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Bis-Alkoxycarbonylation of Acrylic Esters and Amides for the Synthesis of 2-Alkoxycarbonyl or 2-Carbamoyl Succinates

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Abstract. The first example of the bis-alkoxycarbonylation of acrylic esters and acrylic amides, leading to differently substituted 1,1,2-ethanetricarboxylate compounds and 2-carbamoylsuccinates respectively, is reported. The catalyst is formed *in situ* by mixing $Pd(TFA)_2$ (TFA = trifluoroacetate) and the ligand bis(2,6-dimethylphenyl)butane-2,3-diimine. The reaction, that proceeds using *p*-benzoquinone as oxidant and *p*-toluenesulfonic acid as additive, has been applied to variously substituted electron-poor alkenes, employing different alcohols as nucleophiles, under very mild reaction conditions (4 bar of carbon monoxide at 20 °C). Remarkably, this catalytic system is able to promote the carbonylation of both the β- and the generally unreactive α-positions of acrylic esters and amides, allowing the formation of bis-alkoxycarbonylated products in good to excellent yields (up to 98%). The trend of reactivity, observed with the different electron-deficient olefins, has been rationalized on the basis of the proposed catalytic cycle and DFT calculations.

Keywords: aryl α-diimine ligands; carbonylation; electron-deficient compounds; oxidative carbonylation; palladium

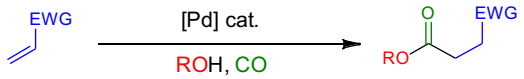
Introduction

Palladium-catalyzed carbonylation reactions represent a very powerful methodology that converts inexpensive feedstocks, such as carbon monoxide, alkenes or alkynes, into useful carbonylated compounds like aldehydes, esters or ketones.[1] In the last decade many contributions have been made in this area utilizing an oxidizing agent[2] and an alcohol as nucleophile,[3] for the synthesis of high added value esters. In spite of the remarkable advances made in the field of alkoxycarbonylation and bis-alkoxycarbonylation reactions of terminal[4] and internal olefins,[4a,5] so far, the carbonylation of electron-poor alkenes has not been extensively developed and remains a major challenge.[4a,6] This is probably due to the low coordination ability of the carbon-carbon double bond[7] and to the possible interaction of the functional group of the electron-deficient olefin with the catalyst.[7a-b] In addition, the alkoxycarbonylation of electron-poor alkenes is restricted to the β-position with respect to the electron-withdrawing group (EWG) of the olefin (Scheme 1a), while the α-carbon turns out to be not enough nucleophile to allow the prompt insertion of the carbonyl group.[8] To our knowledge, only Nozaki et al. showed, in the regiocontrolled copolymerization process of methyl acrylate with CO, that it is possible to carbonylate both the α- and the β- positions of acrylic esters, using a phosphine-sulfonate palladium catalyst (Scheme 1b).[9] Recently, we have developed a very efficient catalytic system able to promote the bis-alkoxycarbonylation of terminal alkenes,[4e] 1,2-disubstituted olefins[5a] and internal alkynes.[10] The catalyst was based on the combination of a palladium salt with bis(aryl)acenaphthenequinonediimine (BIAN) or 1,4-diaryl-2,3-diazabutadiene ligands. Similar Pd(II) complexes bearing aryl α-diimine ligands were also used by us in the copolymerization of styrenes with CO, yielding copolymers with a high degree of tacticity.[11]

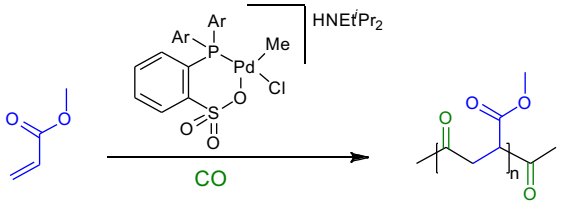
In this work, we have studied the possibility to effectively realize the bis-alkoxycarbonylation of electron-deficient olefins to give 2-EWG-substituted succinates, employing palladium/aryl α-diimine complexes as catalysts, as shown in Scheme 1c.

Succinic acid and their derivatives find applications in many industrial fields,[12] including pharmaceutical chemistry.[13] Moreover, the envisioned bis-alkoxycarbonylation of electron-deficient olefins such as acrylic esters and amides could enable the direct synthesis of 1,1,2-ethanetricarboxylates and 2-carbamoylsuccinates, key building blocks for medicinal[14] and organic[15] chemistry.

