chemoselectivity (Scheme 3).‡

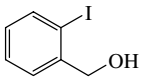
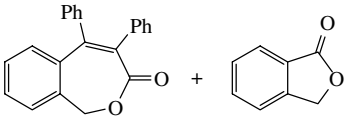
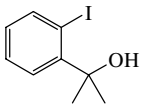
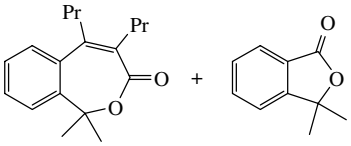
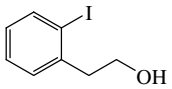
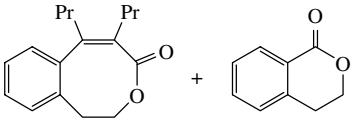
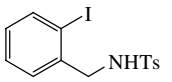
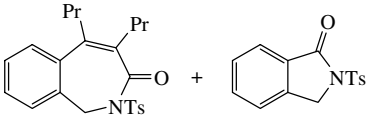
Entry	Catalyst (mol%)	*T*/°C	*t*/h	Isolated yield (%)	
				1	**2**
1	$Pd(OAc)_2$ (5)	120	4	43	24
2		100	8	28	45
3		80	24	<5	67
4	$Pd(dba)_2$ (5)	120	4	42	24
5	$Pd(OAc)_2$ (10)			37	19
6[a]	$Pd(OAc)_2$ (5)			40	19

[a]The reaction was run in 1 ml of DMF.

coumarins, both of these products were obtained in 43 and 24% isolated yields, respectively (Table 1, entry 1). We were gratified to see that even in the presence of an internal nucleophile capable of trapping an acylpalladium complex, carbonylative annulation remains competitive.

We then explored the effect of several reaction parameters on the yield and ratio of the products. The results are summarized in Table 1. It can be seen that the temperature of the reaction has a dramatic effect on the reaction outcome (entries 1–3). The rate of CO insertion into the arylpalladium bond apparently does not significantly depend on the reaction temperature, while the rate of alkyne insertion drops substantially when the reaction temperature is lowered to 80 °C. The use of a different palladium catalyst, $Pd(dba)_2$ (entry 4), or the use of higher amounts of the palladium catalyst (entry 5) do not significantly alter the outcome of the reaction. A five-fold reduction of the reaction volume (to 1 ml, entry 6) should lead to a five-fold increase in the alkyne/carbon monoxide ratio. This change, however, did not have a favorable effect on the reaction progress. While, the ratio of seven-membered ring lactone **1** to five-membered ring lactone **2** improved slightly (2.1:1 *vs.* 1.8:1, entries 6 and 1, respectively), the overall yield of lactone **1** decreased (40 *vs.* 43%). Thus, the standard coumarin reaction conditions appear at present to be the best to obtain the highest yields of seven-membered ring lactones.

Table 2 Synthesis of seven- and eight-membered ring heterocycles by the palladium-catalysed carbonylative annulation of internal alkynes.§

Entry	Alcohol	Alkyne	Products	Isolated yield (%)
1			 **3** + **2**	16 + 46
2	 **4**		 **5** + **6**	0 + 78
3	 **7**		 **8** + **9**	42 + 16
4	 **10**		 **11** + **12**	0 + 58

‡ *Typical reaction procedure:* 2-iodobenzyl alcohol (0.5 mmol), an alkyne (2.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol%, 0.025 mmol) and DMF (5 ml) were placed in a 4 dram vial. The vial was purged with CO for 2 min, then connected to a balloon of CO, and the reaction mixture was heated. For the reaction temperatures and times, see Table 1.

