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The first palladium-catalyzed 1,4-addition of terminal alkenes to acrylate esters†

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A novel and efficient procedure for the synthesis of δ,γ-alkenyl esters with complete *E*-stereochemistry by the 1,4-addition of alkenes to acrylate esters in the presence of a catalytic amount of palladium chloride has been developed. This method provides a rapid and efficient access to substituted δ,γ-alkenyl esters.

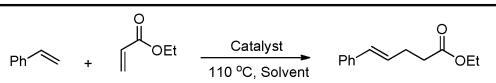
The 1,4-addition of carbanions to α,β-unsaturated carbonyl compounds is one of the most attractive methods for constructing a new carbon–carbon bond in organic synthesis.[1] Among them, a direct and reliable approach to a wide variety of γ,δ-alkynyl ketones and γ,δ-alkynyl esters is the 1,4-addition of terminal alkynes to unsaturated carbonyl compounds catalyzed by transition metals.[2] In contrast, related transition metal-catalyzed 1,4-addition of alkenes to unsaturated carbonyl compounds is relatively rare because C(sp2)–H bonds of simple alkenes are less reactive toward transition metals than alkynes.

In 1989, an efficient reaction between 4-(phenylsulfonyl)butanoic acid and benzaldehyde to generate (*E*)-methyl 5-phenylpent-4-enoate in the presence of *n*-BuLi was reported by Thompson and Frick.[3] Moreover, Chatterjee *et al.* have reported the synthesis of (*E*)-methyl cinnamate along with ethylene release directly from methyl acrylate and styrene catalyzed by a ruthenium complex.[4] Several years later, ruthenium-catalyzed synthesis of enamides from acrylate esters[5] and nickel-catalyzed synthesis of δ,γ-alkenyl esters from alkyl zinc halides[6] were developed. Recently, an efficient 1,4-addition of simple alkenes to enones in the presence of $Ni(cod)_2$ and PCy_3, which led to the synthesis of δ,γ-alkenyl ketones, has been reported.[7] The regiochemistry of the carbon–carbon bond at the β-position could be controlled by the formation of an η^3-oxaallylnickel species. However, to date, direct 1,4-addition of alkenes to alkene esters, which have low reactivity, remains an elusive goal.

More recently, we reported a convenient one-pot process for the synthesis of δ,γ-alkynyl esters from alkynylsilanes and acrylate esters using indium(III) chloride ($InCl_3$) as a catalyst.[8] As a result of the development of the transition-metal-catalyzed addition of alkynyl derivatives,[9] herein, we wish to report a highly efficient reaction for the synthesis of δ,γ-alkenyl esters with complete *E*-stereochemistry from alkenes and acrylate esters using $PdCl_2$ as the catalyst. To our delight, preliminary experiments, in which those substrates were subjected to the standard conditions used for the palladium chloride catalyzed 1,4-addition reaction, revealed that the target products were obtained in good yields.

To identify the suitable conditions for the 1,4-addition reaction, a variety of catalysts and solvents were screened using styrene **1a** with ethyl acrylate **2a** as a model system (Table 1).[10] Initially, the reaction of **1a** and **2a** gave **3aa** in 79% yield in the presence of 6 mol% $PdCl_2$ in chlorobenzene at 110 °C for 72 h (Table 1, entry 1).

Table 1 Optimization of reaction conditions[a]



1a 2a 3aa

Entry	Catalyst	Solvent	Yield[b] (%)
1	$PdCl_2$	PhCl	79
2	$PdCl_2$(3 mol%)	PhCl	50
3	$PdCl_2$(10 mol%)	PhCl	80
4	$Pd(OAc)_2$	PhCl	55
5	$Pd(OH)_2$	PhCl	0
6	$Pd(PPh_3)_4$	PhCl	0
7	$Pd(acac)_2$	PhCl	0
8	PdO	PhCl	0
9	$Pd_2(dba)_3$	PhCl	0
10	$In(OTf)_3$	PhCl	0
11	$FeCl_3$	PhCl	0
12	$RhCl_3$	PhCl	0
13	$AuBr_3$	PhCl	0
14	$PdCl_2$	DMF	15
15	$PdCl_2$	$PhCH_3$	20
16	$PdCl_2$	DMSO	48
17	$PdCl_2$	CH_3COOH	40
18	$PdCl_2$	CH_3NO_3	45
19	$PdCl_2$	THF	46
20	$PdCl_2$	DCE	55

