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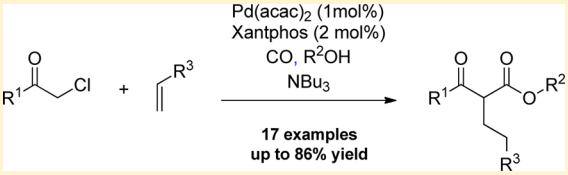
Synthesis of α-Alkylated β-Ketoesters by Alkoxycarbonylation/Michael Addition Domino Reaction

Benoit Wahl, Yann Philipson, Hélène Bonin, André Mortreux, and Mathieu Sauthier*

Unité de Catalyse et Chimie du Solide, UMR CNRS 8181, Université Lille Nord de France, ENSCL BP 90108, 59652 Villeneuve d'Ascq, France

Supporting Information

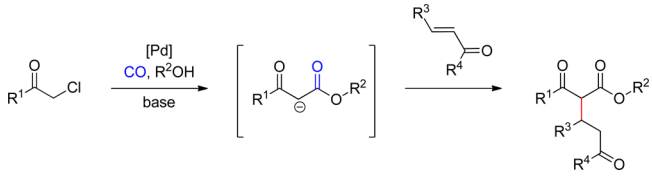
ABSTRACT: The palladium-catalyzed alkoxycarbonylation of an α-chloro ketone can be efficiently combined to a Michael addition reaction in a new two-step domino reaction, allowing the synthesis of original highly functionalized α-alkylated β-ketoesters. The scope of the reaction was extended to several α-chloro ketones and Michael acceptors with moderate to very good yields.



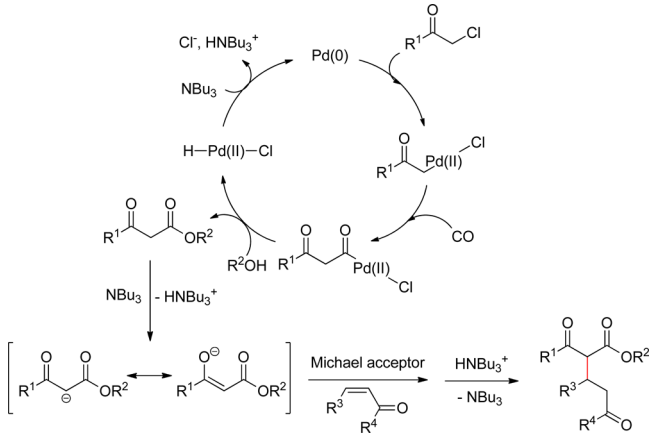
INTRODUCTION

Domino-type transformations have recently emerged as a green and powerful synthetic tool since they allow the reduction of the environmental impact of multistep synthesis by reducing the number of purification procedures.[1,2] One-pot transformations involving a carbonylation step are of particular interest since carbon monoxide is a cheap carbonyl source which is moreover totally incorporated in the final product.[3−5] Several examples of domino-type transformations including carbonylative steps, such as multicomponent carbonylative coupling reactions,[6] hydroformylation/acetal formation and related sequences,[7] or allylic alkylation/Pauson−Khand reactions,[8,9] have already been reported in the literature. In this field, we recently studied palladium-catalyzed domino processes under carbonylative conditions by developing a new palladium-catalyzed pseudo-domino type I sequence combining the alkoxycarbonylation of an α-chloro ketone and the subsequent allylic alkylation of the β-ketoester intermediate.[10] We also developed the palladium-catalyzed pseudodomino carbonylative/decarboxylative allylation of α-chloro ketones that represents a new selective method for the monoallylation of carbonyl compounds.[11] In both cases, the domino sequences involved the methoxycarbonylation of a chloro ketone[12] yielding a β-ketoester, followed by a second palladium-catalyzed step to build additional carbon−carbon bonds. Such sequences are possible only if the two metal-catalyzed reactions are fully compatible with each other. In particular, the second step has to be compatible with the presence of carbon monoxide, which can act as a ligand to palladium and can thus readily block the catalytic reaction by coordinating the metal center. However, this difficulty is obviously overcome in the case of a noncatalyzed second step. Aiming at developing original carbonylative domino sequences, we now wish to report a new domino reaction involving, in a first step, the palladium-catalyzed alkoxycarbonylation of an α-chloro ketone, followed, in a second step, by the addition of the enolate intermediate species to a Michael acceptor to yield new highly functionalized α-alkylated-β-ketoester (Schemes 1 and 2). Several examples of domino reactions including a Michael addition step have been reported in the literature,[13−19] but to the best of our knowledge, this work represents the first example in which the Michael donor is in situ generated via an alkoxycarbonylation reaction.