4,5-Dipropyl-1,3-dihydrobenzo[c]oxepin-3-one **1**: colourless oil. ^{1}H NMR ($CDCl_3$) δ: 7.37–7.48 (m, 3H), 7.31 (ddd, 1H, *J* 1.2, 7.2 and 7.6 Hz), 5.04 (d, 1H, *J* 7.6 Hz), 4.81 (d, 1H, *J* 7.6 Hz), 2.66–2.75 (m, 3H), 2.51–2.58 (m, 1H), 1.59–1.68 (m, 2H), 1.34–1.46 (m, 2H), 1.03 (t, 3H, *J* 7.2 Hz), 0.90 (t, 1H, *J* 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 171.0, 143.5, 139.5, 135.7, 133.2, 129.5, 128.5, 128.3, 127.3, 68.3, 35.1, 34.2, 23.3, 22.5, 14.5, 14.4. IR ($CHCl_3$, ν/cm^{-1}): 2959, 2872, 1707. MS, *m*/*z* (%): 244 (45, M^+), 216 (28), 201 (71), 173 (100). HRMS, found: 244.1468; calc. for $C_{16}H_{20}O_2$: 244.1463.

§ *Typical reaction procedure*: the alcohol or tosylamide (0.5 mmol), an alkyne (2.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol%, 0.025 mmol) and DMF (5 ml) were placed in a 4 dram vial. The vial was purged with CO for 2 min, then connected to a balloon of CO, and the reaction mixture was heated at 120 °C for 4 h.

4,5-Diphenyl-1,3-dihydrobenzo[c]oxepin-3-one **3**: white crystals, mp 200–203 °C. ^{1}H NMR ($CDCl_3$) δ: 7.44–7.50 (m, 3H), 7.39 (ddd, 1H, *J* 1.2, 7.2 and 8.0 Hz), 7.31 (ddd, 1H, *J* 1.2, 7.6 and 8.4 Hz), 7.12–7.19 (m, 6H), 6.96–6.98 (m, 3H), 5.51 (br. s, 1H), 5.05 (br. s, 1H). ^{13}C NMR ($CDCl_3$) δ: 169.3, 145.3, 140.4, 140.2, 136.7, 136.1, 133.0, 131.3, 131.2, 130.7, 129.5, 129.4, 128.4, 128.1, 128.0, 127.9, 127.7, 68.6. IR ($CHCl_3$, ν/cm^{-1}): 3057, 1718. MS, *m*/*z* (%): 312 (29, M^+), 235 (42), 233 (100), 260 (51). HRMS, found: 312.1155; calc. for $C_{22}H_{16}O_2$: 312.1150.

We then examined several other internal alkynes and alcohols in this reaction. The results are shown in Table 2. The reaction of diphenylacetylene with 2-iodobenzyl alcohol afforded only a 16% yield of seven-membered ring lactone **3**, along with a 46% yield of five-membered ring lactone **2** (entry 1). Only five-membered ring lactone **6** was observed when tertiary iodobenzylic alcohol **4** was substituted for 2-iodobenzyl alcohol (entry 2). However, to our delight, the reaction of 2-iodophenethyl alcohol **7** afforded, as the major product, the product of the initial alkyne insertion, eight-membered ring lactone **8**, in 42% yield. Six-membered ring lactone **9** was also obtained in 16% yield. We have also attempted to synthesize a seven-mem-

bered ring lactam. Unfortunately, the reaction of 4-octyne and carbon monoxide with *N*-(2-iodobenzyl)-*p*-toluenesulfonamide **10** resulted in formation of only five-membered ring lactam **12** in 58% yield.

These results illustrate the delicate balance between the formation of products from initial insertion of an alkyne or initial insertion of carbon monoxide. Factors affecting the rates of alkyne insertion and of trapping of the acylpalladium intermediate can significantly shift this equilibrium. Diphenylacetylene is less reactive toward insertion than 4-octyne. Thus, the yield of the seven-membered ring lactone decreases and the yield of the five-membered ring lactone increases, when diphenylacetylene is substituted for 4-octyne. To favour the direct CO insertion product, the nucleophile must either possess sufficient strength, as with the tosylamide, or adopt a proper conformation, as with the tertiary benzylic alcohol, to rapidly trap the acylpalladium intermediate.

In conclusion, we have demonstrated that the palladium-catalyzed carbonylative annulation of internal alkynes can be used to synthesize medium-sized rings, provided that an alkyne and the nucleophile are appropriately selected to maximize the rate of the desired reaction and minimize the rate of the undesired process. The exploration of various strategies to fine tune these rates, for example, the use of labile protecting groups, might further expand the scope of this process.

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