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Oxidative alkoxycarbonylation of terminal alkenes with carbazates†

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Cite this: *Chem. Commun.*, 2013, **49**, 6528

Received 23rd April 2013,
Accepted 14th May 2013

DOI: 10.1039/c3cc42994f

www.rsc.org/chemcomm

A range of terminal alkenes smoothly underwent palladium-catalyzed oxidative alkoxycarbonylation with carbazates under an oxygen atmosphere to afford structurally diverse α,β-unsaturated esters in moderate to good yields with excellent regioselectivity and *E* selectivity.

α,β-Unsaturated esters are present in many biologically relevant molecules, and moreover, they frequently serve as versatile synthetic intermediates that are amenable to a range of transformations such as addition, oxidation, and reduction.[1] Thus, many efforts have been devoted to the preparation of α,β-unsaturated esters, for which convergent approaches commonly used include carbonyl olefination and alkenylation.[2] When compared with carbonyl olefination, alkenylation in general exhibits higher atom-economy in the synthesis of the same α,β-unsaturated esters. Particularly, transformation of vinylic C–H bonds constitutes one of the most ideal methods to synthesize α,β-unsaturated esters. In this regard, acrylates have been widely employed in the Mizoroki–Heck reaction to couple with a variety of aryl sources such as aryl halides and sulfonates.[3] Although the Mizoroki–Heck-type reaction has been extended to aromatics *via* C–H functionalization under oxidative conditions, it suffers from the use of excess starting materials, harsh conditions, and narrow substrate scope.[4]

In sharp contrast, little progress has been made in alternative oxidative cross-coupling of ester groups with vinylic C–H bonds for the synthesis of α,β-unsaturated esters. Although more than forty years ago CO and alcohols (solvents) were reported to serve as the sources of ester groups to couple with terminal alkenes under oxidative conditions,[5] little has been published on the refinement of such oxidative alkoxycarbonylation reaction, which remains challenging in terms of harsh conditions, poor selectivity, and narrow substrate scope.[6,7] Prompted by our recent studies on the removal of the $NHNH_2$ group from sulfonyl hydrazides,[8] together with our interest in alkene synthesis,[9] we envisioned that treatment of simple carbazates ($ROCONHNH_2$) with palladium under oxidative conditions could remove the $NHNH_2$ group to generate certain alkoxycarbonylpalladiums, which would couple with terminal alkenes to afford α,β-unsaturated esters.[5b,6] Since simple carbazates are readily accessible solids, our proposed reaction was expected to be much safer and more convenient to handle than that with CO.

To test our hypothesis, we employed 5 mol% $Pd(OAc)_2$ to catalyze the alkoxycarbonylation of styrene (**1a**) with ethyl carbazate (**2a**) in acetonitrile under an oxygen atmosphere at 70 °C and found that α,β-unsaturated ester **3a** was formed albeit in a trace amount (Table 1, entry 1). To our delight, the addition of CuCl to the reaction mixture led to the formation of α,β-unsaturated ester **3a** in 31% yield with exclusive *E* selectivity (Table 1, entry 3). Molecular oxygen proved to be essential for the oxidative alkoxycarbonylation reaction judging by a control experiment conducted under a nitrogen atmosphere, wherein the desired product was not obtained at all (Table 1, entry 4). While no better yield was obtained by screening a number of solvents and copper sources (Table 1, entries 5–15), the addition of 5 Å molecular sieves improved the yield to 62% (Table 1, entry 16). It is noteworthy that the reaction failed to occur without a palladium source (Table 1, entry 17), and replacing $Pd(OAc)_2$ with $[Pd(allyl)Cl]_2$ gave a better yield (Table 1, entry 20). Whereas the reaction did take place at a lower temperature, the desired product was obtained in a much lower yield (Table 1, entry 21). Finally, the yield was improved to 78% by increasing the amount of ethyl carbazate (**2a**) to 2 equivalents (Table 1, entry 22).