Scheme 1. Alkoxycarbonylation/Michael Addition Domino Reaction



Scheme 2. Mechanism of the Palladium-Catalyzed Alkoxycarbonylation/Michael Addition Domino Reaction



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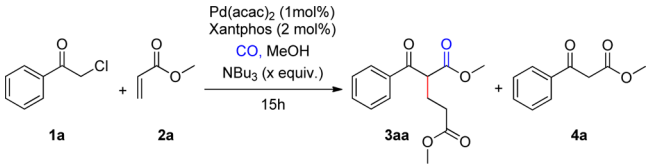
RESULTS/DISCUSSION

Our preliminary task consisted of verifying the feasibility and the compatibility of both reactions involved in the domino sequence as the presence of a reactive acrylate could potentially interfere with the palladium-catalyzed reaction. We had already showed that the best catalytic system for the alkoxycarbonylation reaction consisted of 2 equiv of Xantphos as an ancillary ligand for 1 equiv of palladium (usually [Pd(acac)$_2$], 0.5 mol %).[12] To our great pleasure, early experiments showed that the tri-*n*-butylamine was suitable for both alkoxycarbonylation and Michael addition steps. The tri-*n*-butylamine/tri-*n*-butylammonium chloride buffer, obtained after the alkoxycarbonylation step, was thus basic enough to deprotonate the intermediate *β*-ketoester. We consequently investigated the optimization of the reaction conditions with tri-*n*-butylamine using 2-chloroacetophenone and methyl acrylate as model substrates in the presence of [Pd(acac)$_2$] as palladium source in methanol (Table 1).

Table 1. Methoxycarbonylation/Michael Addition of 2-Chloroacetophenone 1a and Methyl Acrylate 2a: Optimization of the Reaction Conditions[a]



entry	NBu_3 (equiv)	2a (equiv)	T (°C)	CO (bars)	3aa[b] (%)	4a[b] (%)
1	1.2		90	10		68
2	**1.2**	2.5	90	10	26	47
3	**1.5**	2.5	90	10	31	31
4	**2**	2.5	90	10	57	18
5	**3**	2.5	90	10	67	14
6	**4.5**	2.5	90	10	63	14
7	3	**1.2**	90	10	27	41
8	3	**1.2**[c]	90	10	35	39
9	3	**4**	90	10	**73**	**5**
10	3	4	90	**5**	62	14
11	3	4	90	**20**	75	5
12	3	4	90	**40**	73	5
13	3	4	**70**	10	52	27
14	3	4	**110**	10	72	1

[a]Reaction conditions: 2-chloroacetophenone (1 equiv, 3 mmol), methyl acrylate (1.2−4 equiv), NBu_3 (1.2−4.5 equiv), [Pd(acac)$_2$] (1 mol %), Xantphos (2 mol %), CO (5−40 bar), MeOH (10 mL), 70−110 °C, 15 h. [b]Determined by gas chromatography. [c]1 mol % of hydroquinone was added.

In the absence of methyl acrylate **2a**, the reaction yielded 68% of the expected methyl 3-oxo-3-phenylpropanoate **4a** (entry1). In the presence of 2.5 equiv of methyl acrylate, the desired domino product **3aa** could be observed, together with the intermediate *β*-ketoester **4a** after 15 h of reaction (entry 2). Although the major product was the *β*-ketoester, a significant and encouraging amount of the desired product could be obtained (26%), proving the feasibility of the domino sequence. Stronger bases cannot be used as they are known to be detrimental to the carbonylation reaction; the yield could, however, be raised by increasing the quantity of NBu_3 (entries 3−6) with an optimum reached for 3 equiv of NBu_3 (67%, entry 5). Increasing the amount of Michael acceptor **2a** to 4 equiv allowed us to reach an optimized yield of 73% in 15 h (entry 9). The addition of 1 mol % of hydroquinone to prevent the potential competitive radical polymerization of methyl acrylate proved to be ineffective (entry 7 vs 8). It is noteworthy that a minimum of 10 bar CO pressure is required to reach good yields (entries 10−12) as well as a temperature of 90 °C (entries 13 and 14).

