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Palladium-Catalyzed Tandem Carbonylative Diels–Alder Reaction for Construction of Bridged Polycyclic Skeletons

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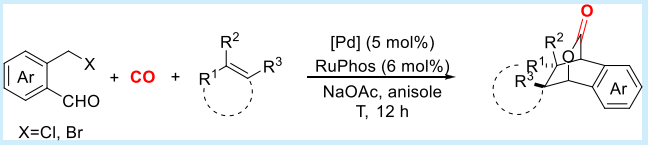
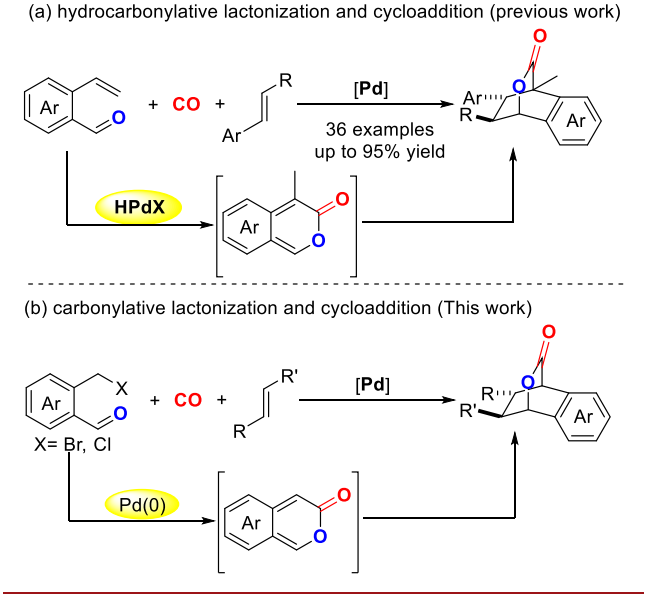
ABSTRACT: A palladium-catalyzed tandem carbonylative lactonization and Diels–Alder cycloaddition reaction between aldehyde-tethered benzylhalides and alkenes has been developed. A range of alkenes and aldehyde-tethered benzylhalides bearing different substituents can be successfully transformed into the corresponding bridged polycyclic compounds in good yields. This strategy provides a unique approach to complex lactone-containing bridged polycyclic compounds.



The carbonyl-containing bridged polycyclic architectures are common structural motifs in natural products.[1] Such cycloadducts are also able to serve as valuable intermediates in the synthesis of functionalized carbocycles and have therefore attracted much attention from synthetic chemists.[2] One reliable and rapid method for the assembly of such complex architectures is the Diels–Alder reaction with carbonyl-containing conjugated cyclic dienes.[3] Despite the tremendous progress, most of the so far known methods have focused on a stepwise protocol requiring tedious procedures for the preparation of the key carbonyl-containing cyclic conjugate dienes, thus restricting the overall scope and practicality of these transformations. Therefore, the development of a cascade annulation reaction with readily available acyclic substrates as starting materials is highly desirable but challenging.

Transition-metal-catalyzed carbonylation is one of the most intensively used methods for the synthesis of carbonyl compounds in both academic and industrial settings.[4,5] Whereas efficient carbonylation reactions have been well developed for the synthesis of saturated lactones, direct carbonylation access to unsaturated lactones that could be employed in the Diels–Alder reaction has rarely been developed. Inspired by the fact that the carbonyl oxygen could attack the acyl-metal species to form a lactone under the appropriate reaction conditions,[6] we have successfully established a palladium-catalyzed hydrocarbonylative cycloaddition reaction with two alkenes in the presence of CO (Scheme 1).[7] The HPdX-catalyzed carbonylative lactonization of the aldehyde-tethered alkenes was involved in the reaction, which paved a way to the synthesis of various lactone-containing bridged polycyclic compounds in good to excellent yields with high regioselectivities. However, the alkene-coupling partner of the reaction was significantly limited to aromatic alkenes. From a mechanistic perspective, the underlying reason for the limitation can probably be assigned to the competitive hydropalladation reaction between the two alkenes. In this context, we envisaged that once the carbonylation is initiated via a Pd(0) other than HPdX, the corresponding competitive hydropalladation reaction would be inhibited. Herein we report a cascade annulation reaction initiated via the Pd(0)-catalyzed carbonylative lactonization of 2-bromomethyl arylaldehydes. The reaction is applicable in synthesizing complex lactone-containing bridged polycyclic

