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Synthesis of 2-Cyclopentenone Derivatives via Palladium-Catalyzed Intramolecular Carbonyl α-Alkenylation

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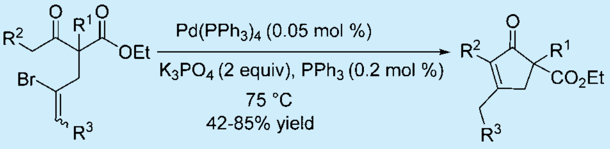
Ⓢ *Supporting Information*

ABSTRACT: 2-Cyclopentenone derivatives have been efficiently synthesized from 5-bromo-5-hexen-2-ones via palladium-catalyzed intramolecular carbonyl α-alkenylation followed by double-bond migration under mild reaction conditions.



The construction of the C−C bond is fundamental to modern-day organic synthesis. To meet the requirements of atom-economy and sustainable development, transition metals have been exploited to activate C−H bonds directly for efficient C−C bond formation from easily available starting materials. Recent decades have witnessed the rapid development and extensive application of direct C−H activation/functionalization of olefins and arenes.[1,2] In contrast, due to the lack of the assistance of π-groups, the selective activation of inert sp^3 C−H bonds still remains a challenging task. With the excellent reactivity and selectivity displayed in the catalytic process compared with other metals, palladium-promoted sp^3 C−H activation/C−C bond formation has emerged as a promising method of considerable interest to both academia and chemical industries. Since the pioneering work of Buchwald,[3] Hartwig,[4] and Miura,[5] the palladium-catalyzed direct α-arylation of carbonyl compounds has been well established and is widely used for the synthesis of polycyclic compounds, including natural products.[3,4,6−8] In contrast, the direct α-alkenylation reaction is less well studied.[9−11] To secure an acceptable yield of the α-alkenylation product, a strong base such as LiHMDS, NaHMDS, LiTMP,[10b,c] KO^{t}Bu, or NaO^{t}Bu[10a,11b] is generally required, and the reactions are believed to proceed via transition-metal-catalyzed addition of enolate anion to a vinyl halide. One of the problems associated with these transformations is the generation of an alkyne or diene side product by elimination of HX from the starting vinyl halide.[11a,b]

2-Cyclopentenone derivatives have likewise drawn much attention from chemists due to their promising biological activities and them being important building blocks for organic synthesis. Many studies have demonstrated that the α,β-unsaturated carbonyl functional group plays a key role in properties such as inhibition of tumors, viruses, inflammation, etc.[12] For instance, (−)-pentenomycin **1** (Figure 1), isolated by Umino et al. from *Streptomyces eurythermus*, exhibits activity by inhibiting both Gram-positive and Gram-negative bacteria.[13] Parthenin **2** and its derivatives have been reported to possess anticancer activity against three human cancer cell lines: SW-620, DU-145, and PC-3.[14]

(-)-pentenomycin
1

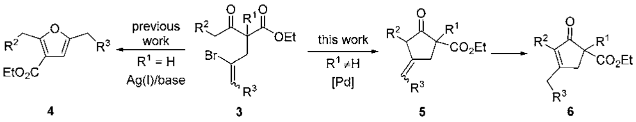
parthenin
2

Figure 1. Two representative natural products possessing the 2-cyclopentenone core.

Many versatile approaches have been developed to synthesize 2-cyclopentenones. These can be divided into three categories: (I) multicomponent ring construction involving Pauson−Khand,[15] (3 + 2),[16] or (4 + 1)[17] type ring assembly; (II) cyclizations that include the Nazarov cyclization,[18] alkene or alkyne metathesis,[19] base-promoted annulation,[20] intramolecular Wittig reaction,[21] Rautenstrauch rearrangement,[22] and hydrative carbocyclization of 1,5-diyn-3-ones;[23] and (III) conversion from other existing rings by way of ring expansion,[24] ring contraction,[25] and rearrangement.[26]

Previously, we developed a silver-mediated cyclization of 3-substituted 2-(2′-bromoallyl)-3-oxo-1-carboxylate **3** (R^1 = H) to provide furan-3-carboxylates **4** (Scheme 1).[27] In the proposed mechanism, it was believed that enolization of the carbonyl group contributed largely to the C−O bond formation. We further envisioned that if the enolization was

Scheme 1. Comparison between the Previous and Present Design



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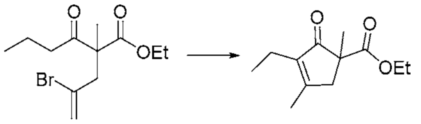
blocked by introducing a substituent group at C-2 of compound **3** ($R^1 \neq H$), olefination of the carbonyl α-C(sp^3)−H bond might occur in the presence of a suitable catalyst to provide cyclopentenone **6** after tautomerization of the initially formed **5**. The majority of intramolecular α-alkenylation reactions of carbonyl compounds reported so far have involved formation of a ring system with an "exo" carbonyl group. To the best of our knowledge, this is the first example of a transition metal-catalyzed intramolecular α-alkenylation reaction to build the cyclopentenone framework.

