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Palladium-Catalyzed Decarboxylation of Allenyl 3-Oxoalkanoates: An Efficient Synthesis of 3,4-Allenyl Ketones

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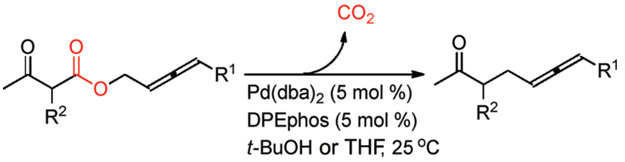
ABSTRACT



An efficient synthesis of 3,4-allenyl ketones via the Pd-catalyzed decarboxylative coupling of the readily available 3-oxoalkanoates is reported. The C−C bond forming reaction occurs under mild conditions producing CO_2 as the only byproduct.

Allenyl ketones are particularly attractive due to the complementary reactivity of the carbonyl and allenyl groups and used as versatile intermediates in various reactions,[1] such as electrophilic additions,[2] nucleophilic additions,[3] transition metal-catalyzed cycloisomerizations,[4] and electrochemical reductive cyclization,[5] etc. Thus, the development of new methods for the synthesis of allenyl ketones is of high interest. On the other hand, decarboxylative coupling reactions[6] have become a powerful method for the construction of C−C

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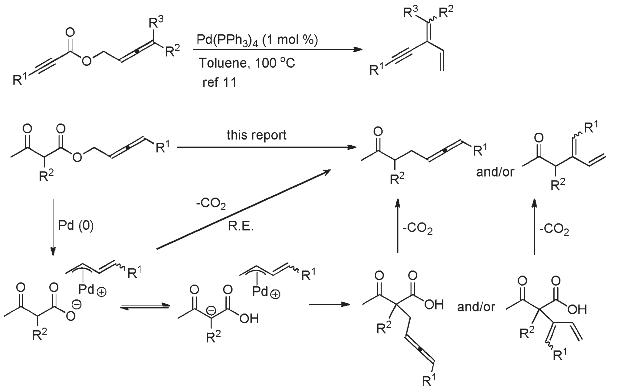
bonds, in part because these reactions may occur under neutral conditions and produce CO_2 as the only byproduct. Notable examples of Pd-catalyzed decarboxylative coupling reactions include decarboxylative alkylation,[7] decarboxylative Heck coupling,[8] aldol addition,[9] decarboxylative cross-coupling,[10] etc. In 2008, Chung et al. reported the synthesis of 2-alkynyl buta-1,3-dienes by decarboxylation of buta-2,3-dienyl 2′-alkynoates (Scheme 1).[11] We envisioned that such a strategy of decarboxylation of allenyl 3-oxoalkanoates would allow a convenient route to dienyl or allenyl ketones via an α-methylene π-allylpalladium intermediate (Scheme 1).[6d,7o] To the best of our knowledge, the synthesis of 3,4-allenyl ketones has not been well established: they may be prepared by the reactions of enolates[1c] or imines[5] with the alkylating agents, usually allenic chlorides or tosylates, using a strong base at low temperature. For the alcohol-oxidation approach, it is difficult to synthesize the corresponding 3,4-allenyl carbinols.[12] Thus, there is still a strong need for the development of a convergent synthesis of 3,4-allenyl ketones under mild conditions from readily available starting materials. Herein, we disclose such an efficient protocol to construct 3,4-allenyl ketones under mild conditions from the easily available allenyl 3-oxoalkanoates.