Scheme 1. Palladium-Catalyzed Carbonylative Lactonization and Cycloaddition



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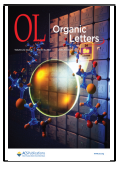

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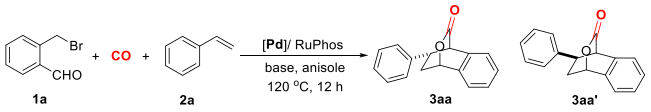
compounds from simple 2-bromomethyl arylaldehydes, a broad range of alkenes, as well as carbon monoxide.

Guided by this hypothesis and on the basis of our previous studies,[7,8] we started our studies by investigating the model reaction among 2-(bromomethyl)benzaldehyde (**1a**), styrene (**2a**), and CO. The initial experiments were conducted in anisole at 120 °C with $[Pd(allyl)Cl]_2$ as a catalyst precursor and RuPhos as the ligand. The extensive screening of the base (Table 1, entries 1−6) showed NaOAc to be the best base,

Table 1. Optimization of the Reaction Conditions[a]



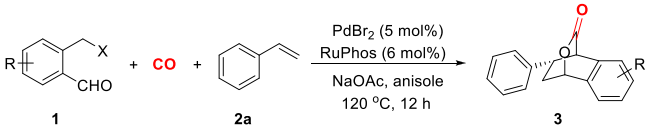
entry	[Pd]	base	yield, 3aa + 3aa′(%)[b]	endo/exo
1	$[Pd(allyl)Cl]_2$	Na_2CO_3	15	93:7
2	$[Pd(allyl)Cl]_2$	$NaHCO_3$	14	93:7
3	$[Pd(allyl)Cl]_2$	NaOAc	35	93:7
4	$[Pd(allyl)Cl]_2$	KOAc	15	93:7
5	$[Pd(allyl)Cl]_2$	*t*-BuONa	trace	
6	$[Pd(allyl)Cl]_2$	DBU	trace	
7	$Pd_2(dba)_3$	NaOAc	49	93:7
8	$PdCl_2$	NaOAc	29	93:7
9	$PdBr_2$	NaOAc	51	93:7
10	$Pd(OAc)_2$	NaOAc	38	93:7
11	$Pd(COD)Br_2$	NaOAc	37	93:7
12	$Pd(CH_3CN)_2Cl_2$	NaOAc	33	93:7
13	$Pd(TFA)_2$	NaOAc	0	
14[c]	$PdBr_2$	NaOAc	64	93:7
15[c,d]	$PdBr_2$	NaOAc	69	93:7
16[c,e]	$PdBr_2$	NaOAc	93 (82)	93:7

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), [Pd] (5 mol %), RuPhos (11 mol %), base (0.75 mmol), anisole (1.0 mL), CO (20 atm), 120 °C, 12 h. [b]Combined yield (**3aa** + **3aa′**) based on the aldehyde and the ratio (**3aa**/**3aa′**) of the crude reaction mixture was determined by GC and GC−MS analysis using *n*-tetradecane as the internal standard. The yield in parentheses is the isolated yield (**3aa** + **3aa′**). [c]RuPhos (6 mol %). [d]CO (40 atm). [e]CO (60 atm).

delivering the desired product **3aa** in 35% yield. This result encouraged us to optimize the reaction conditions by screening the catalyst precursor. To our delight, when $PdBr_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$ were introduced into the catalytic system, the desired product **3aa** could be obtained with high selectivity, albeit in moderate yield. The simple $PdBr_2$ was proved to be the best catalyst precursor (Table 1, entries 7−12), but almost no reaction took place when $Pd(TFA)_2$ was used (Table 1, entry 13). Further investigation of the ligands disclosed that the RuPhos exhibited the highest efficiency. (See the Supporting Information.) By decreasing the ratio of RuPhos/Pd from 2.2:1 to 1.2:1, the desired product was obtained in 64% yield (Table 1, entry 14). The yield rose to 82% when the reaction was conducted under 60 atm of CO (Table 1, entry 16). Moreover, the temperature and solvent were assessed, yet the variation of these parameters delivered no better results. As expected, no desired product was observed in the absence of a palladium catalyst or ligands.