In the presence of $[Pd(allyl)Cl]_2$ (5 mol%), CuCl (2 equiv.), and 5 Å molecular sieves, a range of arylethenes smoothly underwent oxidative alkoxycarbonylation with ethyl carbazate (**2a**) under an oxygen atmosphere to afford structurally diverse α,β-unsaturated esters in moderate to good yields with excellent regioselectivity and *E* selectivity (Table 2, entries 1–16). It is noteworthy that both electron-withdrawing and electron-donating groups were successfully introduced into the aromatic rings of the products by employing the arylethenes bearing such groups, and

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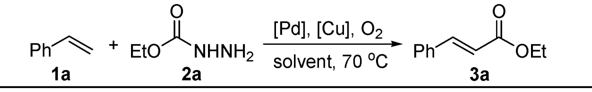
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c3cc42994f

Table 1 Optimization of reaction conditions[a]

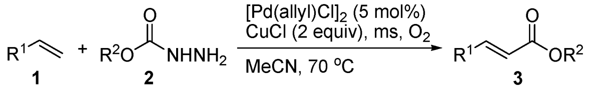


Entry	[Pd]	[Cu]	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	None	MeCN	Trace
2[c]	$Pd(OAc)_2$	CuCl	MeCN	5
3	$Pd(OAc)_2$	CuCl	MeCN	31
4[d]	$Pd(OAc)_2$	CuCl	MeCN	0
5	$Pd(OAc)_2$	CuCl	PhMe	0
6	$Pd(OAc)_2$	CuCl	DCE	0
7	$Pd(OAc)_2$	CuCl	EtOAc	0
8	$Pd(OAc)_2$	CuCl	$MeNO_2$	Trace
9	$Pd(OAc)_2$	CuCl	Dioxane	Trace
10	$Pd(OAc)_2$	CuCl	DMF	0
11	$Pd(OAc)_2$	CuCl	DMSO	0
12	$Pd(OAc)_2$	CuCl	EtOH	0
13	$Pd(OAc)_2$	$CuCl_2$	MeCN	Trace
14	$Pd(OAc)_2$	CuBr	MeCN	30
15	$Pd(OAc)_2$	CuI	MeCN	0
16[e]	$Pd(OAc)_2$	CuCl	MeCN	62
17[e]	None	CuCl	MeCN	0
18[e]	$PdCl_2$	CuCl	MeCN	27
19[e]	$Pd(PPh_3)_2Cl_2$	CuCl	MeCN	Trace
20[e]	$[Pd(allyl)Cl]_2$	CuCl	MeCN	70
21[e,f]	$[Pd(allyl)Cl]_2$	CuCl	MeCN	35
22[e,g]	$[Pd(allyl)Cl]_2$	CuCl	MeCN	78

[a] Reaction conditions: alkene **1a** (0.30 mmol), carbazate **2a** (0.45 mmol), [Pd] (5 mol%), [Cu] (0.60 mmol), O_2 (1 atm), solvent (1.3 mL), 70 °C, 5 h. [b] Isolated yield. [c] 20 mol% CuCl was used. [d] The reaction was run under a nitrogen atmosphere. [e] 5 Å molecular sieves (160 mg) were used. [f] The reaction was run at 50 °C. [g] 0.60 mmol of carbazate **2a** was used.

moreover, the reaction tolerated a variety of functional groups such as fluoro, chloro, bromo, acetoxy, sulfonate, sulfone, nitro, and nitrile. The chemistry was successfully extended to the synthesis of benzyl and *tert*-butyl α,β-unsaturated esters (Table 2, entries 17 and 18), and consequently, the synthetic utilities of this reaction could be significantly expanded in that the benzyl and *tert*-butyl groups can be easily removed under certain reaction conditions.[10]

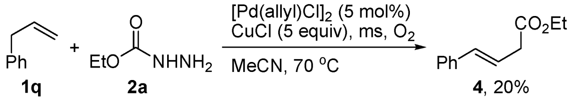
Table 2 Oxidative alkoxycarbonylation of arylethenes with carbazates[a,b]