[a] Reaction conditions: styrene **1a** (0.5 mmol), ethyl acrylate **2a** (0.75 mmol), catalyst (6 mol% to **1a**), solvent (2.0 mL), 110 °C, sealed tube 72 h. [b] Isolated yield of the pure product based on **1a**.

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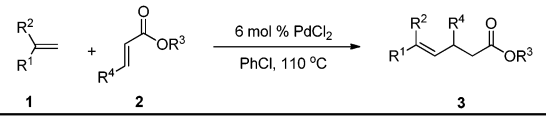
When the amount of $PdCl_2$ was decreased to 3 mol%, the yield of product **3aa** decreased to 50% (Table 1, entry 2). However, no improvement in the yield of **3aa** could be obtained when the amount of $PdCl_2$ was increased to 10 mol% (Table 1, entry 3). A moderate yield was obtained when $Pd(OAc)_2$ was used (Table 1, entry 4). In addition, in the presence of other palladium catalysts such as $Pd(OH)_2$, $Pd(PPh_3)_4$, $Pd(acac)_2$, PdO, or $Pd_2(dba)_3$, most of the starting material **1a** was recovered (Table 1, entries 5–9). Furthermore, with the other metal catalysts such as $In(OTf)_3$, $FeCl_3$, $RhCl_3$, or $AuBr_3$, the product **3aa** was also not obtained at all (Table 1, entries 10–13). Further optimization suggested that solvents had a strong effect on this process. The reactions were obviously restrained when they were performed in DMF and toluene (Table 1, entries 14 and 15). Moreover, in other solvents, such as DMSO, CH_3COOH, CH_3NO_3, THF and DCE, the yields of **3aa** decreased to 40–55% (Table 1, entries 16–20). When organic and inorganic bases were used, such as K_2CO_3, Cs_2CO_3, Et_3N, CH_3COONa, DABCO or DMAP, the reaction failed to afford the desired products. Subsequently, various ligands were tested for this reaction using $PdCl_2$ as the catalyst. No desired product was observed when PPh_3 or 1,10-phen was used as the ligand. Hence, it was concluded that the best conditions involved 6 mol% $PdCl_2$ in chlorobenzene at 110 °C for 72 h.