A kinetic study was done under the optimized conditions by analyzing the composition of the reaction mixture by gas chromatography (Figure 1). This experiment evidenced the

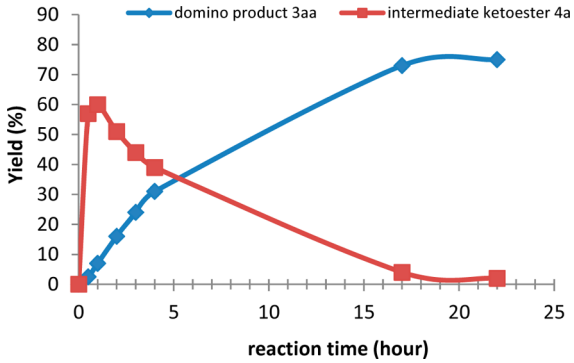


Figure 1. Evolution of the formation of the intermediate *β*-ketoester **4a** and the expected product **3aa** (reaction performed at 90 °C, under 10 bar CO, with 6 mmol of 2-chloroacetophenone, 24 mmol of methyl acrylate, 18 mmol of NBu_3, 1 mol % of [Pd(acac)$_2$], 2 mol % of Xantphos, and 20 mL of distilled MeOH).

expected fast formation of the ketoester **4a** under these conditions. The presence of the activated olefin does not prevent the palladium-catalyzed transformation. However, the Michael addition proved to be much slower than the alkoxycarbonylation step in these conditions. Whereas the first step is over in less than 1 h, the second step requires almost 22 h to lead to completion, in agreement with the fact that Michael additions promoted by weak bases are usually quite slow and require long reaction times.[20]

With these optimized conditions in hands, the scope of reaction was then extended using several *α*-chloro ketones with methyl acrylate in MeOH (Table 2). Since the rate of the Michael addition step is quite slow and dependent on the nature of the nucleophile, the reaction time had thus to be optimized for each substrate. The reaction mixture was analyzed by GC in order to check the remaining amount of intermediate *β*-ketoester after 15 h, and the reaction was run until no more ketoester could be detected.

Chloro ketones bearing an electron-withdrawing group in the *para*-position of the phenyl group (**1b−d**) were converted with moderate to good yields (entries 2−4, 49−70%) with, however, slower reaction rates in the presence of strong electron-withdrawing groups on the aryl moiety. The low yield observed with the *p*-carbomethoxyphenyl derivative (**1d**, entry 4) could be explained by the formation of the double Michael adduct. 2-chloro-1-(2,5-dimethyl-1-phenyl-1*H*-pyrrol-3-yl)-1-ethanone **1e** could not be converted to the desired product **3ea**, although the formation of the intermediate *β*-ketoester (49% after 33h of reaction) could be detected (entry 5). The use of chloroacetone **1f** led to a low yield of **3fa** (27%, entry 6), but the formation of the double Michael adduct was observed as well. Finally, when the chloropinacolone **1g** was used, a GC yield of 30% of **3ga**

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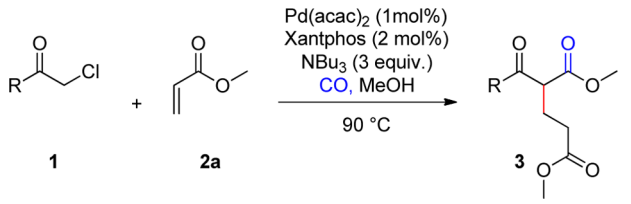
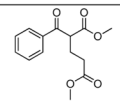
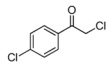
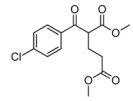
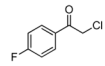
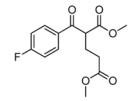
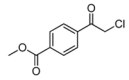
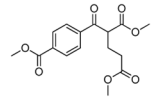
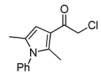
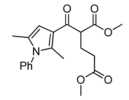
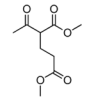
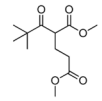
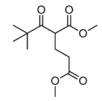
Table 2. Scope of the Reaction with Various Chloro Ketones and Methyl Acrylate in MeOH[a]



Entry	Chloroketone		Product		Reaction time (h)	Yield (%)[b]
1		**1a**		**3aa**	15	76
2		**1b**		**3ba**	15	70
3		**1c**		**3ca**	35	70
4		**1d**		**3da**	86	49
5		**1e**		**3ea**	>100	0
6		**1f**		**3fa**	15	27
7		**1g**		**3ga**	141	(30)
8		**1g**		**3ga**	85	(13)

[a]Reaction conditions: chloro ketone (3 mmol), [Pd(acac)$_2$] (1 mol %), Xantphos (2 mol %), NBu_3 (3 equiv), methyl acrylate (4 equiv), CO (10 bar), MeOH (10 mL), 90 °C. [b]Isolated yield (GC yield).

was obtained despite a prolonged reaction time of 141 h, the major compound being the intermediate β-ketoester (66%, entry 7). The use of a stronger base, such as the proton sponge, did not improve the Michael addition product yield (85% intermediate ketoester remaining after 85 h, entry 8).

