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Palladium-Catalyzed C−H Monoalkoxylation of α,β-Unsaturated Carbonyl Compounds

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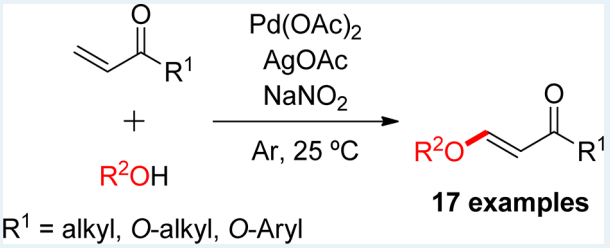
Supporting Information

ABSTRACT: An efficient method for the direct introduction of alkoxy groups into the β-position of alkene moieties of various α,β-unsaturated carbonyl compounds through the palladium-catalyzed C(sp²)−H monoalkoxylation using alcohols in the presence of sodium nitrite was developed; the corresponding enol ethers were selectively synthesized with minimal generation of acetals.

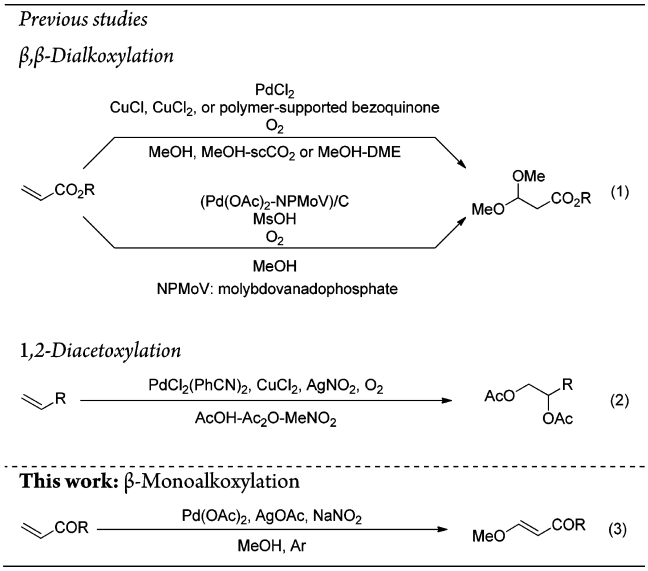


KEYWORDS: *monoalkoxylation, alkene, palladium catalysis, C−H functionalization, mild conditions*

Enol ethers have been widely used as building blocks for the preparation of heterocyclic compounds, such as isoxazoles,[1] quinolines,[2] furans,[3] and pyridines,[3] as well as for the chemical modification of biologically active compounds, such as nucleosides.[4] Furthermore, the α,β-unsaturated ketone-derived enol ethers could be good substrates for the Danishefsky's dienes[5] and Rawal's dienes,[6] which could be used for the Diels−Alder reaction. Recently, transition-metal-catalyzed C−H functionalizations have been in the spotlight in organic chemistry due to the elimination of the partial preactivation of substrates, such as the introduction of a leaving group.[7] The palladium-catalyzed functionalization of a terminal C−H bond of monosubstituted alkenes using nucleophiles under oxidative conditions, which is the so-called Wacker-type reaction, has been applied for C−N[8] and C−C[9−11] bond formations. However, no general methods for the mono C−O functionalization of α,β-unsaturated carbonyl compounds generating β-monoalkoxylated α,β-unsaturated carbonyl compounds have been developed in spite of their valuable utilities, while acetals could be effectively prepared through a further alkoxylation at the β-position (Scheme 1, eq 1).[12,13] Recently, the Pd/Cu-catalyzed 1,2-diacetoxylation of alkenes under aerobic oxidation conditions has been achieved by the addition of the nitrite anion to the acetic acid-acetic anhydride solution (Scheme 1, eq 2).[14] $Pd(MeCN)_2ClNO_2$, a Pd(II) nitrite salt, also mediated the oxidation of cyclic alkenes to afford the corresponding cyclic epoxides, ketones, enols, and enones.[15] Furthermore, palladium acetate [$Pd(OAc)_2$] generally exists as a trimer [$Pd_3(OAc)_6$], and it is also known that the acetate ions of $Pd_3(OAc)_6$ could be partially substituted by nitrite ions, such as $Pd_3(OAc)_5NO$.[16]

In this paper, we demonstrate that $Pd(OAc)_2$ would catalyze the β-monoalkoxylation of α,β-unsaturated carbonyl compounds in the presence of sodium nitrite under mild oxidative conditions to selectively afford the corresponding enol ethers (Scheme 1, eq 3).