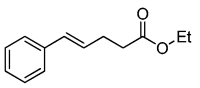
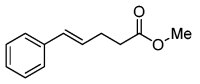
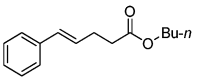
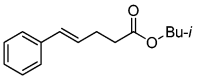
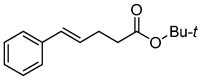
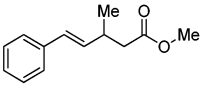
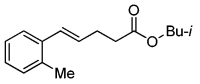
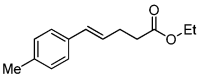
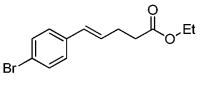
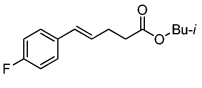
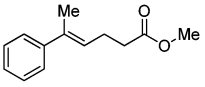
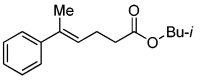
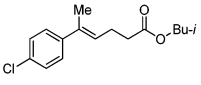
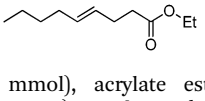
With the optimized reaction conditions established, the scope of the 1,4-addition reaction with respect to various alkenes and acrylate esters was investigated. Typical results are shown in Table 2. Varied acrylate esters were suitable reaction partners for styrene **1a** to form the δ,γ-alkenyl esters with complete *E*-stereochemistry. Promoted by $PdCl_2$, almost all the acrylate esters are effective under the standard conditions. Methyl acrylate **2b**, *n*-butyl acrylate **2c**, isobutyl acrylate **2d**, and *t*-butyl acrylate **2e** gave the corresponding δ,γ-alkenyl esters **3ab–3ae** in 73–85% yields with complete *E*-selectivity (Table 2, entries 2–5). However, the methyl methacrylate **2f** did not form the desired δ,γ-alkenyl ester **3af** with **1a**, presumably due to the steric effect of acrylate ester **2f** (Table 2, entry 6). The terminal aryl alkenes **1b** and **1c** possessing an electron-donating group at the aryl ring (R = 2-MeC_6H_4, 4-MeC_6H_4) reacted without a hitch and afforded the desired products **3bd** and **3ca** in 81% and 85% yields, respectively (Table 2, entries 7 and 8). Substrates **1d** and **1e** possessing an electron-withdrawing group (R = 4-BrC_6H_4, 4-FC_6H_4) at the benzene ring also reacted smoothly and gave the desired δ,γ-alkenyl esters **3da** and **3ed** in 74% and 68% yields with complete *E*-selectivity, respectively (Table 2, entries 9 and 10). Obviously, electron-rich terminal alkenes provided the desired products in higher yields than electron-poor terminal alkenes. Also, α-methylstyrene **1f** reacted smoothly with methyl acrylate **2b** and isobutyl acrylate **2d** affording **3fb** and **3fd** in good yields (Table 2, entries 11 and 12). In addition, the reaction of 4-chloro-α-methylstyrene **1g** under the same conditions resulted in the formation of **3gd** in a good yield (Table 2, entry 13). These results indicated that the steric effect of alkenes has no influence on this process. However, the reaction of 1-hexene **1h** and ethyl acrylate **2a** failed to afford the desired products and led to the recovery of starting materials (Table 2, entry 14).

To our delight, camphene **1i** reacted smoothly with methyl acrylate **2b** giving the corresponding product **3ib** in 65% yield (Scheme 1).

Table 2 Synthesis of δ,γ-alkenyl esters **3** catalyzed by $PdCl_2$[a]

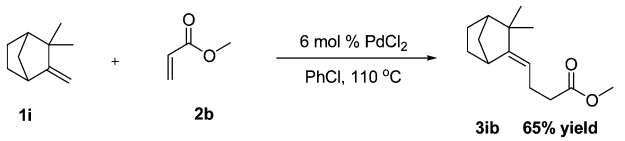


1 2 3

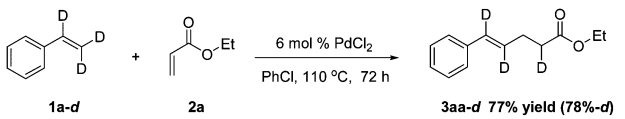
Entry	Alkene	Acrylate ester	Product	Yield[b] (%)
1	**1a**: R^1 = Ph; R^2 = H	**2a**: R^3 = Et; R^4 = H	**3aa**: 	79
2	**1a**: R^1 = Ph; R^2 = H	**2b**: R^3 = Me; R^4 = H	**3ab**: 	78
3	**1a**: R^1 = Ph; R^2 = H	**2c**: R^3 = *n*-Bu; R^4 = H	**3ac**: 	73
4	**1a**: R^1 = Ph; R^2 = H	**2d**: R^3 = i-Bu; R^4 = H	**3ad**: 	85
5	**1a**: R^1 = Ph; R^2 = H	**2e**: R^3 = *t*-Bu; R^4 = H	**3ae**: 	75
6	**1a**: R^1 = Ph; R^2 = H	**2f**: R^3 = Me; R^4 = Me	**3af**: 	0
7	**1b**: R^1 = 2-Me-C_6H_4; R^2 = H	**2d**: R^3 = i-Bu; R^4 = H	**3bd**: 	81
8	**1c**: R^1 = 4-Me-C_6H_4; R^2 = H	**2a**: R^3 = Et; R^4 = H	**3ca**: 	85
9	**1d**: R^1 = 4-Br-C_6H_4; R^2 = H	**2a**: R^3 = Et; R^4 = H	**3da**: 	74
10	**1e**: R^1 = 4-F-C_6H_4; R^2 = H	**2d**: R^3 = i-Bu; R^4 = H	**3ed**: 	68
11	**1f**: R^1 = Ph; R^2 = Me	**2b**: R^3 = Me; R^4 = H	**3fb**: 	78
12	**1f**: R^1 = Ph; R^2 = Me	**2d**: R^3 = i-Bu; R^4 = H	**3fd**: 	77
13	**1g**: R^1 = 4-Cl-C_6H_4; R^2 = Me	**2d**: R^3 = i-Bu; R^4 = H	**3gd**: 	72
14	**1h**: R^1 = C_4H_9; R^2 = H	**2a**: R^3 = Et; R^4 = H	**3ha**: 	0

