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Straightforward Synthesis of Allylated Keto Esters: The Palladium-Catalysed Haloketone Alkoxycarbonylation/ Allylation Domino Reaction

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Abstract: The palladium-catalysed α-chloro ketone methoxycarbonylation and allylic alkylation reactions can be efficiently combined to provide a new catalytic domino reaction. The first, carbonylative, step generates the β-keto ester, which acts as the nucleophile in a subsequent allylation step. The use of allyl phenates in combination with Xantphos ligand are the key features allowing one to obtain the allylated β-keto esters in good yields

Keywords: allylic alkylation; carbon monoxide; catalysis; domino reaction; selectivity

Introduction

The multi-step synthesis of complex organic molecules often results in the generation of large amounts of wastes due to the numerous solvent-consuming purification procedures at each stage of the synthesis.[1] Domino-type transformations that involve metal-catalysed reactions have consequently emerged as green and efficient synthetic tools as they allow the one-step construction of elaborated molecules with a reduced environmental impact.[2] However, the elaboration of a domino reaction may often meet with drastic difficulties and limitations. Indeed, a number of incompatibilities between the reactants and the catalytic system, present from the outset of the reaction, may arise and lead to side products and/or catalyst poisoning. Hence, the consecutive elementary steps building up a domino process have to be carefully and rationally chosen when planning a new such sequence.

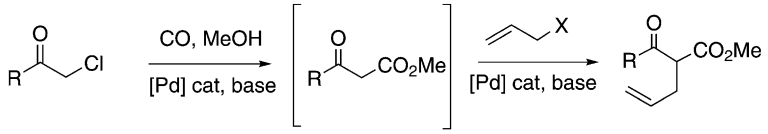
We targeted to develop new catalytic domino[3] sequences involving carbon monoxide as a cheap and readily available carbonyl source,[4] for the straightforward one-pot construction of specific building blocks. The literature witnesses several precedents of domino and/or multicomponent sequences entailing carbonylative steps.[5] The following examples represent a non-exhaustive list: hydroformylation (with syngas)/acetal formation and related sequences,[6] radical reactions involving CO,[7] multicomponent carbonylative coupling reactions[8] such as 1,3-dipolar cycloadditions involving münchnones,[9] carbopalladation/carbonylation sequences,[10] and allylic alkylation/Pauson–Khand sequences.[11] In most cases the carbonylation step occurs at the end of the sequence, which closes through an intra- or intermolecular trapping of a palladium-carbonyl intermediate.

Our project focussed on the development of a palladium-catalysed *pseudo*-domino *type I*[12] sequence involving the alkoxycarbonylation of an α-chloro ketone, followed by allylation of the transiently formed β-keto ester (Scheme 1).

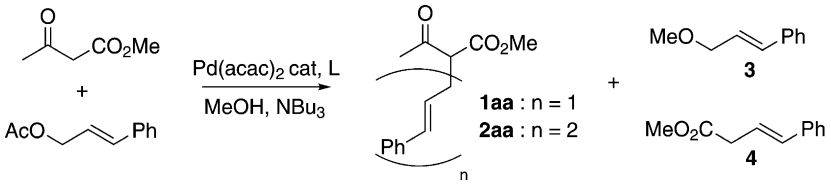
Results and Discussion

Our primary objective was to find out the common key parameters allowing the achievement of the two consecutive reactions using the same catalytic system and enolising system.

We then settled to study first the second step of our sequence, taking as a model the reaction between



Scheme 1. The palladium-catalysed methoxycarbonylation/allylation domino sequence.



Scheme 2. The palladium-catalysed reaction between methyl acetoacetate and cinnamyl acetate.

methyl acetoacetate and cinnamyl acetate (Scheme 2 and Table 1).

The palladium-catalysed methoxycarbonylation of α-chloro ketones[13] (that would represent the first step of our sequence) is best effected using PPh_3 as ancillary ligand, MeOH as the solvent, and tributylamine as the base.[14] Accordingly, we started our study using the catalytic system [$Pd(acac)_2$/PPh_3 (1/4 ratio)], MeOH as the solvent, and NBu_3 as the base.[15] We also decided to use an excess of the allyl acetate (2.5 equiv.), as this reaction partner may be involved (and thus consumed) in side reactions (see below). This experiment gave a mixture of mono- and bis-allylated linear β-keto esters **1aa** and **2aa** in 18:82 ratio (entry 1). The reaction also yielded cinnamyl methyl ether[16] **3** as side product, resulting from attack of methanol on the η^3-allylpalladium intermediate formed in excess. The starting materials were entirely converted and the overall yield in **1aa** and **2aa** was essentially limited by the competitive formation of the methyl ether **3**. A similar result was obtained on switching from PPh_3 to Xantphos (entry 2). In view of the need of carbonylative conditions during the desired domino reaction, the allylic alkylation was also performed under a CO atmosphere. Under such conditions, the allylic alkylation still proceeded, although it was accompanied by the formation of methyl ester **4**, arising from the methoxycarbonylation of cinnamyl acetate.[17] Interestingly, the selectivity of the reaction was strongly dependent on the nature of the ligand used. In particular, large amounts of **4** were obtained when using PPh_3 (entry 3), to the detriment of the targeted products **1aa** and **2aa**, whereas the allylation reaction remained efficient with Xantphos (entry 4). This observation is coherent with the fact that monophosphines are more commonly used than diphosphines for the carbonylation of allylic acetates, halides or carbonates.

