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Palladium-Catalyzed Intramolecular Carboacetoxylation of 4-Pentenyl-Substituted Malonate Esters with Iodobenzene Diacetate

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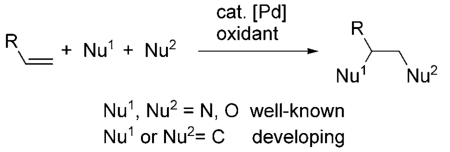
Palladium-catalyzed difuntionalization reactions of alkenes are rapidly emerging as useful tools for synthesizing a diverse range of complex molecules from rather simple alkenes.[1] Among them, oxidative processes involving a Pd^{II}/Pd^{IV} cycle have attracted increasing attention recently owing to their high efficiency as well as their mechanistic interest (Scheme 1). Reactions that oxidatively introduce two heteroatoms into alkene under Pd^{II}/Pd^{IV} catalysis include diamination (Nu^1, $Nu^2=N$),[2] oxyamination ($Nu^1=N$, $Nu^2=O$),[3] and dioxygenation (Nu^1, $Nu^2=O$).[4] On the other hand, Pd^{II}/Pd^{IV}-catalyzed difunctionalization reactions that form a carbon–carbon bond (Nu^1 or $Nu^2=C$) have received less attention.[5–9]

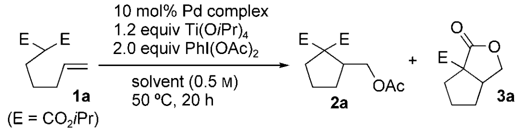


Scheme 1. Palladium-catalyzed oxidative difunctionalization involving a Pd^{II}/Pd^{IV} cycle. Nu^1 and Nu^2 represent nucleophiles. The oxidant may contain a nucleophile.

We envisioned that 4-pentenyl-substituted malonate esters **1** would undergo palladium-catalyzed oxidative cyclization.[10] Therefore, we investigated a variety of reaction conditions and report herein a new versatile intramolecular carboacetoxylation reaction, which yields acetoxymethyl-substituted cyclopentane derivatives **2**.

Treatment of malonate **1a** with iodobenzene diacetate in the presence of titanium tetraisopropoxide and a catalytic amount of $[PdCl_2(MeCN)_2]$ in 1,2-dichloroethane (DCE) at 50 °C for 20 hours afforded the expected carboacetoxylation product **2a** in 49 % yield, along with bicyclic lactone **3a** in 14 % yield (Table 1, entry 1).

Table 1. Screening of palladium catalyst and solvent.



Entry	Pd complex	Solvent	**2a** [%]	**3a** [%]
1	$[PdCl_2(MeCN)_2]$	DCE	49	14
2	$[PdCl_2(MeCN)_2]$	toluene	32	12
3	$[PdCl_2(MeCN)_2]$	THF	42	15
4	$[PdCl_2(MeCN)_2]$	DMF	20	35
5	$[PdCl_2(MeCN)_2]$	AcOH	22	34
6	$[PdCl_2(MeCN)_2]$	Ac_2O	50	7
7	$[PdCl_2(MeCN)_2]$	DCE/Ac_2O (1:1)	57	11
8	$Pd(OAc)_2$	DCE/Ac_2O (1:1)	31	8
9	$[Pd(O_2CCF_3)_2]$	DCE/Ac_2O (1:1)	31	8
10	$PdCl_2$	DCE/Ac_2O (1:1)	23	4
11	$[Pd_2(dba)_3]$	DCE/Ac_2O (1:1)	29	4
12	none	DCE/Ac_2O (1:1)	0	0

The presence of titanium tetraisopropoxide is crucial for the success of the reaction. Other bases, such as sodium *tert*-butoxide and cesium carbonate, did not promote the carboacetoxylation at all. Lewis acids including $Sc(OTf)_3$, $In(OTf)_3$, $ZnCl_2$, $TiCl_4$, and $MgBr_2$ were completely ineffective.

The choice of solvent was also an important factor in the success of the reaction (Table 1, entries 1–7). In nonpolar DCE and toluene and the weakly coordinating THF, **2a** was formed as the major product. On the other hand, the use of strongly coordinating DMF and acetic acid changed product

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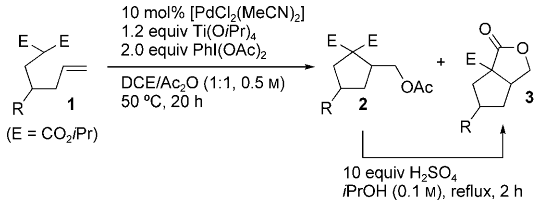
distribution to afford the predominant formation of lactone **3a**. Acetic anhydride was also successful,[11] and finally a 1:1 mixture of DCE and Ac_2O was found to afford the optimal yield.