The domino reaction was then performed using other Michael acceptors such as methyl vinyl ketone (MVK) **2b** or cyclic enones **2c** and **2d** (Table 3) to yield original highly functionalized products.

Interestingly, the intermediate ketoesters that had showed low reactivities with methyl acrylate were fully converted when MVK was used (Table 3, entries 2−3 vs Table 2, entries 5 and 7), even though long reaction times were required. Cyclohexanone **2c** and cyclopentenone **2d** could also be successfully used to afford the expected products with good to excellent yields (Table 3, entries 4−7, 71−86%). The reaction was also efficient with 3-chloro-2-butanone **1h**, a secondary chloro ketone, however requiring a long reaction time (58 h instead of 15 h, 71% GC yield, entry 6). The product was isolated with an unsatisfactory purity. With acrylonitrile **2e** or dimethyl fumarate **2f** as Michael acceptors, disappointing yields were obtained (Table 3, entries 8 and 9). Indeed, after 15 h of reaction, 50% and 30%, respectively, of the intermediate ketoesters were still remaining in the reaction mixture. However, the yields of Michael addition products could not be improved even after prolonged reaction times. Finally, we were pleased to find that acrolein was an interesting reactant. Indeed, the unexpected and original enal spiro derivative **3ah** was isolated as the major product albeit in modest yield (20% isolated yield). The formation of this compound can be explained by the addition of the ketoester to two molecules of acrolein, followed by an intramolecular aldolization/crotonization step leading to the cyclized conjugated compound (Scheme 3). Compound **3ah** is thus obtained from an original multistep reaction that combines inter- and intramolecular transformations, thus showing the high complexity that can be attained through this type of domino transformation.

Finally, we also extended the scope of the reaction to secondary and tertiary alcohols. The reaction turned out to be efficient with 2-propanol (Table 4, entry 1), whereas the yield with the bulkier 2-methyl-2-propanol was not satisfactory even after prolonged reaction times (Table 4, entry 2).

In conclusion, we have developed a new simple and efficient two-step domino reaction starting from α-chloro ketones and carbon monoxide and involving an alkoxycarbonylation reaction followed by a Michael addition. Using optimized conditions, we could prepare highly functionalized α-alkylated-β-ketoesters, including 12 original products, with good yields using the same base in a one-pot reaction. The scope of the domino reaction could be extended to primary and secondary chloro ketones with various Michael acceptors, including methyl acrylate, methyl vinyl ketone, and cyclic enones.

EXPERIMENTAL SECTION

General remarks concerning the reactants, solvents, or equipment used, as well as NMR and HRMS spectra, are given in the Supporting Information.

General Procedure for the Alkoxycarbonylation/Michael Addition Domino Reaction. Reactions were performed in a stainless steel autoclave equipped with a magnetic stirrer. [Pd(acac)$_2$] (9.1 mg, 0.03 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene (34.7 mg, 0.06 mmol), and α-chloro ketone (3 mmol) were weighted and placed in the autoclave under N_2. Then, by using syringes, 10 mL of alcohol, *n*-tributylamine (9 mmol), and the Michael acceptor were successively added into the reactor. The reactor was charged with 10 bar of carbon monoxide, and the mixture was stirred at 90 °C for 15 h. After being cooled at room temperature, the reactor was carefully degassed. The mixture was diluted with diethyl ether, washed with a HCl solution (1 N) and water, dried over $MgSO_4$, and concentrated under vacuum. After flash chromatography column on silica gel (petroleum ether/ethyl acetate 90:10 to 80:20), the domino reaction product was isolated.