Our initial investigations toward the palladium-catalyzed intramolecular α-alkenylation for 2-cyclopentenone synthesis were carried out with substrate **3a**, and the results have been collected in Table 1.

Table 1. Optimization of Reaction Conditions[a]



3a **6a**

entry	cat. (mol %)	base	solvent	temp (°C)	yield[c] (%)
1	Pd/C (0.2)	K_2CO_3	NMP	70	0
2	$Pd_2(dba)_3$ (0.2)	K_2CO_3	NMP	70	0
3	$PdCl_2$ (0.2)	K_2CO_3	NMP	70	16
4	$Pd(OAc)_2$ (0.2)	K_2CO_3	NMP	70	21
5	$PdCl_2(CH_3CN)_2$ (0.2)	K_2CO_3	NMP	70	19
6	$PdCl_2(CH_3CN)_2$ (0.2)[b]	K_2CO_3	NMP	70	46
7	$[PdCl_2(dppf)]\cdot CH_2Cl_2$ (0.2)	K_2CO_3	NMP	70	54
8	$PdCl_2(PPh_3)_2$ (0.2)	K_2CO_3	NMP	70	53
9	$Pd(PPh_3)_4$ (0.2)	K_2CO_3	NMP	70	57
10	$Pd(PPh_3)_4$ (0.2)	Et_3N	NMP	70	37
11	$Pd(PPh_3)_4$ (0.2)	DABCO	NMP	70	30
12	$Pd(PPh_3)_4$ (0.2)	DIPEA	NMP	70	40
13	$Pd(PPh_3)_4$ (0.2)	DBU	NMP	70	66
14	$Pd(PPh_3)_4$ (0.2)	K_3PO_4	NMP	70	75
15	$Pd(PPh_3)_4$ (0.2)	*t*-BuOK	NMP	70	0
16	$Pd(PPh_3)_4$ (0.2)	K_3PO_4	1,4-dioxane	70	22
17	$Pd(PPh_3)_4$ (0.2)	K_3PO_4	DMSO	70	29
18	$Pd(PPh_3)_4$ (0.2)	K_3PO_4	DMF	70	54
19	$Pd(PPh_3)_4$ (0.1)	K_3PO_4	NMP	70	75
20	$Pd(PPh_3)_4$ (0.05)	K_3PO_4	NMP	70	70
21	$Pd(PPh_3)_4$ (0.05)[b]	K_3PO_4	NMP	70	72
22	**$Pd(PPh_3)_4$** **(0.05)**[b]	**K_3PO_4**	**NMP**	**75**	**75**
23	$Pd(PPh_3)_4$ (0.05)[b]	K_3PO_4	NMP	80	68

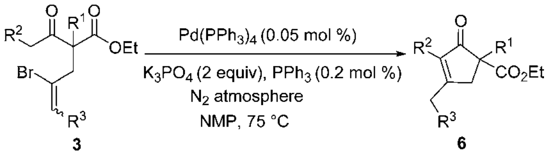
[a] All reactions were conducted in anhydrous solvents under nitrogen atmosphere overnight (15 h). [b] 0.2 mol % of PPh_3 was added. [c] Isolated yields.