Although the side products **3** and **4** were formed in non-negligible amounts, the compatibility of the reaction conditions used for α-chloro ketone methoxycarbonylation in β-keto ester allylation was at this point clearly established.

The feasibility of the complete *pseudo*-domino reaction was studied using chloroacetone as a cheap, commercially available α-chloro ketone and cinnamyl derivatives bearing various leaving groups (Scheme 3 and Table 2).

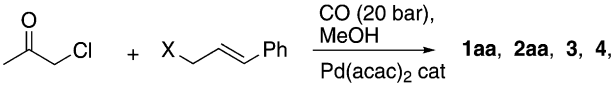
The reactions were performed under 20 bar of carbon monoxide with 1% of palladium catalyst associated with a phosphorus-based ligand (4/1 P/Pd ratio) at 70 °C for 16 h. In line with what was previously observed in the allylation performed under CO pressure (Table 1, entry 3), the reaction with PPh_3 yielded exclusively the carbonylated product **4** (entry 1). Apparently, with the above reaction condi-

Table 1. The allylic alkylation reaction in methanol.[a]

Entry	Ligand[c]	P_{CO}	mmol (Yield [%])[a]			
			1aa	**2aa**	**3**	**4**
1	PPh_3	0	0.5 (16)	2.3 (77)	0.5	–
2	Xantphos	0	0.3 (10)	2.4 (80)	0.7	–
3	PPh_3	20	0.7 (23)	0.6 (20)	0.1	1.2
4	Xantphos	20	0.6 (20)	1.8 (60)	0.8	0.2

[a] The reaction was carried out at 70 °C using methyl acetoacetate (3.0 mmol), NBu_3 (7.5 mmol; 2.5 equiv.), $Pd(acac)_2$ (0.03 mmol), PPh_3 (0.12 mmol) or Xantphos (0.06 mmol) in MeOH (10 mL) for 16 h.

[b] Amounts determined by GC with undecane as internal standard. Yields calculated with respect to methyl acetoacetate.



Scheme 3. The palladium-catalysed methoxycarbonylation/cinnamylation as a *pseudo*-domino sequence.

Table 2. The palladium-catalysed alkoxycarbonylation/allylation domino reaction.[a]

Entry	Ligand[c]	X (equiv.)[c]	mmol (Yield [%])[b]			
			1aa	**2aa**	**3**	**4**
1	PPh_3	OAc (2.2)	traces	traces	traces	4.4
2	Xantphos	OAc (2.2)	0.3 (10)	1.3 (43)	2.2	0.9
3	Xantphos	OAc (3.5)	0.1 (3)	1.3 (43)	4.3	1.6
4[d]	Xantphos	OAc (2.2)	0.3 (10)	1.1 (35)	2.5	0.3
5	Xantphos	Cl (2.2)	0.5 (17)	1.5 (50)	2.1	1.0
6	Xantphos	MeOCOO (2.2)	0.2 (7)	1.8 (60)	1.6	0.5
7	Xantphos	OPh (2.2)	0.4 (13)	2.5 (83)	0.6	0.6

[a] The reaction was carried out at 70 °C using chloroacetone (3.0 mmol), allylic substrate (7.5 mmol, 2.5 equiv.), tributylamine (13.5 mmol; 4.5 equiv.), CO (20 bar), $Pd(acac)_2$ (0.03 mmol), PPh_3 (0.12 mmol) or Xantphos (0.06 mmol) in 10 mL of MeOH for 16 h.

[b] Amounts determined by GC with undecane as internal standard, yields calculated from the amount of chloroacetone used.

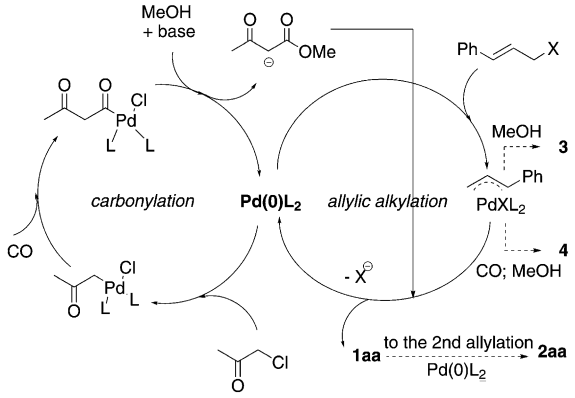
[c] Number of equivalents of allylic derivative *versus* chloroacetone.

[d] The reaction was performed in the presence of AcONa (2.0 equiv. with respect to chloroacetone).

tions, methoxycarbonylation of chloroacetone did not occur, thereby leaving free access to methoxycarbonylation of cinnamyl acetate. However, when PPh_3 was changed for Xantphos, encouraging amounts of the allylated β-keto esters **1aa** and **2aa** were obtained, although the methyl ether **3** was still the major product (entry 2). This result suggests that in this case methoxycarbonylation of the cinnamyl residue occurs concurrently to alkylation. The use of larger amounts of cinnamyl acetate (entry 3) did not produce better yields, leading essentially to an increase of the side products **3** and **4**. Use of chloride, or methyl carbonate as the allylic leaving group, classically exploited in palladium-catalysed allylic substitutions, allowed only slight improvements in the yield of **1** and **2**, the formation of methyl ether **3** remaining in both cases strongly limiting (entries 5 and 6). Finally, use of the less reactive phenoxy leaving group[18] at the allylic position gave the best yields of **1aa** and **2aa**, which almost attained those observed when starting directly from the β-keto ester, to the detriment of the side products **3** and **4** (compare entry 7 of Table 2 with entry 2 of Table 1).