Entry	1, R^1	2, R^2	3	Yield[c] (%)
1	**1a**, Ph	**2a**, Et	**3a**	78
2	**1b**, $4\text{-}MeC_6H_4$	**2a**, Et	**3b**	64
3	**1c**, $4\text{-}AcOC_6H_4$	**2a**, Et	**3c**	85
4	**1d**, $4\text{-}TsOC_6H_4$	**2a**, Et	**3d**	74
5	**1e**, $4\text{-}FC_6H_4$	**2a**, Et	**3e**	68
6	**1f** $4\text{-}ClC_6H_4$	**2a**, Et	**3f**	74
7	**1g**, $4\text{-}BrC_6H_4$	**2a**, Et	**3g**	72
8	**1h**, $4\text{-}F_3CC_6H_4$	**2a**, Et	**3h**	60
9	**1i**, $4\text{-}NCC_6H_4$	**2a**, Et	**3i**	67
10	**1j**, $4\text{-}MeS(O_2)C_6H_4$	**2a**, Et	**3j**	65
11	**1k**, $4\text{-}O_2NC_6H_4$	**2a**, Et	**3k**	62
12[d]	**1l**, $3\text{-}O_2NC_6H_4$	**2a**, Et	**3l**	64
13	**1m**, $2\text{-}ClC_6H_4$	**2a**, Et	**3m**	83
14	**1n**, $2\text{-}O_2NC_6H_4$	**2a**, Et	**3n**	56
15	**1o**, 2-naphthyl	**2a**, Et	**3o**	72
16[d]	**1p**, 1-naphthyl	**2a**, Et	**3p**	56
17	**1a**, Ph	**2b**, CH_2Ph	**3q**	53
18	**1a**, Ph	**2c**, CMe_3	**3r**	56

[a] Reaction conditions: alkene **1** (0.30 mmol), carbazate **2** (0.60 mmol), $[Pd(allyl)Cl]_2$ (5 mol%), CuCl (0.60 mmol), 5 Å molecular sieves (160 mg), O_2 (1 atm), acetonitrile (1.3 mL), 70 °C, 5 h. [b] Unless otherwise stated, the product was obtained with >99 : 1 *E*/*Z* selectivity. [c] Isolated yield. [d] 97 : 3 *E*/*Z*.

The oxidative alkoxycarbonylation of alkylethenes and polysubstituted alkenes was found to proceed sluggishly under the standard reaction conditions. Moreover, carbon–carbon double bond migration was observed in the reaction with 3-phenyl-1-propene (**1q**), which afforded β,γ-unsaturated ester **4** in 20% yield (eqn. (1)). Such migration probably arises from selective β-hydride elimination of the alkylpalladium intermediate generated during the reaction (see below).



(1)

We did not observe any desired reaction between styrene (**1a**) and ethyl 2-benzylhydrazinecarboxylate (**5**) under the standard conditions (Fig. 1), and this result indicates that the $NHNH_2$ group is essential for the oxidative alkoxycarbonylation of terminal alkenes with carbazates. In the reaction of styrene (**1a**) with ethyl carbazate (**2a**), both alcohols **6** and ketones **7** were not detected by ^1H NMR spectroscopic analysis of the crude products. Moreover, treatment of ethyl carbazate (**2a**) with 2,2,6,6-tetramethyl-1-piperidine-1-oxyl (TEMPO) under the standard conditions did not result in the formation of carbonate **8** (Fig. 1). These results are in sharp contrast to Taniguchi and coworkers' report on the generation of methoxycarbonyl radicals from methyl carbazate in the presence of iron phthalocyanine and air,[11] and consequently, they suggested that it is unlikely for alkoxycarbonyl radicals to serve as intermediates in the oxidative alkoxycarbonylation of terminal alkenes with carbazates.

To gain more insights into the reaction mechanism, we carried out electrospray ionization (ESI) mass spectrometric analysis of a 1 : 1 mixture of ethyl carbazate (**2a**) and $[Pd(allyl)Cl]_2$ in acetonitrile. Diazene **9a**, carbazates **10a** and **11a**, and carbazate–Pd(II) complexes **12a** and **13a** were tentatively assigned according to the high resolution mass data (Fig. 1).[12] These results suggest that diazenes and Pd(0) are generated during the reaction through the intermediacy of carbazate–Pd(II) complexes (see below).