Scheme 1. Pd-Catalyzed Introduction of Hydroxy Groups into Alkenes



When a solution of benzyl acrylate (**1**) and $Pd(OAc)_2$ (10 mol %) in MeOH was stirred at 110 °C under O_2 atmosphere, nearly no reaction took place (Table 1, entry 1), whereas the desired benzyl (*E*)-β-methoxyacrylate (**2**)[17] was obtained together with dimethylacetal (**3**) and benzyl methyl malonate

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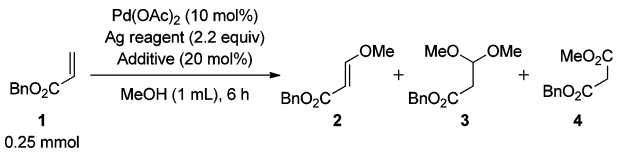
Table 1. Optimization of Reaction Conditions[a]

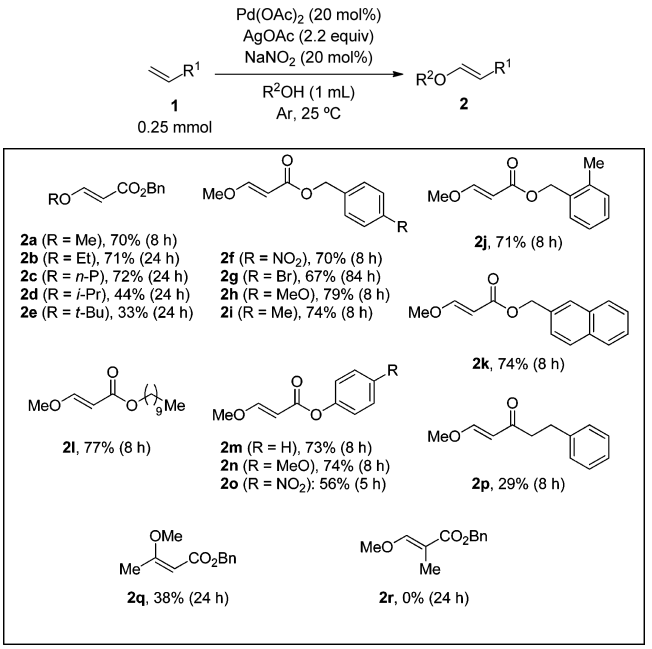


entry	Ag	additive	temp (°C)	gas	ratio[b] 1/2/3/4
1	–	–	110	O_2	94/5/1/0
2	Ag_2O	–	110	O_2	58/28/8/6
3	$AgOCOCF_3$	–	110	O_2	42/24/32/2
4	AgOAc	–	110	O_2	22/59/2/17
5	AgOAc	$NaNO_2$	110	O_2	4/80/2/14
6	–	$NaNO_2$	110	O_2	92/8/0/0
7[c]	AgOAc	$NaNO_2$	110	O_2	100/0/0/0
8	AgOAc	$NaNO_2$	80	O_2	5/80/2/13
9	AgOAc	$NaNO_2$	80	Ar	1/76/2/21
10	AgOAc	KNO_2	80	Ar	4/75/3/18
11	AgOAc	$NaNO_3$	80	Ar	15/61/2/22
12	AgOAc	NaOAc	80	Ar	36/43/0/21
13[d]	AgOAc	$NaNO_2$	80	Ar	4/81/3/12
14	AgOAc	$NaNO_2$	25	Ar	45/50/5/0
15[e]	AgOAc	$NaNO_2$	25	Ar	15/75/10/0
16[e,f]	AgOAc	$NaNO_2$	25	Ar	11/79 (70%)[g]/9/1
17[e,h]	AgOAc	$NaNO_2$	25	Ar	6/82/11/1
18[e,f,i]	AgOAc	$NaNO_2$	25	Ar	1/77/20/2

[a]Reaction conditions: **1** (0.25 mmol), Pd(OAc) (10 mol %), Ag reagent (2.2 equiv), additive (0 or 20 mol %) in MeOH (1 mL) at 110, 80, or 25 °C for 6 h. [b]Determined by ^{1}H NMR analysis [c]Without $Pd(OAc)_2$. [d]Freshly distilled MeOH was used. [e]20 mol % of $Pd(OAc)_2$ was used. [f]8 h. [g]Isolated yield. [h]12 h. [i]MeOH (0.5 mL) was used.