This result indicates that under these conditions methoxycarbonylation of chloroacetone proceeds very efficiently and faster than methoxycarbonylation of the cinnamyl derivative.

The global transformation involves two sequential catalytic cycles, both initiated by an oxidative addition step at the Pd(0) centre (Scheme 4). The former one is started by the α-chloro ketone, whereas the latter one by the allylic derivative. As the product of the former catalytic cycle becomes the substrate for the latter one, the success of this *pseudo*-domino sequence depends on the relative rates of the two cycles. More specifically, the carbonylation rate of the ketone derivative has to be higher than leakage of the allyl derivative from the second cycle to give the side



Scheme 4. Catalytic cycles involved in the *pseudo*-domino sequence. The dashed arrows emphasise the competing oxidative addition paths.

products. If not, the allylic derivative would be irremediably transformed into the ether **3** or the methyl ester **4**, and the tardily generated β-keto ester would not find any more η^3-allyl complex intermediate to intercept.

We believe that the rates of oxidative addition of cinamyl acetate, chloride or methyl carbonate to the palladium (0) centre are higher than or of the same order of magnitude as that of α-chloroacetone. Consequently, when using these leaving groups, products **3** and **4** are obtained in proportions similar to the allylated derivatives **1aa** and **2aa**. On the other hand, use of the less reactive phenoxy leaving group allows the chloro ketone oxidative addition to take place first, thereby permitting the *pseudo*-domino chain to work efficiently. This picture is clearly confirmed by the comparison of the reaction profiles of catalytic runs performed with cinnamyl acetate and phenyl cinnamyl ether (Figure 1). The reaction with cinnamyl acetate is fast and almost complete within 3 h. Both start-

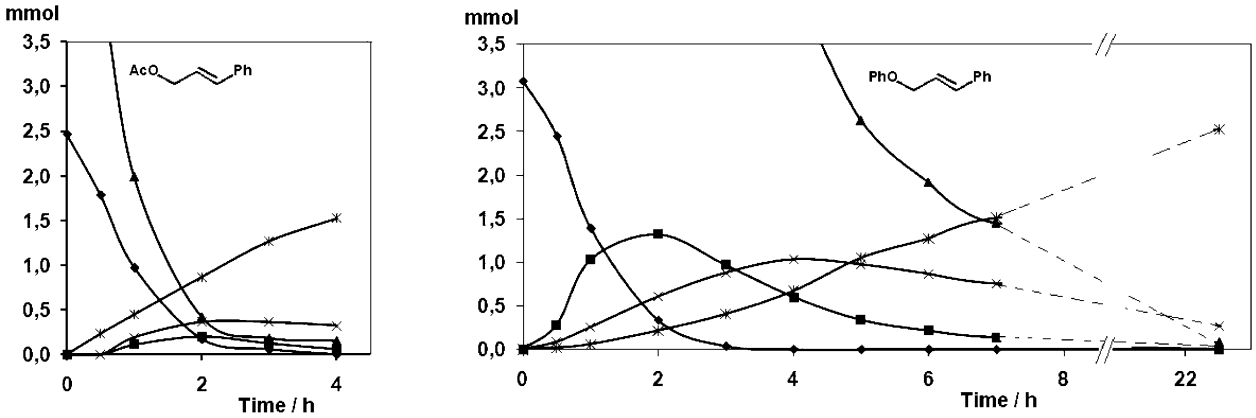
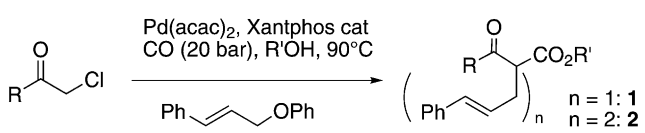


Figure 1. Evolution of the allylic starting material (▲), chloroacetone (◆), methyl acetoacetate(■), reactions products **1** (×) and **2** (✱), during the domino reaction under 20 bar CO. The dotted lines are drawn to guide the eye. The reaction was performed at 70 °C with 6 mmol of chloroacetone, 13.2 mmol of the noted allylic starting material, 27 mmol of tributylamine, 1 mol% of $Pd(acac)_2$, 2 mol% of Xantphos, and 20 mL of distilled MeOH.

ing materials are rapidly converted, and products **1aa** and **2aa** are formed from the early minutes of the reaction. Methyl acetoacetate is only obtained in very small amounts and is likely almost instantaneously converted into the allylated products. On the other hand, the reaction with phenyl cinnamyl ether is much slower and appears to be more sequential. Chloroacetone is still relatively rapidly converted into methyl acetoacetate, whose formation reaches a maximum after 2 h. Due to its lower propensity to oxidatively add to the Pd(0) centre, a delayed consumption of phenyl cinnamyl ether is observed. While most of the cinnamyl acetate has reacted within two hours, more than 8 h of reaction were needed to reach a complete conversion of phenyl cinnamyl ether.

Using these optimised conditions, the scope of the domino reaction was studied with various α-chloro ketones and alcohols (Scheme 5, Table 3).