[a] Reaction conditions: alkenes **1** (0.5 mmol), acrylate esters **2** (0.75 mmol), $PdCl_2$ (6 mol% to **1**), PhCl (2.0 mL), 110 °C, sealed tube 72 h. [b] Isolated yield of the pure product based on **1**.

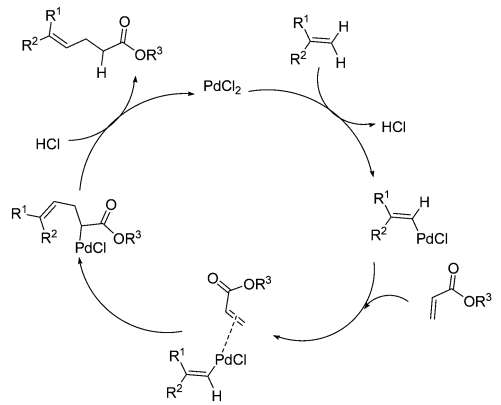
The camphene derivatives have good antiviral effects, particularly noticeable is the activity of the camphene derivatives against influenza A virus.[11] Herein, we have provided a rapid method for the synthesis of the camphene derivative.



Scheme 1 Synthesis of δ,γ-alkenyl ester **3ib** from camphene **1i** and ethyl acrylate **2b**.



Scheme 2 Deuterium labeling experiment.



Scheme 3 Possible reaction mechanism.

A deuterium labeling experiment gave us some information about the reaction pathway. Thus, treatment of styrene-*d* **1a–d** with ethyl acrylate **2a** in PhCl at 110 °C for 72 h gave the δ,γ-alkenyl esters **3aa–d** in 77% yield with complete *E*-stereochemistry, where 78% of deuterium was incorporated (Scheme 2).

On the basis of the above results, a tentative mechanism for the palladium catalyzed 1,4-addition of terminal alkenes to conjugated acrylate esters is illustrated in Scheme 3. The η^2-coordination of the double bond to the palladium center followed by direct deprotonation of the coordinated terminal alkene to the palladium catalyst generated the alkenyl palladium intermediate. Then, η^2-coordination of the C=C double bond to the palladium center followed by carbopalladation and substitution of Pd with hydrogen produced the δ,γ-alkenyl ester products with concomitant regeneration of the Pd catalyst.

In conclusion, we have developed a general and efficient method which is catalyzed by the commercially available palladium catalyst for the synthesis of δ,γ-alkenyl esters from alkenes and acrylate esters in a one-pot manner. Various δ,γ-alkenyl esters were formed in good yields. The reaction showed very good selectivity, and (*E*)-alkenyl esters were found as the sole products in all cases. Further investigation, including the scope, mechanism and synthetic application of this reaction, is in progress in our laboratory.

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