Palladium complexes were then screened in DCE/Ac_2O solvent (Table 1, entries 7–11). Palladium acetate and trifluoroacetate was less efficient than $[PdCl_2(MeCN)_2]$. Simple $PdCl_2$ was less active than its acetonitrile complex, possibly owing to its poorer solubility. Zerovalent $[Pd_2(dba)_3]$ exhibited lower catalytic activity. It is worth noting that a complex mixture was obtained in the absence of any palladium complexes; therefore, a transition-metal-free mechanism[12] is excluded.

Only hypervalent iodine compounds showed reactivity as the oxidant. Although iodobenzene bis(trifluoroacetate) successfully induced the reaction, the yields of **2a** and **3a** were lower (11% and 23%, respectively). Other typical oxidants, such as $Cu(OAc)_2$, AgOAc, $K_2S_2O_8$, and $Mn(OAc)_3{\cdot}2H_2O$ failed to induce the carboacetoxylation.

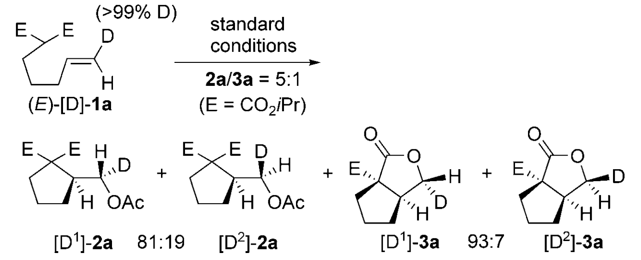
Several substrates bearing a substituent on the methylene tether were prepared and subjected to the carboacetoxylation reaction (Table 2). The products formed were diastereomeric mixtures of both **2** and **3**. The crude mixtures were treated with sulfuric acid in refluxing isopropyl alcohol to convert **2** into **3** for easy characterization. All reactions shown in Table 2 afforded **3** in good yields. In particular, **1g**, which contained an electron-rich anisyl group, was tolerated under the highly oxidative conditions (Table 2, entry 7). Bromobenzene derivative **1f** was tolerated under these conditions without undergoing oxidative addition to palladium (Table 2, entry 6). When the corresponding ethyl ester of **1a** was used, a mixture of **2a**, **3a**, and their ethyl ester analogues was obtained.

Table 2. Scope of Substrate. DCE = 1,2-dichloroethane.



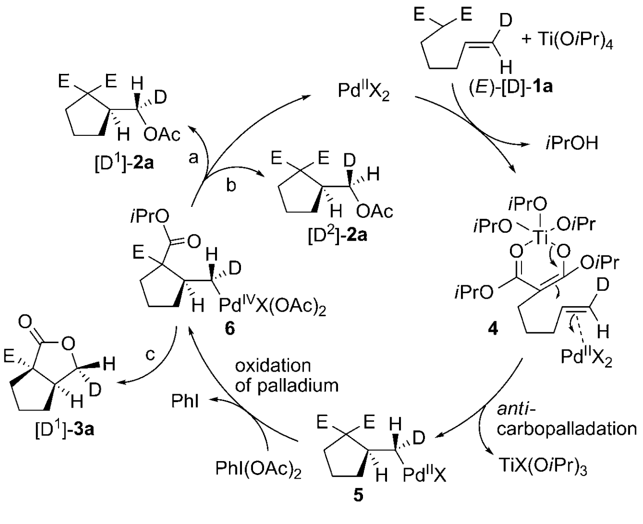
Entry	R	1	2 [%]	3 [%]	Yield of 3 [%]	d.r.
1	H	**1a**	57	11	68	–
2	Ph	**1b**	72	11	71	66:34
3	1-naphthyl	**1c**	67	20	71	67:33
4	*n*Bu	**1d**	59	16	61	60:40
5	4-F-C_6H_4	**1e**	65	20	65	68:32
6	4-Br-C_6H_4	**1f**	62	19	62	73:27
7	4-MeO-C_6H_4	**1g**	58	22	59	66:34

To investigate the reaction mechanism, monodeuterated (*E*)-[D]-**1a** was subjected to the carboacetoxylation reaction (Scheme 2). The carboacetoxylation product was obtained as an 81:19 mixture of diastereomers [D^1]-**2a** and [D^2]-**2a**.[13] The major isomer [D^1]-**2a** was derived from a formal *anti*-carboacetoxylation of the olefin. As a side reaction, the formation of lactone [D^1]-**3a** predominated over the formation of [D^2]-**3a**[13] under the palladium catalysis, which indicates that formal *syn*-carbolactonization is the major process.