As MeOH is the main alcohol used in alkoxycarbonylation reactions, we settled to extend our study to other less common alcohols, featuring different electronic and/or steric properties. In the event, *n*-BuOH and *i*-PrOH showed reactivities similar to that observed with MeOH, affording the mono- and bis-allylated β-keto esters with comparable ratios and yields (entries 2 and 3). However, with the latter solvent, generation of the ether **3** was favored, to the detriment of the alkoxycarbonylated ester **4**. This fact suggests that *i*-PrOH intercepts more readily the η^3-allyl palladium complex than its corresponding acylpalladium complex.



Scheme 5. Scope of the reaction.

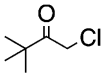
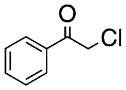
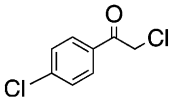
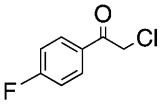
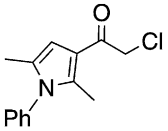
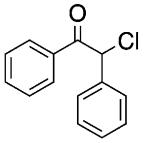
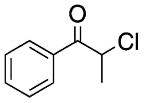
While chloroacetone always led to mixtures of mono- and bis-allylated β-keto esters **1aa** and **2aa**, the analogous reaction with chloropinacolone resulted in the exclusive formation of the mono-allylated product (entry 4). This fact is very likely due to the steric hindrance of the enolate of **1b**, which bears a tetrasubstituted alkene with a vicinal quaternary carbon atom. α-Chloroacetophenone yielded 23% of **1** and 55% of **2** (entry 5). On the other hand, variable and more balanced proportions of allylation products **1** and **2** were obtained on moving to different aryl-substituted chloroketones (entries 6 and 7). With 2-chloro-1-(2,5-dimethyl-1-phenyl-1*H*-pyrrol-3-yl)-1-ethanone (entry 8) the bis-allylated derivative **2** is obtained as minor product. No correlation could be drawn between the electronic effect of the ketone substituent and the **1**/**2** ratio.

Secondary chloro ketones led to the formation of quaternary carbons through the allylic alkylation step. In this case half the amount of allylic starting material was used. The derivatives efficiently yielded the expected products, albeit with lower yields (entries 9–11).

Conclusions

In conclusion, we have shown that the alkoxycarbonylation of α-chloro ketones and their allylic alkylation reactions can be efficiently combined to build a new Pd-catalyzed *pseudo*-domino *type I* sequence wherein the same catalytic system drives the two concatenated cycles. The β-keto ester is intermediately generated through a carbonylation reaction before being *in situ* engaged as nucleophile in the final allylic alkylation cycle. Tuning the allylic leaving group in the starting material, as well as the ancillary ligand proved to be keys to attain the successful combination of the two

Table 3. Scope of the reaction.[a]

Entry	α-Chloro ketone	R′OH	(Yield [%][b]) 1	2
1		MeOH	**1aa** (13)	**2aa** (83)
2		*n*-BuOH	**1ab** (14)	**2ab** (77)
3[c]		*i*-PrOH	**1ac** (12)	**2ac** (85)
4		MeOH	**1b** (62)	**2b** (0)
5		MeOH	**1c** (23)	**2c** (55)
6		MeOH	**1d** (37)	**2d** (39)
7		MeOH	**1e** (30)	**2e** (54)
8		MeOH	**1f** (65)	**2f** (5)
9[d]		MeOH	**1g** (53)	–
10[d]		MeOH	**1h** (20)	–
11[d]		MeOH	**1i** (23)	–

[a] The reaction were carried out at 90 °C using chloro ketone (3.0 mmol), phenylcinamyl phenyl ether (7.5 mmol, 2.5 equiv.), tributylamine (13.5 mmol, 4.5 equiv.), $Pd(acac)_2$ (0.03 mmol), Xantphos (0.06 mmol) in 10 mL of alcohol for 16 h.

[b] Isolated yields calculated from the amount of chloroacetone.

[c] With MeOH, **3** (0.6 mmol) and **4** (0.6 mmol); with *i*-PrOH **3** (1 mmol) and **4** (0.1 mmol).

[d] Reaction performed with 3.75 mmol of phenyl cinnamyl ether.

metal-catalysed reactions in the correct succession. In particular, the use of less reactive phenates allowed great improvements compared to acetates, as revealed by kinetic experiments. Noteworthy, the reaction involves only a single palladium catalyst to promote the two steps at relatively moderate catalyst loadings. Further studies are aimed at applying this procedure to intramolecular domino sequences for the synthesis of highly functionalised cyclic structures.

Experimental Section

General Procedure for the Carbonylation/Allylation Domino Reaction (Table 3)

Reactions were performed in a stainless steel autoclave equipped with a magnetic stirrer. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (34.7 mg, 0.06 mmol), and (*E*)-cinnamyl phenyl ether (1.577 g, 7.5 mmol) were placed in the reactor, and the contents were placed under N_2. In a Schlenk tube, and under N_2, a solution of $Pd(acac)_2$ (9.1 mg, 0.03 mmol), tributylamine (3.2 mL, 13.5 mmol) and chloro ketone (3 mmol) in 10 mL of alcohol was stirred until a homogeneous solution was obtained. Then, this solution was transferred to the reactor with a syringe and the reactor was charged with 15 bar of carbon monoxide. The mixture was stirred at 90 °C for 16 h. Then, the reactor was cooled until room temperature and carefully degassed. The mixture was diluted with diethyl ether, washed with an HCl solution (1 N), followed by an NaOH solution (1 N) until neutralisation, dried over $MgSO_4$ and concentrated under vacuum. After flash column chromatography on silica gel (petroleum ether/ethyl acetate 100:0 to 90:10), the mono-allylated, bis-allylated, ether and ester were isolated.