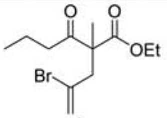
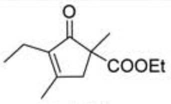
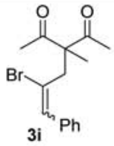
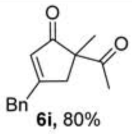
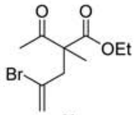
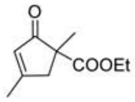
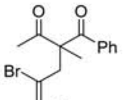
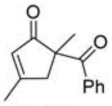
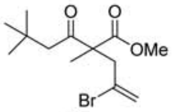
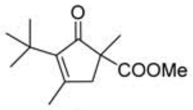
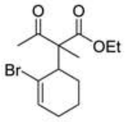
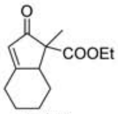
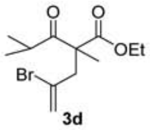
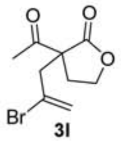
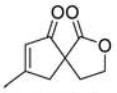
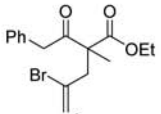
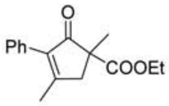
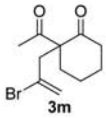
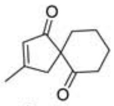
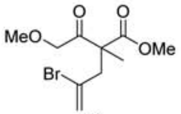
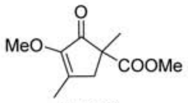
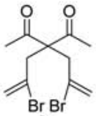
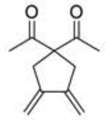
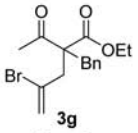
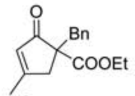
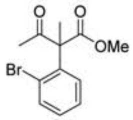
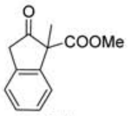
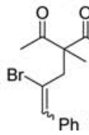
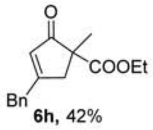
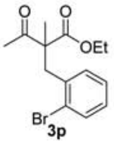
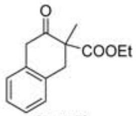
The palladium catalysts were examined first. With K_2CO_3 as base (2 equiv) and NMP as solvent, neither Pd/C (entry 1) nor $Pd_2(dba)_3$ (entry 2) could catalyze the desired reaction. In each case, only the unreacted **3a** was recovered. Delightfully, employment of $PdCl_2$ gave rise to promising results. After the reaction mixture was heated at 70 °C for 15 h, cyclopentenone **6a** was isolated in 16% yield (entry 3). Similar results were obtained when $Pd(OAc)_2$ or $PdCl_2(CH_3CN)_2$ was applied as catalyst (entries 4 and 5). The conversion rate of **3a** was greatly improved in the presence of $[PdCl_2(dppf)]\cdot CH_2Cl_2$, and **6a** could be isolated in 54% yield (entry 7). The catalytic efficiency of triphenylphosphine-based catalyst $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ was equally good, with a slightly higher product yield (57%) obtained in the latter case (entries 8 and 9). The results indicated that a proper ligand might be necessary for the reaction. Indeed, when 0.2 mol % of PPh_3 was added to the $PdCl_2(CH_3CN)_2$ catalytic system, the yield of **6a** was elevated substantially (entry 6 vs 5), although the result was still not as good as when $Pd(PPh_3)_4$ was applied. With $Pd(PPh_3)_4$ as the optimized catalyst, other bases such as Et_3N, DABCO, DIPEA, DBU, K_3PO_4, and *t*-BuOK and solvents such as 1,4-dioxane, DMSO, and DMF were screened. It was found that the reaction was best carried out in NMP (entry 14 vs 16−18) with K_3PO_4 as the base (entry 14 vs 9−13, 15). Next, the catalyst loading was examined. The yield of **6a** was not reduced in the presence of 0.1 mol % of $Pd(PPh_3)_4$ (entry 19). Further reduction of catalyst loading to 0.05 mol % resulted in slightly lower product yield (entry 20). However, with additional PPh_3 added (0.2 mol %), the isolated yield of **6a** could be improved to 72% (entry 21). Even better results were acquired when the reaction temperature was raised to 75 °C (entry 22). The product yield began to decrease at 80 °C (entry 23). Thus, by considering the efficiency and cost, the optimized reaction conditions were $Pd(PPh_3)_4$ (0.05 mol %) as catalyst, K_3PO_4 (2.0 mol %) as base, PPh_3 as added ligand (0.2 mol %), and NMP as solvent (entry 22).