Having the effective reaction conditions identified for this transformation, the substrate scope and generality were next explored. First, 2-(chloromethyl)benzaldehyde was tested under the standard reaction conditions, which disclosed that this catalytic reaction was not only suitable for 2-(bromomethyl)benzaldehyde but also suitable for 2-(chloromethyl)benzaldehyde (Table 2, entry 1). Subsequently,

Table 2. Substrate Scope of Aromatic Aldehyde[a]



entry	R	X	3	yield (%)[b]	endo/exo[c]
1	H	Cl	**3aa**	78	93:7
2	H	Br	**3aa**	82	93:7
3[d]	4-MeO	Br	**3ba**	77	96:4
4[d]	3-MeO	Br	**3ca**	78	95:5
5[d]	5-MeO	Br	**3da**	72	93:7
6	4-F	Br	**3ea**	55	96:4
7	4-Cl	Br	**3fa**	60	96:4
8	4-Br	Br	**3ga**	70	96:4
9	5-Br	Br	**3ha**	53	93:7
10	3-Br	Br	**3ia**	35	96:4
11	4-Ph	Br	**3ja**	61	97:3

[a]Reaction conditions: **1** (0.50 mmol), **2a** (0.75 mmol), $PdBr_2$ (5 mol %), RuPhos (6 mol %), NaOAc (0.75 mmol), anisole (1.0 mL), CO (60 atm), 120 °C, 12 h. [b]Isolated yield (endo + exo) based on the aldehyde. [c]Ratio (endo/exo) of the crude reaction mixture was determined by GC and GC−MS. [d]$Pd_2(dba)_3$ (2.5 mol %), 80 °C.

we evaluated a series of aldehyde-tethered benzyl bromides. It was found that 2-(bromomethyl)benzaldehydes carrying both electron-rich and -deficient groups tethered with the phenyl ring reacted smoothly with styrene (**2a**) in the presence of CO, affording the corresponding tandem cycloadducts in 35−82% yields with good to excellent diastereoselectivities. There was no necessary connection between the position of the substituent and the reaction efficiency for methoxy-substituted 2-(bromomethyl)benzaldehydes (Table 2, entries 3−5). Besides, the halogen substituents, such as fluoro, chloro and bromo atoms, were also compatible with this protocol, leading to the corresponding products in 53−70% yields (Table 2, entries 6−10). Notably, the desired product was obtained in only 35% yield with 3-bromo-2-(bromomethyl)benzaldehyde as the substrate, as most of the starting material underwent nucleophilic substitution reaction with NaOAc (Table 2, entry 10). Furthermore, 2-bromomethyl aromatic aldehyde derived from biphenyl could also run the reaction in 61% yield (Table 2, entries 11).

In addition to styrene **2a**, a series of aryl alkenes bearing a variety of substituents were subsequently examined. Methyl, methoxyl, chloro, and fluoro substituents on the phenyl ring of the styrenes were well tolerated, and the desired products **3ab**−**3al** were successfully obtained in 61−76% yields. The reaction efficiency was more sensitive to the position of the substituent, and para-substituted styrenes exhibited higher reactivities (Table 3, entries 2−4). No obvious electronic effect was observed. Both electron-rich and -poor aryl alkenes could react smoothly (Table 3, entries 2−10). Prop-1-en-2-ylbenzene and (*E*)-prop-1-en-1-ylbenzene were also compatible with this process but gave the corresponding products in moderate yields, presumably due to the steric hindrance (Table 3, entries 11 and 12). It is noteworthy that the structure of the product *endo*-**3ae** was confirmed by X-ray single-crystal diffraction analysis.

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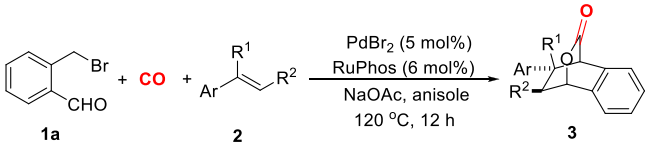
Table 3. Scope of Aryl Alkenes[a]