(*E*)-Methyl 2-acetyl-2-cinnamyl-5-phenylpent-4-enoate (2aa): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.27$–7.14 (m, 10 H, Ph), 6.40 (d, 2 H, $J = 15.0$ Hz, Ph-CH), 5.94 (dt, 2 H, $^3J = 15.0$, 7.5 Hz, CH-CH_2), 3.68 (s, 3 H, O-CH_3), 2.79 (br dd, $J = 7.5$, 14.5 Hz, 2 H, CH_2), 2.72 (br dd, $J = 7.5$, 14.5 Hz, 2 H, CH_2), 2.18 (s, 3 H, O=C−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 204.2$ (CH_3−C=O), 172.1 (O−C=O), 137.0 (C_{Ar}), 134.3 (CH=CH<−CH_2), 128.6 (CH_{Ar}), 127.6 (CH_{Ar}), 126.3 (CH_{Ar}), 123.7 (CH=CH−CH_2), 64.0 (O=C−C−C=O), 52.6 (O−CH_3), 35.9 (CH_2−CH=CH), 27.3 (O=C−CH_3); HR-MS (ESI): $m/z = 349.18034$, calcd. for $C_{23}H_{25}O_3$ [M + H$^+$]: 349.17982.

(*E*)-Butyl 2-acetyl-2-cinnamyl-5-phenylpent-4-enoate (2ab): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.33$–7.23 (m, 10 H, H_{Ar}), 6.47 [d, 2 H, $J = 15.0$ Hz, (−CH=CH−CH_2−)$_2$], 6.03 [dt, 2 H, $J = 15.0$, 7.5 Hz, (CH=CH−CH_2−)$_2$], 4.18 (t, $J = 7.2$ Hz, 2 H, CH_2), 2.88 (br dd, $J = 7.5$, 14.5 Hz, 2 H, CH_2), 2.80 (br dd, $J = 7.5$, 14.5 Hz, 2 H, CH_2), 2.22 (s, 3 H, O=C−CH_3), 1.63 (quint, $J = 7.2$ Hz, 2 H, O−CH_2−CH_2), 1.37 (sext, $J = 7.2$ Hz, 2 H, O−CH_2−CH_2), 0.92 (t, $J = 7.2$ Hz, 3 H, CH_2−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 204.3$ (CH_3−C=O), 171.7 (O−C=O), 137.0 (C_{Ar}), 134.2 (CH=CH−CH_2), 128.6 (CH_{Ar}), 127.6 (CH_{Ar}), 126.3 (CH_{Ar}), 123.8 (CH=CH−CH_2), 65.5 (CH_2−CH_2−CH_2), 64.0 (O=C−C−C=O), 35.9 (CH_2−CH=CH), 30.6 (CH_2−CH_2−CH_2), 27.3 (O=C−CH_3), 19.3 (CH_2−CH_3), 13.7 (CH_2−CH_3); HR-MS (ESI): $m/z = 391.22738$, calcd. for $C_{26}H_{31}O_3$ [M + H$^+$]: 391.22677.

(*E*)-Isopropyl 2-acetyl-5-phenylpent-4-enoate (1ac): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.23$–7.13 (m, 5 H, H_{Ar}), 6.38 (d, $J = 16.0$ Hz, 1 H, −CH=CH−CH_2−), 6.04 (dt, $J = 16.0$, 6.0 Hz, 1 H, −CH=CH−CH_2−), 5.00 (sept, $J = 6.3$ Hz, 1 H, O−CH), 3.48 (t, $J = 7.4$ Hz, 1 H, O=C−CH), 3.48 (t, $J = 7.4$ Hz, 2 H, CH_2), 2.18 (s, 3 H, O=C−CH_3), 1.17 (d, $J = 6.0$ Hz, 3 H, CH−CH_3), 1.16 (d, $J = 6.0$ Hz, 3 H, CH−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 202.7$ (CH_3−C=O), 168.9 (O−C=O), 137.1 (C_{Ar}), 132.8 (CH=CH−CH_2), 128.6 (CH_{Ar}), 127.5 (CH_{Ar}), 126.3 (CH_{Ar}), 125.9 (CH=CH−CH_2), 69.3 [$(CH_3)_2$−CH], 59.9 (CH_2−CH−C=O), 31.6 (CH_2−CH=CH),

29.3 (O=C−CH_3), 21.9 (CH−CH_3), 21.8 (CH−CH_3); HR-MS (ESI): m/z = 261.14857, calcd. for $C_{16}H_{21}O_3$ [M+H$^+$]: 261.14852.