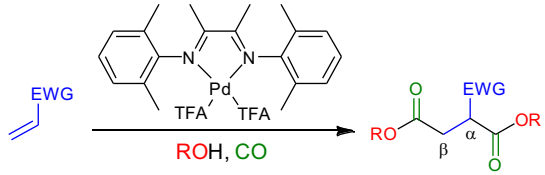
(a) Alkoxycarbonylation of electron-deficient olefins:



(b) Copolymerization Methyl Acrylate/CO:



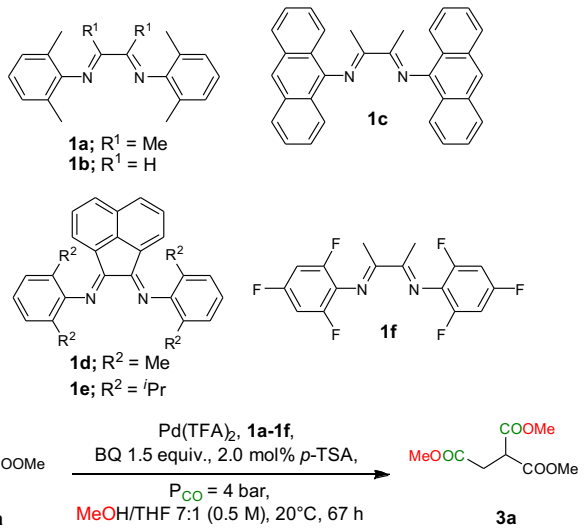
(c) Bis-alkoxycarbonylation of electron-deficient olefins (*this work*):



Scheme 1. Mono- and bis-carbonylation of electron-deficient olefins.

Results and Discussion

We started our investigation on the bis-alkoxycarbonylation of electron-poor alkenes, choosing methyl acrylate **2a** as the model substrate (Table 1). We have previously underlined the importance of the *ortho*-disubstitution on the aryls of α-diimine ligands to promote an efficient olefin bis-alkoxycarbonylation reaction, under mild reaction conditions.[4e,5a] Here a further investigation on the effects of the backbone structure and on the nature of the *ortho*-substituents has been performed testing ligands **1a-f** (Table 1). As expected, no reaction was observed using only $Pd(TFA)_2$ as catalyst (entry 1). Employing ligands 2,6-dimethyl aryl α-diimine **1a** or 9-anthryl α-diimine **1c** together with 0.5 mol% of $Pd(TFA)_2$, conversions of 22% and 13% were achieved respectively, with the selective formation of trimethyl ethane-1,1,2-tricarboxylate **3a** (entries 2 and 3). After these initial encouraging results, we decided to rising up the catalyst loading to 2 mol%, obtaining 90% of olefin conversion with both ligands **1a** and **1c** (entries 4 and 6). Instead, using ligand **1b**, where the two methyl groups of the backbone were replaced with two hydrogen atoms, only 45% of methyl acrylate reacted (entry 5). With the *o*-dimethyl BIAN ligand **1d**, the result was just slightly less satisfactory with respect to those obtained with ligands **1a** and **1c** (entry 7). On the other hand, the presence of bulky



isopropyl groups on the aromatic rings (ligand **1e**) drastically reduced the conversion (entry 8).

Table 1. Bis-alkoxycarbonylation of methyl acrylate **2a**. Effect of the ligands **1a-f** and of the catalyst loading.

Entry[a]	Catalyst Loading (mol%)[b]	Ligand **1a – 1f**	Conversion (%)[c]
1	3	-	< 5
2	0.5	**1a**	22
3	0.5	**1c**	13
4	2	**1a**	90
5	2	**1b**	45
6	2	**1c**	90
7	2	**1d**	85
8	2	**1e**	37
9	2	**1f**	< 5

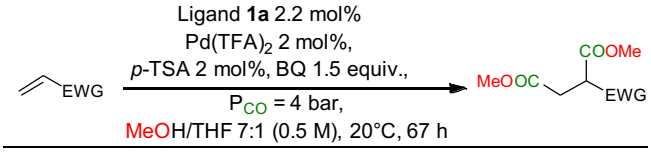
[a]Reaction performed in autoclave at P_{CO} = 4 bar, with methyl acrylate **2a** (2 mmol-scale), $Pd(TFA)_2$ 0.5 - 2 mol%, ligands **1a-f** 0.55 - 2.2 mol%, using 2 mol% of *p*-TSA and 1.5 equiv. of BQ, in 7:1 MeOH/THF (0.5 M) as the reaction medium, for 67 h. [b]$Pd(TFA)_2$/Ligand = 1 : 1.1. [c]Determined by direct ^{1}H NMR analysis on a sample of the reaction mixture.