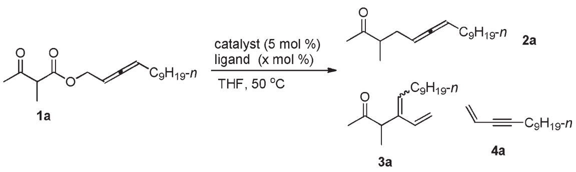
Scheme 1. Decarboxylation Reactions via an α-Methylene π-Allylpalladium Intermediate



To test our hypothesis, allenyl 3-oxoalkanoate **1a** was conveniently synthesized from readily available β-methylene-β-lactone[13] and the allenyl alcohol. When it was heated in THF at 50 °C in the presence of $Pd(PPh_3)_4$, the reaction failed to afford either the expected allenyl ketone **2a** or the 1,3-dienyl ketone **3a** (Table 1, entry 1). An initial catalyst screening revealed that $Pd(OAc)_2/PPh_3$, $Pd(dba)_2/PPh_3$, and $Pd(dba)_2$/LB-phos systems show similar results as $Pd(PPh_3)_4$ (Table 1, entries 2–4). However, the reaction afforded the allenyl ketone **2a** in 33% isolated yield as the only product by using $Pd(dba)_2$/dppf as the catalyst (Table 1, entry 5). Encouraged by this result, a series of ligands, such as dppe, binap, MeOBIPHEP, Xantphos, and DPEphos were screened for this transformation (Table 1, entries 6–10). Among them, DPEphos was shown to be the best with **2a** being formed in 59% isolated yield, and the formation of dienyl ketone **3a** was not observed. In this case, 1-vinylalkyne **4a** was also formed in 17% NMR yield (Table 1, entry 10).

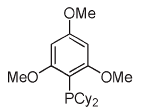
Using 5 mol % $Pd(dba)_2$ and 5 mol % DPEphos as the catalyst, subsequent comprehensive study on the solvent effect indicated that the reaction may proceed smoothly in all the tested solvents (Table 2): the reaction in *t*-BuOH afforded the best result with **2a** being formed in 66% isolated yield (Table 2, entry 10). By conducting the reaction at 25 °C, the yield of **2a** was improved to 77% although the reaction time was longer. In addition, the formation of **4a** was reduced to 6% NMR yield (Table 2, entry 11). Thus, the following optimized reaction conditions, i.e., 5 mol % $Pd(dba)_2$, 5 mol % DPEphos, *t*-BuOH, and 25 °C (Table 2, entry 11), were established for further study.

Table 1. Effect of Catalysts on the Decarboxylation of **1a**[a]

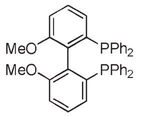


entry	catalyst	ligand (*x*/mol %)	time (h)	NMR yield (%)[b] 2a	4a
1	$Pd(PPh_3)_4$	–	21	complicated	
2	$Pd(OAc)_2$	PPh_3 (15)	21	complicated	
3	$Pd(dba)_2$	PPh_3 (15)	21	complicated	
4	$Pd(dba)_2$	LB-phos (15)	33	complicated	
5	$Pd(dba)_2$	dppf (5)	5.5	(33)[c]	–
6	$Pd(dba)_2$	dppe (5)	2.2	<14	–
7	$Pd(dba)_2$	binap (5)	2.3	30	19
8	$Pd(dba)_2$	MeOBIPHEP (5)	1.5	<48	16
9	$Pd(dba)_2$	Xantphos (5)	1.2	57	16
10	$Pd(dba)_2$	DPEphos (5)	0.5	66 (59)[c]	17

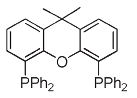
[a] Under argon, a mixture of **1a** (0.2 mmol) and the indicated catalyst in 2 mL of THF was stirred at 50 °C. [b] The yield was determined by ^1H NMR analysis using 1,3,5-trimethylbenzene as the internal standard. [c] The numbers shown in the parentheses are the isolated yields of **2a**.



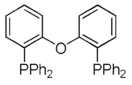
LB-phos



MeOBIPHEP



Xantphos



DPEphos

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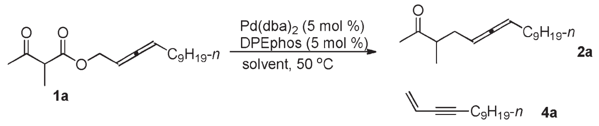
Table 2. Effect of Solvent on the Decarboxylation of **1a**[a]