With the optimized conditions in hand, an array of 2-(2′-bromoallyl)-1,3-dicarbonyl compounds and analogues were examined for the palladium-catalyzed carbonyl α-alkenylation to synthesize cyclopentenone derivatives. The results are displayed in Table 2. While the palladium-catalyzed α-alkenylation of butanoyl and acetyl acetate derivatives **3a** and **3b** proceeded smoothly to provide **6a** and **6b** in good isolated yield, reaction of tertiary butyl derivative **3c** was sluggish with only a trace amount of cyclopentenone **6c** obtained after 15 h. It was also found that the isobutyryl derivative **3d** did not give any desired product under the standard reaction conditions, probably because the double bond of the corresponding cyclopentanone (if formed) could not be stabilized by conjugation. Both the phenyl and methoxy derivatives **3e** and **3f** reacted to give **6e** and **6f** in 60% and 42% isolated yield, respectively. It should be noted that although the product yield was only moderate, the reaction of **3f** proceeded very fast and was complete in 30 min. This could be attributed to the electron-withdrawing nature of the methoxy group which made the activating α-hydrogen more acidic.[28] Under the conditions, the 2-benzyl derivative **3g**, the phenyl-substitued alkenes **3h** and **3i**, as well as the 1,3-diketone derivative **3j** could all cyclize to provide the corresponding cyclopentenones **6g−j** in moderate to good isolated yield. Next, we turned our attention to the synthesis of bicyclic and spirocyclic compounds. The intramolecular α-alkenylation reaction of bromocyclopentene derivative **3k** proceeded cleanly to give the bicyclic compound **6k** in excellent yield. While the spirocyclic compounds **6l** and **6m** could be successfully accessed from the lactone derivative **3l** and the cyclohexanone derivative **3m**, respectively, the reaction of dibromoallyl dicarbonyl compound **3n** resulted exclusively in the formation of the Ullman coupling product **6n** (77% isolated yield) instead of the desired spirodicyclopentenone resulting from double α-alkenylation.

Inspired by the aforementioned results, we finally tested the feasibility of the intramolecular carbonyl α-arylation reaction under the standard conditions. Gratifyingly, the reactions of

Table 2. Substrate Scope for the Palladium-Catalyzed Direct Carbonyl α-Alkenylation/Arylation Reaction



entry	substrate	product	entry	substrate	product
1	 **3a**	 **6a**, 75%	9	 **3i**	 **6i**, 80%
2	 **3b**	 **6b**, 81%	10	 **3j**	 **6j**, 65%
3	 **3c**	 **6c**, trace	11	 **3k**	 **6k**, 85%
4	 **3d**	–[a]	12	 **3l**	 **6l**, 47%
5	 **3e**	 **6e**, 60%	13	 **3m**	 **6m**, 75%
6	 **3f**	 **6f**, 42%	14	 **3n**	 **6n**, 77%
7	 **3g**	 **6g**, 75%	15	 **3o**	 **6o**, 36%
8	 **3h**	 **6h**, 42%	16	 **3p**	 **6p**, 74%

[a] Mixtures of products.

both bromophenyl ketoester derivative **3o** and bromobenzyl ketoester derivative **3p** were successful, leading to the formation of annulated cyclopentenone **6o** and cyclohexenone **6p** in 36% and 74% isolated yields, respectively.

A plausible mechanism for the palladium-catalyzed α-alkenylation is depicted in Scheme 2. Oxidative addition of Pd(0) to the alkenyl bromide moiety generates intermediate **I**,[29] which undergoes C–H activation to give **III** via **II**.[30] Reductive elimination then gives **5** and regenerates the Pd(0) species. Finally, tautomerization of **5** provides the cyclopentenone **6**. However, without further evidence, the enolate alkenylation[9] or Heck-type pathway[11a] cannot be ruled out, although these mechanisms are less likely under our reaction conditions (the pK_a value of the conjugate acid of K_3PO_4 is 12.3).

In conclusion, we have displayed the first example of palladium-catalyzed α-alkenylation of carbonyl compounds for the construction of 2-cyclopentenone derivatives. The substrates are easily prepared. The reaction conditions are mild. The products are obtained in good yield in a highly regioselective mannar. Future work will be focused on the synthesis of cycloalkenones with different ring sizes and related heterocyclic analogues.

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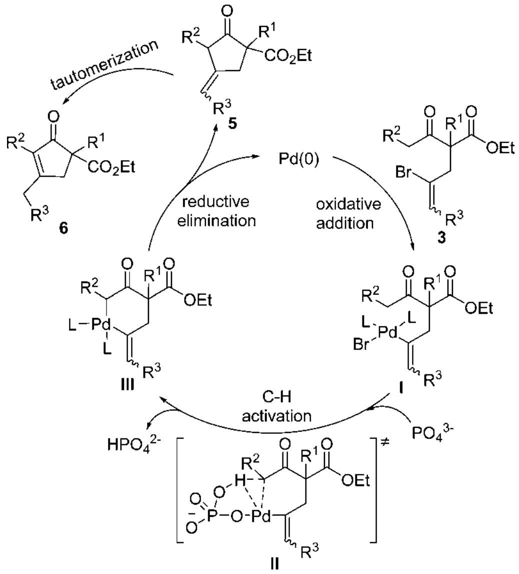
Scheme 2. Proposed Mechanism



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01955.

Detailed experimental procedures and characterization data for the new compounds (PDF)

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Author Contributions

†P.C. and Y.M. contributed equally.

Notes

The authors declare no competing financial interest.

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