Employing the ligand **1f**, with fluorine substituents in *ortho* and *para* positions, the reaction did not proceed at all (entry 9), probably due to the low basicity of the ligand that makes the catalyst less stable.[16] These results clearly indicate that not only the electronic character and the steric hindrance of the *ortho*-substituents of the aromatic rings, but also the rigidity of the resulting catalysts, influenced by the backbone,[17] greatly affected the reactivity.[18]

Since further experiments, carried out to optimize the other parameters of the reaction, did not lead to appreciable improvements (Table S1, SI), we decided to continue our investigation applying the catalytic system indicated in entry 4 of Table 1. With the catalyst formed *in situ* from the easily synthesizable ligand **1a** and $Pd(TFA)_2$, the bis-alkoxycarbonylation reaction proceeded in the presence of 1.5 equivalents

of *p*-benzoquinone (BQ) and 2 mol% of *p*-TSA, in methanol/THF 7:1 (0.5 M) as reaction medium, under a CO pressure of 4 bar at 20 °C. These conditions were then applied to various conjugated polar alkenes, in order to get preliminary insights on the generality of the process (Table 2).

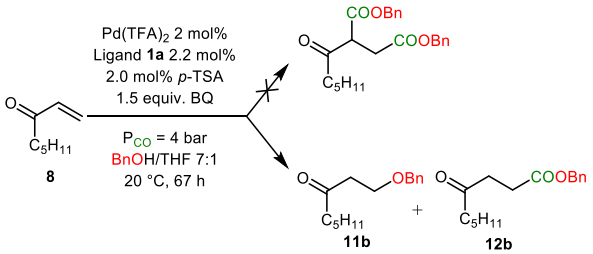
Table 2. Bis-methoxycarbonylation of various electron-deficient olefins.



Entry[a]	Olefin	EWG	Conversion (%)[b]	Yield (%)[c]
1	**4g**	$CONMe_2$	> 98	95
2	**2a**	COOMe	90	78
3	**6**	$P(O)(OEt)_2$	32	25
4	**8**	$C(O)C_5H_{11}$	100[d]	0
5	**9**	CN	< 5	-
6	**10**	SO_2Ph	< 5	-

[a]Reaction performed in autoclave at P_{CO} = 4 bar, with olefin (2 mmol), $Pd(TFA)_2$ (2 mol%), ligand **1a** (2.2 mol%), *p*-TSA (2 mol%) and BQ (1.5 equiv), in 7:1 MeOH/THF (4 mL) as the reaction medium, for 67 h. [b]Determined by ^1H NMR analysis of the reaction crude. [c]Isolated yields after column chromatography. [d]The olefin **8** was mainly converted into 1-methoxyoctan-3-one **11a**.