On the basis of our experimental results, we propose the following reaction pathways for the oxidative alkoxycarbonylation of terminal alkenes with carbazates (Scheme 1). Displacement of $[Pd(allyl)Cl]_2$ with carbazate **2** results in the formation of carbazate–Pd(II) complex **12**, which undergoes reductive elimination to

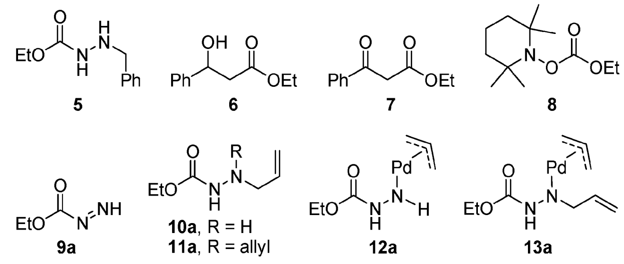
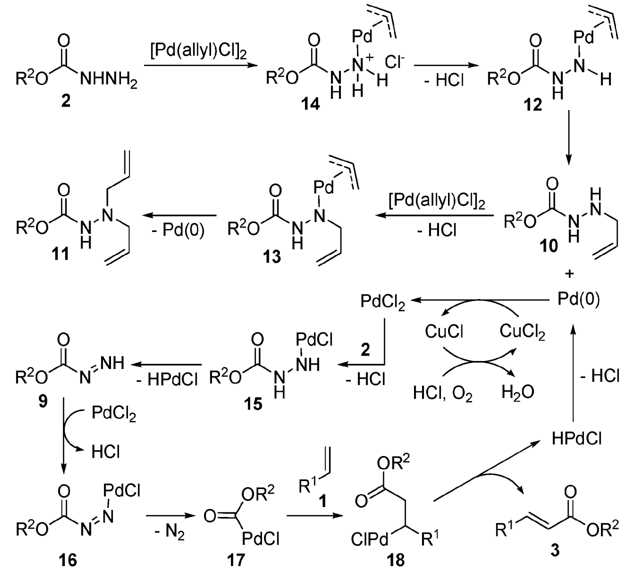


Fig. 1 Compounds **5–13a**.



Scheme 1 Proposed reaction pathways.

give carbazate **10**. Similar reaction of [Pd(allyl)Cl]$_2$ with carbazate **10** gives carbazate **11**. These displacement–elimination sequences allow the generation of Pd(0), which is converted to PdCl$_2$ through copper-mediated oxidation.[13–15] Displacement of PdCl$_2$ with carbazate **2** followed by β-hydride elimination gives diazene **9** and releases HPdCl. The attack of diazene **9** to PdCl$_2$ followed by extrusion of molecular nitrogen leads to the formation of alkoxycarbonyl-palladium **17**, which undergoes regioselective alkene insertion followed by β-hydride elimination to give α,β-unsaturated ester **3** and release HPdCl.[6] Reductive elimination of HPdCl regenerates Pd(0) to continue the catalytic cycle.

In summary, we have developed an unprecedented oxidative alkoxycarbonylation reaction of terminal alkenes with carbazates for the synthesis of α,β-unsaturated esters in a highly regio- and stereoselective manner. In the presence of [Pd(allyl)Cl]$_2$ (5 mol%), CuCl (2 equiv.), and 5 Å molecular sieves, a range of terminal alkenes smoothly underwent oxidative alkoxycarbonylation with carbazates under an oxygen atmosphere to afford structurally diverse α,β-unsaturated esters in moderate to good yields with excellent regioselectivity and *E* selectivity. The reaction tolerated a variety of functional groups such as fluoro, chloro, bromo, acetoxy, sulfonate, sulfone, nitro, and nitrile. Moreover, plausible reaction pathways have been proposed for the palladium-catalyzed oxidative alkoxycarbonylation of terminal alkenes with carbazates.

We are grateful for the financial support from the National Natural Science Foundation of China (21232007 and 21172206), the National Basic Research Program of China (973 Program 2010CB833300), and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1189).

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