A variety of alcohols was applicable for the β-monoalkoxylation of benzyl acrylate, although *i*-PrOH and *t*-BuOH indicated somewhat lower reactivities due to possible steric hindrance (Table 2, **2a**–**2e**). The methoxylation of the benzyl

Table 2. C–H Alkoxylation of Alkenes Using Alcohols[a]



[a]Reaction conditions: **1** (0.25 mmol), Pd(OAc) (20 mol %), Ag reagent (2.2 equiv), $NaNO_2$ (20 mol %) in alcohol (1 mL) at 25 °C. Isolated yields are shown.

(**4**) by the addition of a silver(I) salt (2.2 equiv) as an oxidant (entries 2–4); AgOAc was the most effective for the consumption of **1** (entry 4) among the silver(I) salts that we investigated. The production of **2** significantly increased by the addition of $NaNO_2$ (entry 5), and $Pd(OAc)_2$ (entry 7) was found to be essential for the β-monomethoxylation of **1**. The reaction proceeded with a similar product distribution at 80 °C (entry 8) and even under Ar atmosphere (entry 9). It was found out that only the nitrite anion showed a positive effect regardless of the metal cation elements by comparison with the alternative salts of $NaNO_2$ (entries 9 and 10 vs 11 and 12). Although the formation ratio of benzyl methyl acrylate (**4**) was only slightly decreased by the use of freshly distilled MeOH as the solvent, a further study was performed using commercial MeOH without any purification from a practical point of view (entries 13 vs 8 and 9). The decrease in the reaction temperature from 80 to 25 °C led to a low conversion of **1** (entry 14), whereas the reaction efficiency was significantly enhanced with a low level of the byproduct formation by increasing the catalyst use to 20 mol % (entry 15) and the extension of the reaction time to 8 h (entry 16) to give the desired **2** in 70% isolated yield; however, the product balance was not virtually improved by further extension of the reaction time (entry 17). The decrease in the use of MeOH from 1 to 0.5 mL caused a significant increase in the formation ratio of the acetal **3** possibly due to the Pd-mediated further addition of MeOH based on the high concentration of $Pd(OAc)_2$ (entry 18).[12g]

acrylate derivatives and 2-naphthylmethyl acrylate smoothly proceeded regardless of the kinds and substitution pattern of the substituents on the aromatic ring (**2f**–**2k**). Aliphatic and aryl esters of acrylic acid as well as vinyl alkyl ketone also underwent the β-monomethoxylation to afford the desired methyl enol ethers (**2l**–**2p**). Furthermore, the methoxy group was successfully introduced to the β-position of the β-methyl acrylate derivative, benzyl crotonate, in a completely stereoselective manner (**2q**),[18] while benzyl metacrylate possessing a methyl substituent at the α-position was not suitable as a substrate for the present reaction (**2r**).

The present oxidative conditions for the C(sp^2)–H β-monoalkoxylation of α,β-unsaturated carbonyl compounds could be applied to the C–H β-amination[8a] and β-arylation[9] of benzyl acrylate. When 3 equiv of benzyl acrylate was used for the reaction with diphenylamine in 1,2-dichloroethane in the presence of $Pd(OAc)_2$, AgOAc, and $NaNO_2$, the desired enamine was obtained in 84% yield (Scheme 2, eq 1). The phenylation of benzyl acrylate could be achieved by the use of $PhB(OH)_2$ as a nucleophile to give the corresponding benzyl cinnamate in 89% yield (Scheme 2, eq 2).

Benzyl methyl malonate (**4**) could be obtained under elevated temperature conditions at 80 °C in 60% yield from benzyl (*E*)-β-methoxyacrylate (**2**), the major product of the present C–H β-monomethoxylation reaction (Scheme 3, eq 1), whereas no reaction took place in the case of the acetal (**3**) as the starting material (Scheme 3, eq 2).[19] Therefore, there is no doubt that **2** is an intermediate for the formation of the byproduct (**4**) of the C–H β-methoxylation.