entry	Ar, R^1, R^2	3	yield (%)[b]	endo/exo[c]
1	C_6H_5, H, H	**3aa**	82	93:7
2	2-MeC_6H_4, H, H	**3ab**	61	91:9
3	3-MeC_6H_4, H, H	**3ac**	70	95:5
4	4-MeC_6H_4, H, H	**3ad**	72	95:5
5	4-MeOC_6H_4, H, H	**3ae**	68	91:9
6	4-*t*-BuC_6H_4, H, H	**3af**	71	92:8
7	4-$CF_3C_6H_4$, H, H	**3ag**	71	92:8
8	2-ClC_6H_4, H, H	**3ah**	73	91:9
9	4-ClC_6H_4, H, H	**3ai**	76	91:9
10	4-FC_6H_4, H, H	**3aj**	70	95:5
11	C_6H_5, Me, H	**3ak**	54	82:18
12	C_6H_5, H, Me	**3al**	34	85:15

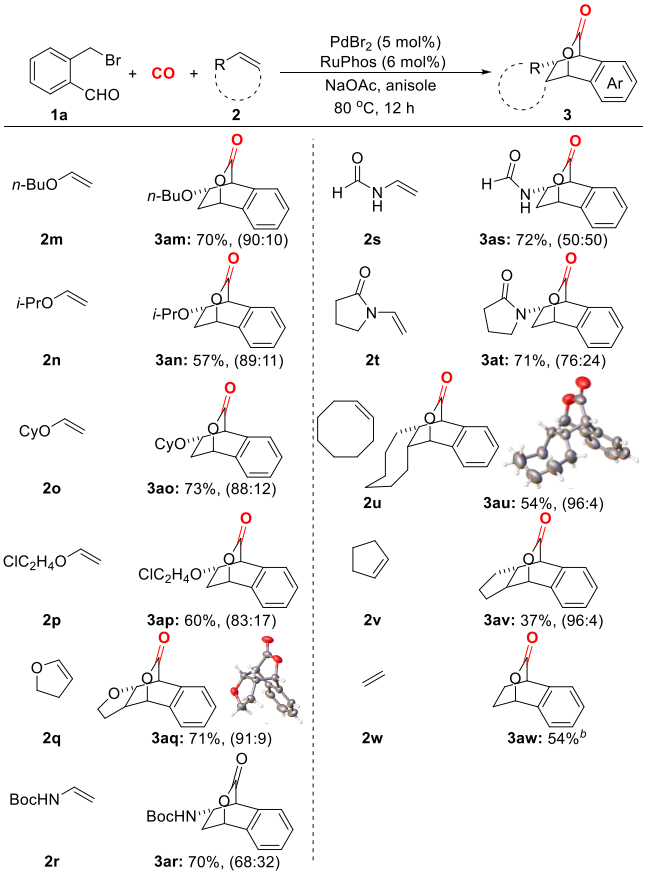
[a]Reaction conditions: **1a** (0.50 mmol), **2** (0.75 mmol), $PdBr_2$ (5 mol %), RuPhos (6 mol %), NaOAc (0.75 mmol), anisole (1.0 mL), CO (60 atm), 120 °C, 12 h. [b]Isolated yield (endo + exo) based on the aldehyde. [c]Ratio (endo/exo) of the crude reaction mixture was determined by GC and GC−MS.

After the exploration with aryl alkenes, we turned our attention to the electron-rich functionalized alkenes. As shown in Scheme 2, such substrates containing aliphatic vinyl ethers and an *N*-vinyl amide moiety were investigated under the optimized reaction conditions, preferentially affording the corresponding products in moderate to good yields (57−73%) with slightly lower regioselectivity (Scheme 2, **3am**−**3at**). However, attempts to investigate the methyl acrylate, dimethyl maleate, and cyclohexene were unsuccessful. These results indicated that they were not effective coupling partners for this transformation.[9] Nevertheless, because of the high ring strain, the *cis*-cyclooctene **2u** and cyclopentene **2v** were subjected to the reaction to afford the desired products in moderate yields with excellent diastereoselectivities (Scheme 2, **3au** and **3av**). Moreover, the simple ethylene was employed for this reaction under the standard conditions, providing the desired product **3aw** in 54% yield. Meanwhile, the structures of products of *endo*-**3aq** and *endo*-**3au** were confirmed by X-ray single-crystal diffraction analysis.