Scheme 2. Reaction of deuterium-labeled **1a**.

A plausible mechanism that accounts for the deuterium-labeling experiments is shown in Scheme 3. The nucleophilic malonate moiety and olefinic moiety of (*E*)-[D]-**1a** would be activated by $Ti(O\textit{i}Pr)_4$ and PdX_2, respectively, to give **4**. Intramolecular *anti*-carbopalladation would then afford **5**.[14] The oxidation of the palladium of **5** by $PhI(OAc)_2$ would furnish alkyl Pd^{IV} species **6**.[1,15] Reductive elimination from **6** would be the most favorable process, providing [D^1]-**2a** as the major product (path a). Intermolecular S_N2 reaction of **6** with an acetate anion would compete, producing [D^2]-**2a** (path b). Lactone [D^1]-**3a** would be formed as a byproduct from an intramolecular S_N2 lactonization reaction (path c).[16,17]



Scheme 3. Plausible reaction mechanism. (E = $CO_2\textit{i}Pr$, X = Cl or OAc) a) Reductive elimination. b) Intermolecular nucleophilic attack by an acetate anion. c) Intramolecular nucleophilic substitution by an ester carbonyl group.

In summary, we have developed a new approach to cyclopentane derivatives using the palladium-catalyzed carboacetoxylation of 4-pentenyl-substituted malonate esters. This represents the first example of oxidative difunctionalization of simple olefins using a malonate anion as a nucleophile and the first Pd^{II}/Pd^{IV} catalytic oxidative process that forms an C_{sp^3}–C_{sp^3} bond.

Experimental Section

Representative procedure for the palladium-catalyzed reactions of 4-pentenyl-substituted malonate esters with iodobenzene diacetate: Bis(acetonitrile)dichloropalladium (7.8 mg, 0.030 mmol) and iodobenzene diacetate (0.19 g, 0.60 mmol) were added to a 20 mL two-necked reaction flask. The flask was filled with argon using the standard Schlenk technique. A mixture of 1,2-dichloroethane and acetic anhydride (1:1, 0.30 mL) was then added at room temperature. After the suspension was stirred for 3 min, titanium tetraisopropoxide (0.10 g, 0.36 mmol) and **1a** (0.077 g 0.30 mmol, 0.30 mL of a 1:1 mixture of 1,2-dichloroethane and acetic anhydride) were added to the flask at ambient temperature. The mixture was heated at 50 °C for 20 h. After the flask was cooled to room temperature, hydrochloric acid (1 M, 5 mL) was added to quench the reaction. The mixture was extracted with hexane/AcOEt (1:1, 3 x 10 mL). The combined organic layer was then washed with aqueous sodium hydrogencarbonate, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was dissolved in isopropyl alcohol (3.0 mL). Sulfuric acid (0.29 g, 3.0 mmol) was then added at 0 °C, and the resulting mixture was heated at reflux for 2 h. After the flask was cooled to room temperature, aqueous sodium hydrogencarbonate was added to quench the reaction. The mixture was extracted with AcOEt (3×10 mL each). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel with hexane/AcOEt (5:1) as eluent to provide isopropyl 3-oxa-2-oxobicyclo-[3.3.0]octane-1-carboxylate (**3a**, 0.043 g, 0.20 mmol, 68 %).

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Keywords: carboacetoxylation · cyclization · lactones · oxidation · palladium

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[16] The palladium-catalyzed reaction of **1a** in the presence of 1.0 equiv of lithium acetate afforded **2a** and **3a** in 50 % and 8 % yields, respectively. Virtually no change in the **2a**/**3a** ratio was observed. Further investigation of the reaction mechanism is necessary.

[17] We confirmed that interconversion between **2** and **3** did not take place under the reaction conditions.

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