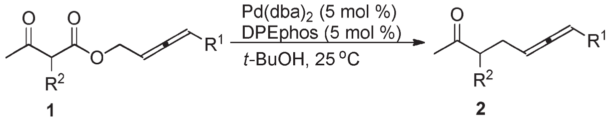


entry	solvent	time (h)	NMR yield (%)[b]	
			2a	**4a**
1	THF	0.5	66 (59)[c]	17
2	Dioxane	0.6	63	18
3	DME	0.6	62	18
4	Toluene	0.6	59	13
5	Benzene	0.6	58	15
6	CH_3CN	0.6	66	19
7	MTBE	0.6	59	15
8	DMF	0.6	65	18
9	EtOH	8	55	4
10	*t*-BuOH	0.6	70 (66)[c]	10
11[d]	*t*-BuOH	6.5	80 (77)[c]	6

[a] Under argon, the reaction was carried out with **1a** (0.2 mmol), Pd(dba)$_2$ (5 mol %), and DPEphos (5 mol %) in solvent (2 mL). [b] The yield was determined by ^{1}H NMR analysis using 1,3,5-trimethylbenzene as the internal standard. [c] The numbers shown in the parentheses are the isolated yields. [d] The reaction was carried out at 25 °C.

Then the substrate scope and generality of the reaction was investigated (Table 3): the reaction of allenyl 3-oxoalkanoates bearing a substituent at the terminal position of allenyl moieties **1a**–**1c** afforded the corresponding 3,4-allenyl ketones **2a**–**2c** as a mixture of ~1:1 diastereoisomers in 63–76% isolated yields; the reaction of **1d** with a terminal allene unit afforded the corresponding 3,4-allenyl ketone in 62% isolated yield; in addition, the reaction of **1a** proceeded smoothly to afford the allenyl ketone **2a** on a 1 g scale in 77% yield (Table 3, entry 2).

Table 3. Decarboxylative Coupling of 2-Oxoalkanoate **1**[a]

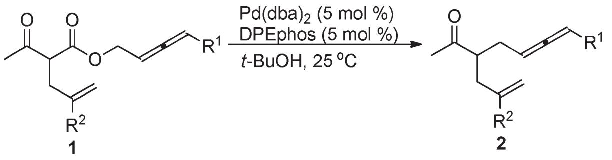


entry	**1**		time (h)	isolated yield of **2** (%)
	R^1	R^2		
1	n-C_9H_{19}	CH_3 (**1a**)	5	76 (**2a**)
2[b]	n-C_9H_{19}	CH_3 (**1a**)	3	77 (**2a**)
3	n-C_9H_{19}	Bn (**1b**)	4	65 (**2b**)
4	n-C_4H_9	Bn (**1c**)	4.5	63 (**2c**)
5	H	Bn (**1d**)	2.5	62 (**2d**)

[a] Under argon, the reaction was carried out with **1** (0.4 mmol), Pd(dba)$_2$ (5 mol %), and DPEphos (5 mol %) in solvent (2 mL). [b] The reaction was carried out on a 1 g scale.

As is known, enallenes, allenynes, and bisallenes are useful substrates in organic synthesis.[14–17] The enallenes **2e**–**2i** could be obtained in moderate to good yields starting from 2-allylic substituted substrates **1e**–**1i** (Table 4). The diastereoisomer ratio of **2e**–**2g** is about 1:1.

Table 4. Synthesis of 2-Allylic Substituted 3,4-Allenyl Ketones by Decarboxylative Coupling of **1**[a]

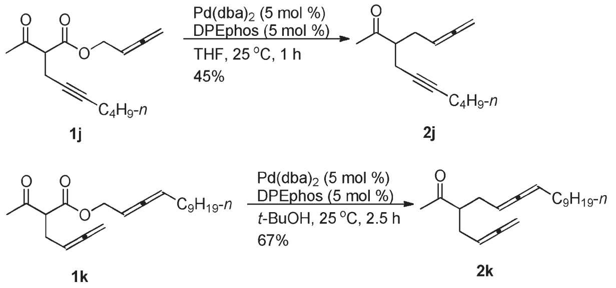


entry	**1**		time (h)	isolated yield of **2** (%)
	R^1	R^2		
1	n-C_9H_{19}	H (**1e**)	4	72 (**2e**)
2	cyclohexyl	H (**1f**)	5.5	74 (**2f**)
3[b]	*tert*-butyl	H (**1g**)	0.8	48 (**2g**)
4	H	Ph (**1h**)	7.5	70 (**2h**)
5	H	CO_2Me (**1i**)	3	60 (**2i**)

[a] Under argon, the reaction was carried out with **1** (0.4 mmol), Pd(dba)$_2$ (5 mol %), and DPEphos (5 mol %) in solvent (2 mL). [b] THF was used as the solvent.