Several transformations of the obtained compounds **3aq** were conducted to expand the synthetic potential of the present reaction. As shown in Scheme 3, the reaction of **1a** with **2q** on a 5 mmol scale was completed under the standard conditions, yielding 778 mg of the corresponding product **3aq** in 72% yield with a good diameter. Alcoholysis of the ester group afforded **4** in 78% yield under acidic conditions at room temperature.[9] Meanwhile, compound **5** was obtained in 49% yield at 100 °C under otherwise identical conditions. The solid structure of **5** was further confirmed by X-ray single-crystal diffraction analysis. Subsequently, the ester group could be reduced with triethylsilane to give the bridged cyclic ether **6** in 82% yield.[10]

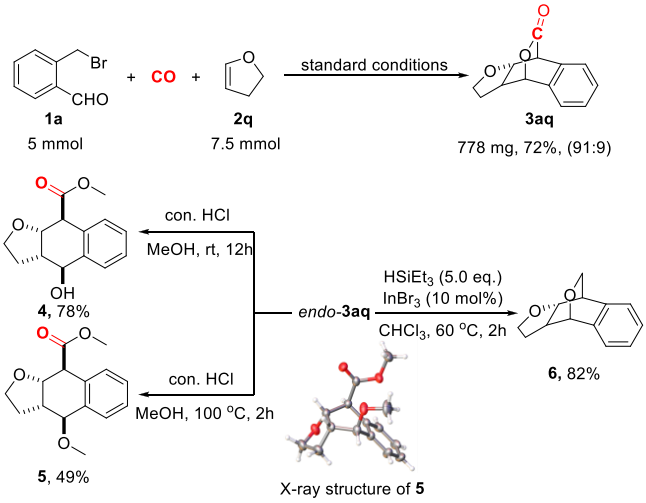
On the basis of the results the above and previous reports,[7,8] a plausible mechanism of this carbonylative cycloaddition reaction is proposed as the following catalytic cycle (Figure 1). The Pd(II) catalyst precursor is reduced by CO or a phosphine ligand to the (RuPhos)Pd(0) **I** species, which subsequently

Scheme 2. Substrate Scope of Alkenes[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), $PdBr_2$ (5.0 mol %), RuPhos (6.0 mol %), NaOAc (0.75 mmol), anisole (1.0 mL), CO (20 atm), 80 °C, 12 h. The isolated yield (endo + exo) is based on aldehyde. The ratio (endo/exo) of the crude reaction mixture was determined by GC and GC−MS. [b]Ethylene (10 atm).

Scheme 3. Synthetic Utility of the Present Reaction



undergoes oxidative addition to **1a**, producing the benzylpalladium species **II**. The insertion of CO into the C−Pd bond of **II** affords the acylpalladium species **III**, followed by reductive elimination to give the intermediate **IV** and regenerate the active Pd(0) catalyst. With the assistance of the base, the deprotonation of **IV** leads to the transient benzopyran-2-one **V**,

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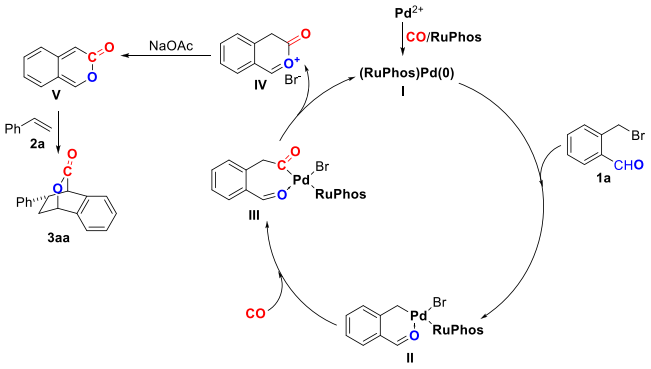

Figure 1. Plausible reaction mechanism.

which undergoes [4 + 2]-cycloaddition with an alkene to give the desired product **3aa**.[11]

In summary, we have successfully developed a novel and efficient palladium-catalyzed tandem carbonylative Diels–Alder reaction. This direct and operationally simple protocol presents a broad functional group tolerance and substrate scope. The present study complements and expands our previous work, providing an alternative and unique approach for preparing complex lactone-containing bridged polycyclic compounds. We speculated that the observed good chemo- and stereoselectivity was probably due to the use of the aldehyde functionality as the reactive directing group. Further studies on Pd-catalyzed carbonylative tandem Diels–Alder reactions with this new strategy are in progress, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00274.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 2054779–2054781 and 2064132 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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