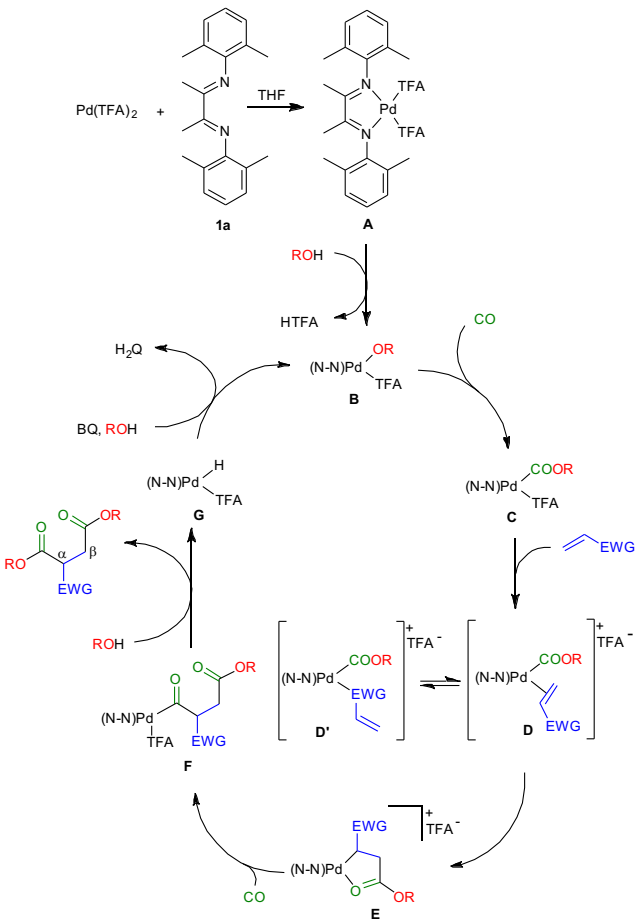
Interestingly, a complete conversion was achieved with *N,N*-dimethylacrylamide **4g**, which resulted to be more reactive than methyl acrylate **2a** (entries 1 and 2, Table 2). The diethyl vinyl phosphonate **6** gave less satisfactory results (entry 3),[19] while with the α,β-unsaturated ketone **8**, no trace of the desired bis-alkoxycarbonylated product was detected (entry 4). In this case, the olefin mainly underwent a methoxylation reaction leading to the formation of 1-methoxyoctan-3-one product **11a** together with other unidentified byproducts. (Table S2, SI). Interestingly, using benzyl alcohol as nucleophile, the mono-carbonylated benzyl 4-oxononanoate product **12b** was formed in 1:1 ratio with the corresponding mono-alkoxylated compound **11b** (Scheme 2 and pages S3-S5, SI). Acrylonitrile **9** and phenyl vinyl sulfone **10** were unreactive under these conditions (entries 5 and 6, Table 2). Notably, conversions in Table 2 seem to be correlated to the nature of the electron-withdrawing group. In particular, olefins bearing an EWG group with a lower electron-attractor character gave higher yields in the desired product.



11b : **12b** = 1 : 1, overall yield 98%

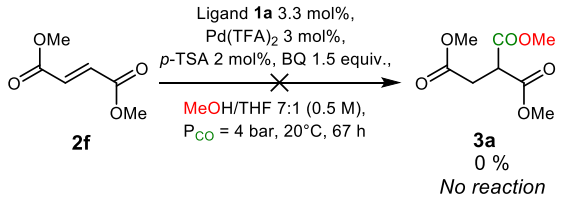
Scheme 2. Reactivity of vinyl ketone **8**, in our bis-alkoxycarbonylation conditions, using BnOH as nucleophile.

On the basis of these results, our previous mechanistic investigations[11,20,21] and literature data,[22,23,9] we propose the catalytic cycle depicted in Scheme 3, which allows to rationalize the observed reactivity of electron deficient olefins. According to a generally accepted mechanism, nucleophilic attack of the alcohol on complex **A**, which has been recently isolated and characterized,[5a] affords the active species **B**.[22,24]



Scheme 3. Proposed catalytic cycle. EWG = electron-withdrawing group, BQ = *p*-benzoquinone and H_2Q = 1,4-hydroquinone.

The subsequent insertions of CO[25] and of the electron-deficient olefin lead to the 5-membered palladacycle intermediate **E**.[9,11,20-23,26,27] Further CO insertion gives complex **F**,[9a,21] which then undergoes nucleophilic displacement by the alcohol, to afford the final bis-alkoxycarbonylated product and the palladium hydride intermediate **G**. The latter is finally oxidized by *p*-benzoquinone with regeneration of the active catalyst **B**.[28,29] Intermediates similar to **E** and **F** have been previously isolated by Nozaki et al. with phosphine-sulfonate ligands[9] and by us with aryl α-diimine ligands.[11,27] Ancillary experiments were conducted to further support the first steps of the proposed catalytic cycle, but the low solubility of the complex **A**[5a,30] and the high instability of the formed species, precluded the isolation of the intermediates (see pag. S6, SI). However, after one catalytic cycle, in a stoichiometric reaction with olefin **2a**, the formation of trifluoroacetic acid and hydroquinone in quantitative amount was possible to detected, together with product **3a** (Scheme S2, SI). The alternative mechanism, which involves *β*-hydride elimination from intermediate **E** leading to a mono-carbonylated compound of the type EWG-CH=CH-COOR and its successive alkoxycarbonylation, has been excluded since, utilizing the dimethyl fumarate **2f** as substrate, the formation of the expected carbonylated product **3a** was not observed (Scheme 4).