(*E*)-Isopropyl 2-acetyl-2-cinnamyl-5-phenylpent-4-enoate (2ac): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.24–7.15 (m, 10H, H_{Ar}), 6.39 [d, 2H, J = 15.0 Hz, (−CH=CH−CH_2−)$_2$], 5.95 [dt, 2H, J = 15.0, 7.5 Hz, (CH=CH−CH_2−)$_2$], 5.02 (sept, J = 6.3 Hz, 1H, O−CH), 2.77 (br dd, J = 7.5, 14.5 Hz, 2H, CH_2), 2.70 (br dd, J = 7.5, 14.5 Hz, 2H, CH_2), 2.13 (s, 3H, O=C−CH_3), 1.17 [d, J = 6.0 Hz, 6H, $(CH_3)_2$]; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 204.3 (CH_3−C=O), 171.0 (O−C=O), 137.0 (C_{Ar}), 134.0 (CH=CH−CH_2), 128.5 (CH_{Ar}), 127.5 (CH_{Ar}), 126.2 (CH_{Ar}), 123.7 (CH=CH−CH_2), 69.2 [$(CH_3)_2$−CH], 63.8 (O=C−C−C=O), 35.7 (CH_2−CH=CH), 27.1 (O=C−CH_3), 21.7 [$(CH_3)_2$]; HR-MS (ESI): m/z = 377.21170, calcd. for $C_{25}H_{29}O_3$ [M+H$^+$]: 377.21112.

(*E*)-Methyl 5-phenyl-2-pivaloylpent-4-enoate (1b): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.28 (m, 5H, H_{Ar}), 6.46 (d, J = 16.0 Hz, 1H, −CH=CH−CH_2−), 6.12 (dt, J = 16.0, 7.0 Hz, 1H, −CH=CH−CH_2−), 4.07 (dd, J = 7.2, 7.2 Hz, 1H, CH), 3.72 (s, 3H, O−CH_3), 2.77 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2), 2.73 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2), 1.19 [s, 9H, $(CH_3)_3$]; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 209.5 [$(CH_3)_3$CH−C=O), 169.8 (O−C=O), 137.1 (C_{Ar}), 132.8 (CH=CH−CH_2), 128.6 (CH_{Ar}), 127.5 (CH_{Ar}), 126.2 (CH=CH−CH_2 and CH_{Ar}), 52.5 (O−CH_3 and CH−C=O), 45.5 [$C(CH_3)_3$], 33.5 (CH_2−CH=CH), 26.2 [$(CH_3)_3$]; HR-MS (ESI): m/z = 275.16441, calcd. for $C_{17}H_{23}O_3$ [M+H$^+$]: 275.16417.

(*E*)-Methyl 2-benzoyl-5-phenylpent-4-enoate (1c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.94 (d, J = 8.0 Hz, 2H, H_{ortho}), 7.52 (t, J = 7.5 Hz, 1H, H_{para}), 7.42 (t, J = 7.6 Hz, 2H, H_{meta}), 7.22–7.13 (m, 5H, H_{Ar}), 6.40 (d, J = 16.0 Hz, 1H, −CH=CH−CH_2−), 6.14 (dt, J = 16.0, 7.0 Hz, 1H, -CH=CH−CH_2−), 4.42 (dd, J = 7.2, 7.2 Hz, 1H, CH), 3.62 (s, 3H, O−CH_3), 2.85 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2), 2.83 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.5 (Ph−C=O), 170.0 (O−C=O), 137.2 (C_{Ar}), 136.2 (C_{Ar}), 133.8 (CH=CH−CH_2), 132.9 (CH_{Ar}), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 127.5 (CH_{Ar}), 126.3 (CH_{Ar}), 126.1 (CH=CH−CH_2), 54.2 (CH_2−CH−C=O), 52.7 (O−CH_3), 32.6 (CH_2−CH=CH); HR-MS (ESI): m/z = 295.13306, calcd. for $C_{19}H_{19}O_3$ [M+H$^+$]: 295.13287.

(*E*)-Methyl 2-benzoyl-2-cinnamyl-5-phenylpent-4-enoate (2c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.88 (d, J = 8.0 Hz, 2H, H_{ortho}), 7.57 (t, J = 7.5 Hz, 1H, H_{para}), 7.47 (t, J = 7.6 Hz, 2H, H_{meta}), 7.34–7.22 (m, 10H, H_{Ar}), 6.38 [d, J = 16.0 Hz, 2H, (−CH=CH−CH_2−)$_2$], 6.02 [dt, J = 16.0, 7.5 Hz, 2H, (−CH=CH−CH_2−)$_2$], 3.69 (s, 3H, O−CH_3), 3.06 (br dd, J = 7.5, 14.5 Hz, 2H, CH_2), 2.99 (br dd, J = 7.5, 14.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 196.2 (Ph−C=O), 176.3 (O−C=O), 137.2 (C_{Ar}), 136.0 (C_{Ar}), 134.4 (CH=CH−CH_2), 133.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 127.6 (CH_{Ar}), 126.4 (CH_{Ar}), 123.6 (CH=CH−CH_2), 61.4 (O=C−C−C=O), 52.6 (O−CH_3), 37.1 (CH_2−CH=CH); HR-MS (ESI): m/z = 411.19575, calcd. for $C_{28}H_{27}O_3$ [M+H$^+$]: 411.19547.