Dimethyl 2-benzoylpentanedioate (3aa): yellowish oil; R_f = 0.30 (petroleum ether/ethyl acetate 80:20); yield 76%, 528 mg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04−8.00 (m, 2H), 7.62−7.56 (m, 1H), 7.52−7.45 (m, 2H), 4.52 (t, J = 7.1 Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 2.48−2.42 (m, 2H), 2.34−2.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 173.3, 170.1, 136.0, 133.8, 128.9, 128.9, 52.7, 52.6, 51.8, 31.4, 24.1; HRMS (ESI-) calcd for $C_{14}H_{15}O_5$ [M − H]$^-$ 263.0925, found 263.09122.

Dimethyl 2-(4-chlorobenzoyl)pentanedioate (3ba): yellowish oil; R_f = 0.15 (petroleum ether/ethyl acetate 90:10); yield 70%, 302 mg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 4.47 (t, J = 7.0 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 2.43 (t, J = 7.0 Hz, 2H), 2.27 (q, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 172.7, 169.4, 139.7, 133.9, 129.9, 128.8, 52.1, 52.0,

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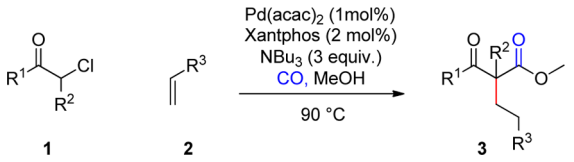
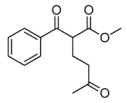
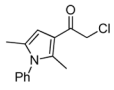
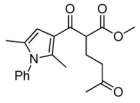
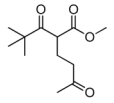
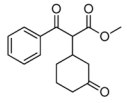
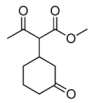
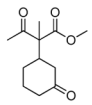
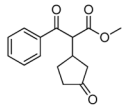
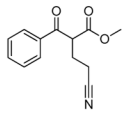
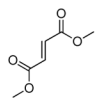
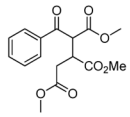
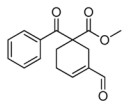
Table 3. Scope of the Reaction with Various Chloro Ketones and Other Michael Acceptors in MeOH[a]



1 2 3

Entry	Chloroketone		Michael acceptor		Product		Reaction time (h)	Yield (%)[b]
1		**1a**		**2b**		**3ab**	15	74
2[c]		**1e**		**2b**		**3eb**	250	73
3		**1g**		**2b**		**3gb**	43	85
4[c]		**1a**		**2c**		**3ac**	15	86
5[c]		**1f**		**2c**		**3fc**	15	75
6[c]		**1h**		**2c**		**3hc**	58	(71)[d]
7[c]		**1a**		**2d**		**3ad**	19	75
8		**1a**		**2e**		**3ae**	15	16
9[c]		**1a**		**2f**		**3af**	15	35
10[c]		**1a**		**2h**		**3ah**	15	20

[a]Reaction conditions: chloro ketone (3 mmol), [Pd(acac)$_2$] (1 mol %), Xantphos (2 mol %), NBu$_3$ (3 equiv), Michael acceptor (4 equiv), CO (10 bar), MeOH (10 mL), 90 °C. [b]Isolated yield. [c]MeOH: 2 mL [d]Gas chromatography yield

51.2, 30.7, 23.6; HRMS (ESI-) calcd for $C_{14}H_{14}ClO_5$ [M − H]$^-$ 297.05352, found 297.05237.

Dimethyl 2-(4-fluorobenzoyl)pentanedioate (3ca): yellowish oil; R_f = 0.20 (petroleum ether/ethyl acetate 90:10); yield 70%, 258 mg; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.10−8.02 (m, 2H), 7.18−7.10 (m, 2H), 4.49 (t, J = 7.0 Hz, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 2.44 (m, 2H), 2.28 (q, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 193.4, 173.3, 170.0, 167.9, 164.5, 132.5, 132.4, 131.7, 131.6, 116.3, 116.0, 52.7, 52.6, 51.8, 31.2, 24.1; HRMS (ESI-) calcd for $C_{14}H_{14}FO_5$ [M − H]$^-$ 281.08308, found 281.08170.

Dimethyl 2-(4-(methoxycarbonyl)benzoyl)pentanedioate (3da): yellowish oil; R_f = 0.10 (petroleum ether/ethyl acetate 90:10); yield 49%, 142 mg; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.10−8.01 (m, 4H), 4.51 (t, J = 6.9 Hz, 1H), 3.90 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 2.44−2.39 (m, 2H), 2.28−2.21 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 194.6, 173.3, 169.8, 166.2, 139.1, 134.5, 130.1, 128.8, 52.9, 52.8, 52.7, 51.9, 31.2, 23.9; HRMS (ESI-) calcd for $C_{16}H_{17}O_7$ [M − H]$^-$ 321.09798, found 321.09671.