Scheme 4. Study on the alternative mechanism involving *β*-H elimination in the intermediate **E**.

Previous investigations, aimed at rationalizing the low reactivity of electron-deficient olefins in copolymerization reactions,[6-9] allowed to draw some important conclusions, which can be summarized in the following three points, i) the coordination ability of the C-C double bond of olefins is reduced by the presence of an electron-withdrawing group[7] (Scheme 3, intermediate **D**), ii) a competitive coordination by the heteroatom-containing functional group of the olefin can take place (intermediate **D'**)[7a-b] and iii) the second CO insertion, forming the intermediate **F**, is inhibited by the low nucleophilicity of the carbon, bearing the EWG group and linked to the Pd center in complex **E**.[8,9]

In order to assess whether such effects were also at work in our catalytic cycle, and if they were responsible for the different reactivity of the EWG-substituted alkenes shown in Table 2, we performed some preliminary DFT calculations. In particular, we focused our attention on the insertion of the second molecule of CO, analyzing in detail the energies of the intermediates that are part of the process.

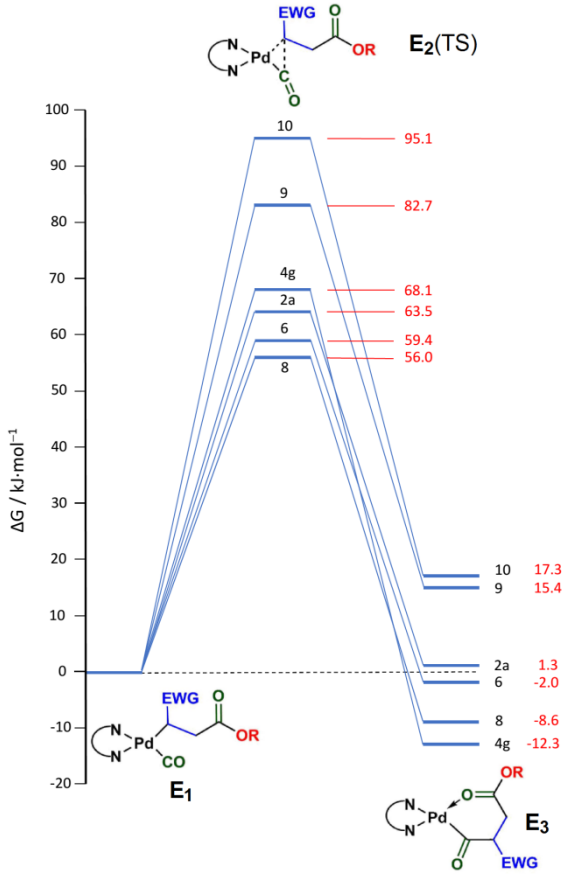


Figure 1. Gibbs free energies (in kJ/mol) diagrams relative to the insertion of the second CO molecule, for the olefins listed in Table 2. The energy of the open chain intermediate $\mathbf{E_1}$, with the CO coordinated to the Pd centre, has been taken as common reference.

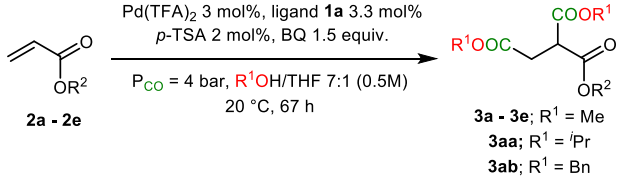
In addition, to have a first evaluation of the EWG capability to coordinate the Pd center, we have calculated the Natural Population Analysis (NPA) partial charges on the oxygen of the carbonyl group of the EWGs (see Table S3, SI). For the olefins of Table 2, we have then calculated the energy of the open-chain intermediate $\mathbf{E_1}$, in which a second CO molecule is coordinated to Pd, the energy of the 6-membered palladacycle complex $\mathbf{E_3}$, where the CO is inserted, and the energy of the relative transition state $\mathbf{E_2(TS)}$ (Figure 1). The intermediates $\mathbf{E_1}$ and $\mathbf{E_3}$, not explicitly reported in the proposed catalytic cycle, are the expected species leading to the formation of intermediate **F** starting from the 5-membered palladacycle complex **E** (Scheme 3). The free energy values $\Delta G^{\ddagger}$ of $\mathbf{E_2(TS)}$ for phenyl vinyl sulfone **10** (95.1 kJ/mol) and for acrylonitrile **9** (82.7 kJ/mol) are the highest among those calculated, while for *N,N*-dimethylacrylamide **4g** (68.1 kJ/mol), methyl acrylate **2a** (63.5 kJ/mol) and diethyl vinyl phosphonate **6** (59.4 kJ/mol) the values are similar and lower by at least 15 kJ/mol. The unreactivity of sulfone **10** and