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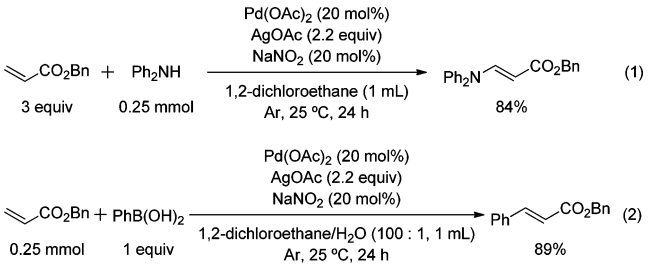
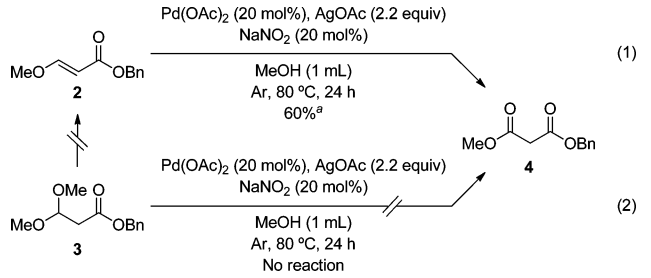
Scheme 2. Application of Other Nucleophiles

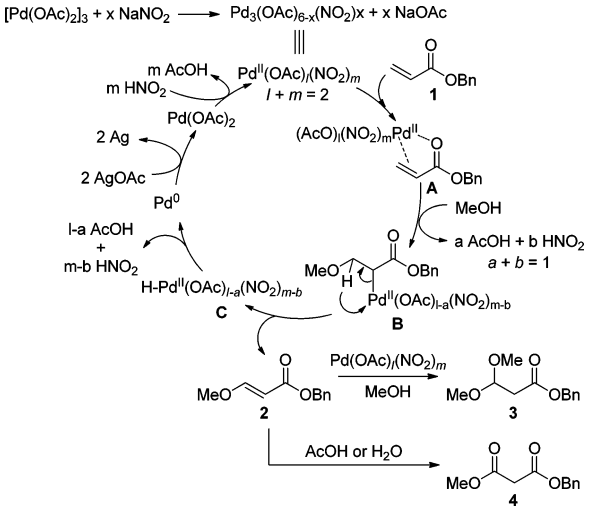


Scheme 3. Mechanistic Studies



The proposed reaction mechanism of the C(sp^2)−H monoalkoxylation at the β-position of the α,β-unsaturated carbonyl compounds is depicted in Scheme 4. Palladium salts

Scheme 4. Proposed Mechanism



are simply expressed as $Pd(OAc)_l(NO_2)_m$ ($l + m = 2$) for the reason that palladium acetate would be present as $Pd_3(OAc)_{6-x}(NO_2)_x$ in the presence of $NaNO_2$. It coordinates with benzyl acrylate (**1**) to afford a Pd^{II} complex (**A**), and the subsequent nucleophilic attack by MeOH to the β-position would give a Pd^{II} intermediate (B), which undergoes β-hydrogen elimination to generate the desired benzyl β-methoxyacrylate (**2**) with emission of the Pd^{II}−H complex (C). The succeeding reductive elimination gives the Pd^0 species, which is oxidized to $Pd(OAc)_2$ by AgOAc. $Pd(OAc)_l(NO_2)_m$ would be regenerated by the disproportionation of $Pd(OAc)_2$ with HNO_3. The acetal **3** should be obtained by the further Pd-mediated addition of MeOH to **2** as reported in ref 12g, and benzyl methyl malonate (**4**) must be generated from **2** as already described.

In conclusion, we have developed an effective and selective C(sp^2)−H monoalkoxylation at the β-position of α,β-unsaturated carbonyl compounds in the presence of $NaNO_2$ under Pd-catalyzed oxidative conditions. A wide variety of enol ethers could be synthesized from acrylates and α,β-unsaturated ketones in good yields. Furthermore, the protocol could be applied to the C−N and C−C bond-forming reactions using amine and arylboronic acid derivatives as nucleophiles. One of the distinctive features of the present reaction is the mild conditions (25 °C) and no need of the special purification of reagents. Further study for the application of the present conditions to the novel C(sp^2)−H monofunctionalization of terminal alkenes is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01084.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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