Dimethyl 2-acetylpentanedioate (3fa): yellowish oil; R_f = 0.25 (petroleum ether/ethyl acetate 90:10); yield 27%, 165 mg; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.73 (s, 3H), 3.66 (s, 3H), 3.56 (t, J = 7.2 Hz, 1H), 2.38−2.32 (m, 2H), 2.24 (s, 3H), 2.18−2.10 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.4, 173.1, 169.8, 58.2, 52.6, 51.8, 31.4, 29.2, 23.1; HRMS (ESI-) calcd for $C_9H_{13}O_5$ [M − H]$^-$ 201.07685, found 201.07555.

Methyl 2-benzoyl-5-oxohexanoate (3ab):[21] yellowish oil; R_f = 0.20 (petroleum ether/ethyl acetate 80:20); yield 74%, 549 mg; ^{1}H

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Scheme 3. Methoxycarbonylation Followed by Double Michael Addition of Acrolein and Subsequent Cyclization

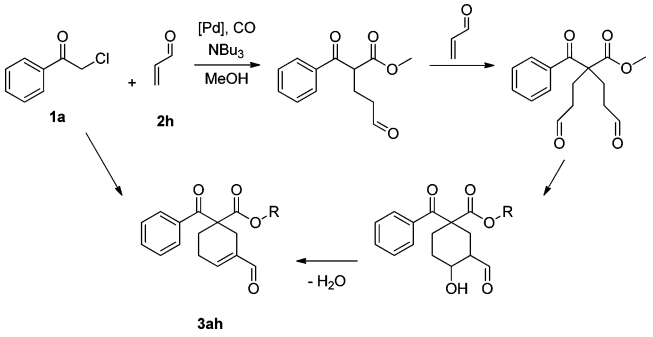
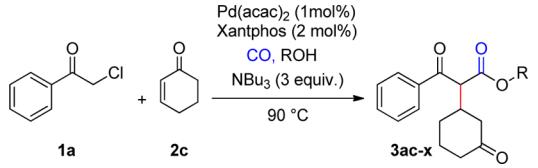


Table 4. Scope of the Reaction with 2-Chloroacetophenone 1a and Cyclohexenone 2c with Secondary and Tertiary Alcohols[a]



Entry	Alcohol	Product	Reaction time (h)	Yield (%)[b]
1	*i*-PrOH	**3ac-iPr**	37	66
2	*t*-BuOH	**3ac-tBu**	60	13

[a]Reaction conditions: 2-chloroacetophenone (3 mmol), [Pd(acac)$_2$] (1 mol %), Xantphos (2 mol %), NBu$_3$ (3 equiv), cyclohexenone (4 equiv), CO (10 bar), alcohol (10 mL), 90 °C. [b]Isolated yield.

NMR (300 MHz, $CDCl_3$) δ 8.04−8.00 (m, 2H), 7.61−7.55 (m, 1H), 7.51−7.45 (m, 2H), 4.47 (dd, J = 7.7, 6.5 Hz, 1H), 3.67 (s, 3H), 2.69−2.48 (m, 2H), 2.30−2.16 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 195.3, 170.4, 135.9, 133.9, 128.9, 128.8, 52.6, 52.4, 40.6, 30.1, 22.9; HRMS (ESI-) calcd for $C_{14}H_{15}O_4$ [M − H]$^-$ 247.09758, found 247.09639.

Methyl 2-(2,5-dimethyl-1-phenyl-1*H*-pyrrole-3-carbonyl)-5-oxohexanoate (3eb): yellowish oil; R_f = 0.20 (petroleum ether/ethyl acetate 80:20); yield 73%, 218 mg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.42 (m, 3H), 7.16 (dd, J = 7.7, 1.7 Hz, 2H), 4.13 (t, J = 7.2 Hz, 1H), 3.71 (s, 3H), 2.68−2.47 (m, 2H), 2.30 (s, 3H), 2.28−2.16 (m, 2H), 2.13 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 191.2, 171.2, 138.1, 137.2, 129.6, 129.3, 128.9, 128.1, 119.2, 107.7, 54.5, 52.4, 41.0, 30.1, 23.2, 13.3, 12.8; HRMS (ESI+) calcd for $C_{20}H_{24}NO_4$ [M + H]$^+$ 342.16998, found 342.16831.