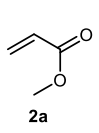
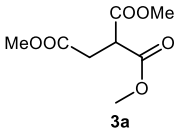
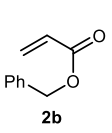
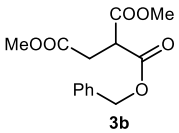
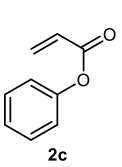
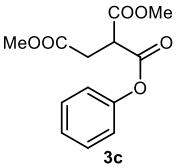
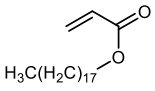
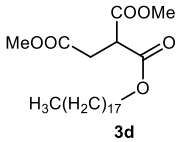
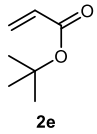
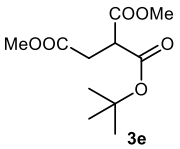
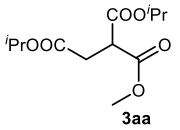
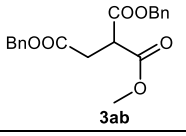
acrylonitrile **9** (Table 2, entries 6 and 5) was in agreement with both the very high $\Delta G^{\ddagger}$ values of **E_2(TS)** and the high coordination ability of sulphonic oxygens and of the –CN group towards Pd (entries 14 and 13, Table S3). Indeed, it has been found, in Pd-catalyzed insertion copolymerizations, that the inertia of acrylonitrile can be ascribed to a strong σ-bond between the nitrogen atom and palladium, making the π-coordination less likely.[7a] In a similar manner, the low phosphonate conversion (Table 2, entry 3) could be justified by the high coordination ability of the phosphonic oxygen (entry 11, Table S3), even if the $\Delta G^{\ddagger}$ value was comparable with those of the much more reactive olefins **2a** and **4g**. Using the acrylic ester **2a** and the acrylic amide **4g**, nearly quantitative conversions were achieved (Table 2, entries 2 and 1). Accordingly, the values of $\Delta G^{\ddagger}$ and of the partial charges on the carbonyl oxygen were similar (entries 1 and 10, Table S3) and in line with a good productivity. The higher reactivity of **4g** could be attributed to the greater stability of intermediate **E_3** (Figure 1). For the vinyl ketone **8**, the value of $\Delta G^{\ddagger}$ would be potentially favorable but, owing to its different reactivity, this step cannot be reached. Actually, the main problem with the olefin **8** (Table 2, entry 4) was the preferential competitive alkoxylation reaction to afford compounds **11**. However, using benzyl alcohol as nucleophile, the concomitant formation of the mono-carbonylated product **12b** (Scheme 2 and Table S2, entry 4) suggests that the coordination and insertion of olefin **8** is possible. Although in this case it has not been possible to obtain the bis-alkoxycarbonylated derivatives, this interesting reactivity will be further studied to selectively obtain γ-ketoesters.

The process described here represents the first example of bis-alkoxycarbonylation of electron-deficient olefins. In fact, although several examples of 5-membered palladacycles of type **E** with diverse ligands and various electron-poor alkenes have been reported,[23] the subsequent CO insertion was not observed.