(*E*)-Methyl 2-(4-chlorobenzoyl)-5-phenylpent-4-enoate (entry 1d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.88 (d, J = 8.0 Hz, 2H, H_{ortho}), 7.38 (d, J = 8.0 Hz, 2H, H_{meta}), 7.22–7.14 (m, 5H, H_{Ar}), 6.40 (d, J = 16.0 Hz, 1H, −CH=CH−CH_2−), 6.09 (dt, J = 16.0, 7.0 Hz, 1H, −CH=CH−CH_2−), 4.36 (dd, J = 7.2, 7.2 Hz, 1H, CH), 3.62 (s, 3H, O−CH_3), 2.83 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2), 2.81 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.3 (Ar−C=O), 169.7 (O−C=O), 140.4 (C_{Ar}), 137.0 (C_{Ar}), 134.5 (C_{Ar}), 133.0 (CH=CH−CH_2), 130.2 (CH_{Ar}), 129.3 (CH_{Ar}), 128.6 (CH_{Ar}), 127.6 (CH_{Ar}), 126.3 (CH_{Ar}), 125.8 (CH=CH−CH_2), 54.2 (CH_2−CH−C=O), 52.8 (O−CH_3), 32.5 (CH_2−CH=CH); HR-MS (ESI): m/z = 329.09433, calcd. for $C_{19}H_{18}ClO_3$ [M+H$^+$]: 329.09390.

(*E*)-Methyl 2-(4-chlorobenzoyl)-2-cinnamyl-5-phenylpent-4-enoate (2d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.74 (d, J = 8.0 Hz, 2H, H_{ortho}), 7.35 (d, J = 8.0 Hz, 2H, H_{meta}), 7.22–7.13 (m, 10H, H_{Ar}), 6.29 [d, J = 16.0 Hz, 2H, (−CH=CH−CH_2−)$_2$], 5.89 [dt, J = 16.0, 7.5 Hz, 2H, (−CH=CH−CH_2−)$_2$], 3.60 (s, 3H, O−CH_3), 2.95 (br dd, J = 7.5, 14.5 Hz, 2H, CH_2), 2.87 (br dd, J = 7.5, 14.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 195.0 (Ar−C=O), 173.2 (O−C=O), 139.6 (C_{Ar}), 137.1 (C_{Ar}), 134.6 (C_{Ar}), 134.3 (CH=CH−CH_2), 130.0 (CH_{Ar}), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 127.7 (CH_{Ar}), 126.4 (CH_{Ar}), 123.3 (CH=CH−CH_2), 61.4 (O=C−C−C=O), 52.7 (O−CH_3), 37.1 (CH_2−CH=CH); HR-MS (ESI): m/z = 445.15802, calcd. for $C_{28}H_{26}ClO_3$ [M+H$^+$]: 445.15650.

(*E*)-Methyl 2-(4-fluorobenzoyl)-5-phenylpent-4-enoate (1e): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.07 (m, 2H, H_{Ar}), 7.38–7.14 (m, 7H, H_{Ar}), 6.50 [d, J = 16.0 Hz, 2H, (−CH=CH−CH_2−)$_2$], 6.19 [dt, J = 16.0, 7.0 Hz, 2H, (−CH=CH−CH_2−)$_2$], 4.47 (dd, J = 7.2, 7.2 Hz, 1H, CH), 3.72 (s, 3H, O−CH_3), 2.94 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2), 2.92 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.8 (Ar−C=O), 169.7 (O−C=O), 137.0 (C_{Ar}), 132.9 (C_{Ar}), 131.5 (C_{Ar}), 131.4 (CH=CH−CH_2), 128.5 (CH_{Ar}), 127.4 (CH_{Ar}), 126.2 (CH_{Ar}), 125.8 (CH_{Ar}), 116.2 (CH_{Ar}), 115.9 (CH=CH−CH_2), 54.1 (CH_2−CH−C=O), 52.7 (O−CH_3), 32.4 (CH_2−CH=CH); HR-MS (ESI): m/z = 313.12385, calcd. for $C_{19}H_{18}FO_3$ [M+H$^+$]: 313.12345.

(*E*)-Methyl 2-cinnamyl-2-(4-fluorobenzoyl)-5-phenylpent-4-enoate (2e): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.93 (m, 2H, H_{Ar}), 7.38–7.21 (m, 10H, H_{Ar}), 7.15 (m, 2H, H_{Ar}), 6.39 [d, J = 16.0 Hz, 2H, (−CH=CH−CH_2−)$_2$], 5.99 [dt, J = 16.0, 7.5 Hz, 2H, (−CH=CH−CH_2−)$_2$], 3.69 (s, 3H, O−CH_3), 3.05 (br dd, J = 7.5, 14.5 Hz, 2H, CH_2), 2.98 (br dd, J = 7.5, 14.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.6 (Ar−C=O), 173.3 (O−C=O), 137.1 (C_{Ar}), 134.6 (C_{Ar}), 131.4 (C_{Ar}), 131.2 (CH=CH−CH_2), 128.7 (CH_{Ar}), 127.6 (CH_{Ar}), 126.4 (CH_{Ar}), 123.4 (CH_{Ar}), 116.1 (CH_{Ar}), 115.8 (CH=CH−CH_2), 61.3 (O=C−C−C=O), 52.7 (O−CH_3), 37.1 (CH_2−CH=CH); HR-MS (ESI): m/z = 429.18749, calcd. for $C_{28}H_{26}FO_3$ [M+H$^+$]: 429.18605.