Methyl 5-oxo-2-pivaloylhexanoate (3gb): yellowish oil; R_f = 0.20 (petroleum ether/ethyl acetate 80:20); yield 85%, 581 mg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, 0.25H), 4.00 (dd, J = 8.0, 5.9 Hz, 1H), 3.67 (s, 3H), 3.62 (t, J = 6.2 Hz, 0.5H), 3.32 (s, 0.75H), 2.66 (t, J = 6.2 Hz, 0.5H), 2.51 (t, J = 6.9 Hz, 2H), 2.17 (s, 0.75H), 2.11 (s, 3H), 2.09−1.93 (m, 2H), 1.16 (s, 9H), 1.10 (s, 2.25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 207.8, 170.2, 52.4, 50.7, 45.5, 40.7, 30.0, 28.3, 26.1, 23.6; HRMS (ESI+) calcd for $C_{12}H_{21}O_4$ [M + H]$^+$ 229.14344, found 229.14250.

Methyl 3-oxo-2-(3-oxocyclohexyl)-3-phenylpropanoate (3ac): yellowish oil; R_f = 0.20 (petroleum ether/ethyl acetate 80:20); yield 86%, 263 mg; obtained as a 1:1 mixture of diastereomers with a single stereogenic center at the cyclohexanone ring: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98−7.93 (m, 4H), 7.60−7.53 (m, 2H), 7.48−7.41 (m, 4H), 4.30 (dd, J = 9.0 Hz, J = 6.6 Hz, 2H), 3.63 (d, J = 5.1 Hz, 3H), 2.83−2.72 (m, 1H), 2.42−1.33 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 209.7, 193.5, 193.4, 168.9, 168.6, 136.5, 134.1, 134.0, 129.1, 129.1, 128.7, 128.7, 59.4, 59.0, 52.8, 52.8, 45.8, 45.4, 41.3, 38.4, 38.4, 29.6, 28.9, 24.7, 24.7; HRMS (ESI-) calcd for $C_{16}H_{17}O_4$ [M − H]$^-$ 273.11214, found 273.11188.

Methyl 3-oxo-2-(3-oxocyclohexyl)butanoate (3fc):[22] yellowish oil; R_f = 0.15 (petroleum ether/ethyl acetate 80:20); yield 75%, 398 mg; obtained as a 1:1 mixture of diastereomers with a single stereogenic center at the cyclohexanone ring: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.71 (s, 3H), 3.40 (d, J = 6.0 Hz, 1H), 3.38 (d, J = 5.7 Hz, 1H), 2.63−2.47 (m, 2H), 2.43−2.23 (m, 6H), 2.21 (s, 3H), 2.19 (s, 3H), 2.16−1.97 (m, 4H), 1.91−1.78 (m, 2H), 1.75−1.59 (m, 2H), 1.50−1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 209.5, 201.6, 201.5, 168.8, 168.6, 65.0, 64.6, 52.66, 52.6, 45.4, 45.1, 41.2, 41.1, 37.9, 29.7, 29.1, 28.7, 24.6, 24.6; HRMS (ESI-) calcd for $C_{11}H_{15}O_4$ [M − H]$^-$ 211.09649, found 211.09595.

Methyl 3-oxo-2-(3-oxocyclopentyl)-3-phenylpropanoate (3ad):[23] yellowish oil; R_f = 0.20 (petroleum ether/ethyl acetate 80:20); yield 75%, 279 mg; obtained as a 1:1 mixture of diastereomers with a single stereogenic center at the cyclopentanone ring: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91−7.86 (m, 4H), 7.49−7.43 (m, 2H), 7.37−7.31 (m, 4H), 4.30 (dd, J = 9.6 Hz, J = 6.9 Hz, 2H), 3.52 (s, 3H), 3.49 (s, 3H), 2.99−2.88 (m, 2H), 2.34 (td, J = 19.2 Hz, J = 7.8 Hz, 2H), 2.16−1.94 (m, 7H), 1.75−1.69 (m, 1H), 1.65−1.56 (m, 1H), 1.46−1.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.3, 217.3, 193.7, 193.5, 169.2, 169.1, 136.4, 136.2, 134.1, 129.1, 128.8, 59.2, 58.9, 52.8, 43.4, 43.0, 38.4, 38.3, 36.9, 36.7, 28.1, 27.6; HRMS (ESI-) calcd for $C_{15}H_{15}O_4$ [M − H]$^-$ 259.09758, found 259.09653.