Allenyne **2j** could be obtained in 45% isolated yield when THF was used as the solvent instead of *t*-BuOH (Scheme 2). In addition, the 2-(2,3-allenyl) substituted oxoalkanoate **1k** could be applied in the transformation affording the bisallene **2k** as a mixture of ~1:1 diastereoisomers in 67% yield (Scheme 2).

Scheme 2. Synthesis of Allenyne **2j** and Bisallene **2k** by Decarboxylative Coupling of **1j** and **1k**



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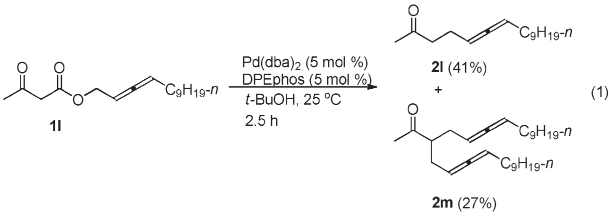
In addition, the reaction of 2-unsubstituented 3-oxoalkanoates **1l** afforded the monoallenylation product **2l** together with the diallenylation product **2m** in 41% and 27% isolated yields, respectively (eq 1).[18]



(1)

Unfortunately, reactions of the substrates **1m**−**1o** were complicated and failed to afford the corresponding decarboxylation products (Figure 1).

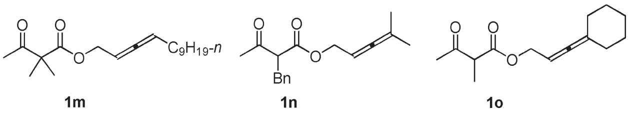
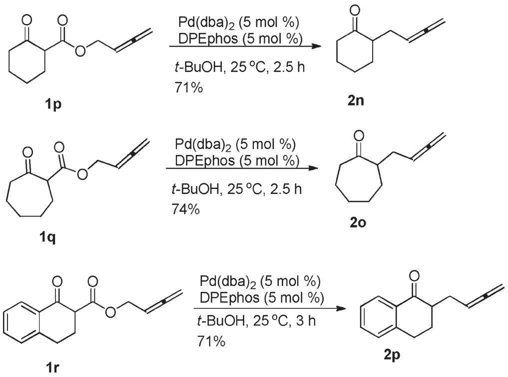


Figure 1. Other 3-oxoalkanoates tested for decarboxylation.

While the previous examples have focused on alkylation of acyclic 3-oxoalkanoates, the decarboxylative coupling of cylic substrates is also investigated. To our delight, the reaction of 3-oxoalkanoates **1p**−**1r** also afforded the corresponding allenyl ketones **2n**−**2p** in 71%, 74%, and 71% isolated yields, respectively (Scheme 3).

Scheme 3. Decarboxylative Coupling of Cyclic Substrates **1p**−**1r**



In conclusion, we have developed an efficient Pd-catalyzed decarboxylative coupling protocol for the synthesis of 3,4-allenyl ketones. The reaction occurs under mild conditions without external bases and produces CO_2 as the only byproduct. Due to the existence of both the carbonyl and allenyl moieties as well as the unsaturated C−C bond introduced by the substitution at the 2-position, this method will be useful for further application in organic synthesis. Further studies in this area including asymmetric synthesis of 3,4-allenyl ketones via this protocol are ongoing in our laboratory.

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Supporting Information Available. Analytical data for all products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] The formation of diallylated product in decarboxylation allylation has been reported by Tsuji and co-workers; see ref 7b.