(*E*)-Methyl 2-(2,5-dimethyl-1-phenyl-1*H*-pyrrole-3-carbonyl)-5-phenylpent-4-enoate (1f): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.52–7.46 (m, 3H, H_{Ar}), 7.34–7.16 (m, 7H, H_{Ar}), 6.49 (d, J = 16.0 Hz, 1H, −CH=CH−CH_2−), 6.40 (s, 1H, $CH_{pyrrole}$), 6.23 (dt, J = 16.0, 6.0 Hz, 1H, −CH=CH−CH_2−), 4.20 (t, J = 7.2 Hz, 1H, CH), 3.74 (s, 3H, O−CH_3), 2.90 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2), 2.88 (ddd, J = 7.0, 7.2, 14.5 Hz, 1H, CH_2), 2.32 (s, 3H, $CH_{3pyrrole}$), 1.98 (s, 3H, $CH_{3pyrrole}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 190.3 (pyrr−C=O), 170.8 (O−C=O), 138.0 (C_{Ar}), 137.4 (C_{Ar}), 137.1 (C_{Ar}) 132.1 (C_{Ar}), 129.5 (C_{Ar}), 129.2 (CH=CH−CH_2), 128.8 (CH_{Ar}), 128.5 (CH_{Ar}), 128.0 (CH_{Ar}), 127.2 (CH_{Ar}), 127.1 (CH_{Ar}), 126.2 (CH_{Ar}), 119.3 (CH=CH-CH_2), 107.6 ($CH_{pyrrole}$), 56.0 (O=C−CH−), 52.3 (O−CH_3), 32.7 (CH_2), 13.2 ($CH_{3pyrrole}$), 12.8 ($CH_{3pyrrole}$); HR-MS (ESI): m/z = 388.19156, calcd. for $C_{25}H_{26}NO_3$ [M$^+$]: 388.19072.

(*E*)-Methyl 2-acetyl-2-methyl-5-phenylpent-4-enoate (1g): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.33$–7.23 (m, 5H, H_{Ar}), 6.45 (d, $J = 16.0$ Hz, 1H, −CH=CH−CH_2−), 6.06 (dt, $J = 16.0$, 6.0 Hz, 1H, −CH=CH−CH_2−), 3.76 (s, 3H, O−CH_3), 2.81 (br dd, $J = 7.5$, 14.5 Hz, 2H, CH_2), 2.67 (br dd, $J = 7.5$, 14.5 Hz, 2H, CH_2), 2.20 (s, 3H, O=C−CH_3), 1.41 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 205.1$ (CH_3−C=O), 173.0 (O−C=O), 137.0 (C_{Ar}), 134.0 (CH=CH−CH_2), 128.5 (CH_{Ar}), 127.4 (CH_{Ar}), 126.2 (CH_{Ar}), 124.2 (CH=CH−CH_2), 59.9 (O=C−C−C=O), 52.5 (O−CH_3), 38.7 (CH_2−CH=CH), 26.4 (O=C−CH_3), 19.2 (CH_3); HR-MS (ESI): $m/z =$ 247.13340, calcd. for $C_{15}H_{19}O_3$ [M + H$^+$]: 247.13287.

(*E*)-methyl 2-benzoyl-2,5-diphenylpent-4-enoate (1h): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.65$ (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.53 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.33–7.11 (m, 11H, H_{Ar}), 6.18 (d, $J = 16.0$ Hz, 1H, −CH=CH−CH_2−), 6.06 (dt, $J = 16.0$, 6.0 Hz, 1H, −CH=CH−CH_2−), 3.51 (s, 3H, O−CH_3), 3.25 (br dd, $J = 7.5$, 14.5 Hz, 2H, CH_2), 2.96 (br dd, $J = 7.5$, 14.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 195.1$ (Ph−C=O), 171.5 (O−C=O), 138.2 (C_{Ar}), 137.4 (C_{Ar}), 135.8 (C_{Ar}), 133.8 (CH−CH−CH_2), 132.7 (CH_{Ar}), 129.7 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.3 (CH_{Ar}), 128.0 (CH_{Ar}), 127.6 (CH_{Ar}), 127.4 (CH_{Ar}), 126.3 (CH_{Ar}), 124.9 (CH=CH−CH_2), 66.3 (O=C−C−C=O), 52.5 (O−CH_3), 43.6 (CH_2−CH=CH); HR-MS (ESI): $m/z = 371.16519$, calcd. for $C_{25}H_{23}O_3$ [M + H$^+$]: 371.16417.

(*E*)-Methyl 2-benzoyl-2-methyl-5-phenylpent-4-enoate (1i): ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.86$ (d, $J = 8.0$ Hz, 2H, H_{ortho}), 7.56 (t, $J = 7.5$ Hz, 1H, H_{para}), 7.46 (t, $J = 7.6$ Hz, 2H, H_{meta}), 7.31–7.22 (m, 5H, H_{Ar}), 6.39 (d, $J = 16.0$ Hz, 1H, −CH=CH−CH_2−), 6.07 (dt, $J = 16.0$, 6.0 Hz, 1H, −CH=CH−CH_2−), 3.67 (s, 3H, O−CH_3), 2.98 (br dd, $J = 7.5$, 14.5 Hz, 2H, CH_2), 2.89 (br dd, $J = 7.5$, 14.5 Hz, 2H, CH_2), 1.59 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 197.0$ (Ph−C=O), 174.3 (O−C=O), 137.1 (C_{Ar}), 135.4 (C_{Ar}), 134.0 (CH=CH−CH_2), 132.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 127.4 (CH_{Ar}), 126.3 (CH_{Ar}), 124.1 (CH=CH−CH_2), 57.3 (O=C−C−C=O), 52.5 (O−CH_3), 40.4 (CH_2−CH=CH), 21.3 (CH_3); HR-MS (ESI): $m/z = 309.14909$, calcd. for $C_{20}H_{21}O_3$: 309.14852 [M + H$^+$].

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