Methyl 2-benzoyl-4-cyanobutanoate (3ae): yellowish oil; R_f = 0.10 (petroleum ether/ethyl acetate 80:20); yield 16%, 112 mg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−7.97 (m, 2H), 7.67−7.59 (m, 1H), 7.57−7.46 (m, 2H), 4.57 (t, J = 7.0 Hz, 1H), 3.71 (s, 3H), 2.63−2.41 (m, 2H), 2.40−2.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 169.3, 135.7, 134.3, 129.1, 128.9, 118.8, 53.0, 51.8, 24.7, 15.4; HRMS (ESI-) calcd for $C_{13}H_{12}NO_3$ [M − H]$^-$ 230.08172, found 230.08088.

Methyl 1-benzoyl-3-formylcyclohex-3-enecarboxylate (3ah): yellowish oil; R_f = 0.15 (petroleum ether/ethyl acetate 90:10); yield 20%, 125 mg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.87−7.82 (m, 2H), 7.65−7.53 (m, 1H), 7.50−7.41 (m, 2H), 6.84−6.78 (m, 1H), 3.69 (s, 3H), 2.86 (d, J = 1.5 Hz, 2H), 2.47−2.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 193.1, 173.4, 148.9, 138.6, 133.1, 130.0, 128.7, 128.4, 55.6, 52.8, 28.2, 28.1, 23.5; HRMS (ESI+) calcd for $C_{17}H_{19}O_4$ [M + H]$^+$ 287.12779, found 287.12698.

Isopropyl 3-oxo-2-(3-oxocyclohexyl)-3-phenylpropanoate (3ac-iPr): yellowish oil; R_f = 0.15 (petroleum ether/ethyl acetate 80:20); yield 66%, 202 mg; obtained as a 1:1 mixture of diastereomers with a single stereogenic center at the cyclohexanone ring: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.95 (m, 4H), 7.62−7.56 (m, 2H), 7.50−7.44 (m, 4H), 5.04−4.94 (m, 2H), 4.21 (t, J = 9.3 Hz, 2H), 2.86−2.76 (m, 2H), 2.51−2.39 (m, 2H), 2.29−2.16 (m, 4H), 2.12−1.91 (m, 4H), 1.77−1.67 (m, 2H), 1.61−1.50 (m, 1H), 1.45−1.33 (m, 1H), 1.16−1.10 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 193.6, 193.5, 168.0, 167.8, 136.8, 133.9, 129.0, 128.9, 128.7, 128.6, 69.6, 69.5, 60.0, 59.5, 46.0, 45.3, 41.4, 38.2, 38.1, 29.7, 28.8, 24.7, 21.7, 21.6; HRMS (ESI-) calcd for $C_{18}H_{21}O_4$ [M − H]$^-$ 301.14898, found 301.14815.

***tert*-Butyl 3-oxo-2-(3-oxocyclohexyl)-3-phenylpropanoate (3ac-tBu):** yellowish oil; R_f = 0.15 (petroleum ether/ethyl acetate 80:20); yield 13%, 76 mg; obtained as a 1:1 mixture of diastereomers with a single stereogenic center at the cyclohexanone ring: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97−7.86 (m, 4H), 7.56−7.48 (m, 2H), 7.47−7.36 (m, 4H), 4.07 (t, J = 8.6 Hz, 2H), 2.82−2.62 (m, 2H), 2.51−2.29 (m, 4H), 2.27−2.08 (m, 4H), 2.08−1.80 (m, 4H), 1.73−1.46 (m, 5H), 1.27 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 193.7, 193.6, 167.5, 167.2, 136.8, 136.7, 133.6, 133.5, 128.8, 128.7, 128.5, 128.4, 82.6, 82.5, 60.8, 60.2, 45.8, 45.2, 41.2, 37.9, 37.9, 29.6, 28.6, 27.8, 27.7, 24.6, 24.6; HRMS (ESI-) calcd for $C_{19}H_{23}O_4$ [M − H]$^-$ 315.16018, found 315.15933.

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■ ASSOCIATED CONTENT

Supporting Information

General synthetic procedures; ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: (+33) 3-20-33-63-01. E-mail: mathieu.sauthier@univ-lille1.fr.

Notes

The authors declare no competing financial interest.

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