We then proceeded with the evaluation of the scope of this unprecedented bis-alkoxycarbonylation reaction. Differently substituted acrylic esters were first tested (Table 3). The catalyst loading was raised to 3 mol%, and this enabled the complete conversion of methyl acrylate **2a** into product **3a** (entry 1). Excellent isolated yields of compounds **3b** and **3c** were also obtained starting from benzyl acrylate **2b** and phenyl acrylate **2c** respectively (entries 2 and 3). The formation of products **3d** and **3e** in high yields, demonstrates that this process can be successfully applied to acrylic esters bearing a long alkyl side chain or a sterically demanding substituent[31] on the oxygen (entries 4 and 5). Using the bulky and less nucleophilic isopropanol in place of methanol, the formation of the corresponding compound **3aa** was less satisfactory (entry 6, Table 3), while employing benzyl alcohol the yield of the product **3ab** was still high (entry 7, Table 3).

Table 3. Scope of the bis-alkoxycarbonylation reaction of acrylic esters.



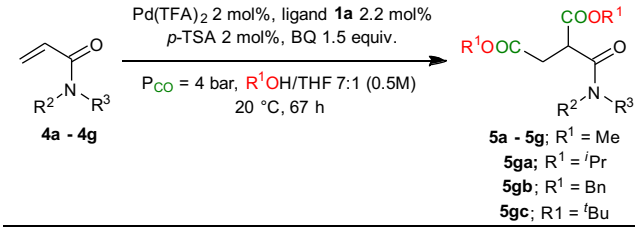
Entry	2	3	Yield [%][b]
1	 **2a**	 **3a**	89
2	 **2b**	 **3b**	91
3	 **2c**	 **3c**	90 (94)[c]
4	 **2d**	 **3d**	92
5[d]	 **2e**	 **3e**	93 (97)[c]
6[d]	 **2a**	 **3aa**	32 (40)[c]
7	 **2a**	 **3ab**	88

[a]Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **2a-2e** (2 mmol), $Pd(TFA)_2$ (3 mol%), ligand **1a** (3.3 mol%), *p*-TSA (2 mol%) and BQ (1.5 equiv), in 7:1 R^1OH/THF (4 mL), for 67 h. [b]Isolated yields after column chromatography. [c]Incomplete conversions (%) in brackets. [d]Reaction performed with 5 mol% of catalyst loading.

Regarding the more reactive acrylic amides, after a further optimization study (Table S5, SI), we proceeded using the same conditions employed for acrylic esters, but reducing the catalyst loading to 2

mol%. Besides acrylamide **4a**, differently substituted *N*-alkylacrylamides and *N*,*N*-dialkylacrylamides were tested, and, in all cases, the corresponding 2-carbamoylsuccinates **5a-5gc** were formed with complete selectivity and high isolated yields (Table 4). Noteworthy, the bulky *tert*-butyl acrylamide **4d** gave 78% yield of the product **5d** with 85% of conversion.

Table 4. Scope of the bis-alkoxycarbonylation reaction of acrylic amides.



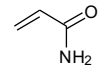
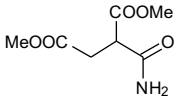
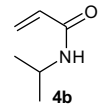
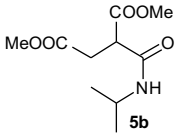
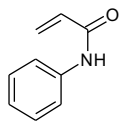
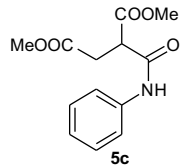
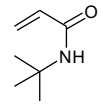
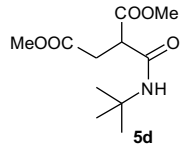
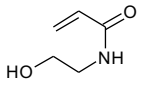
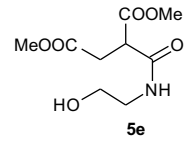
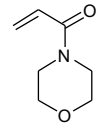
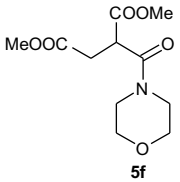
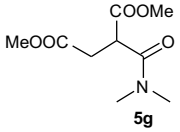
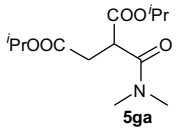
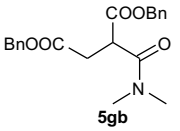
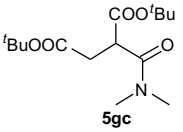
Entry[a]	4	5	Yield [%][b]
1	 **4a**	 **5a**	91
2	 **4b**	 **5b**	92
3	 **4c**	 **5c**	90
4	 **4d**	 **5d**	78 (85)[c]
5	 **4e**	 **5e**	98
6	 **4f**	 **5f**	98
7	 **4g**	 **5g**	95

Table 4. Continue

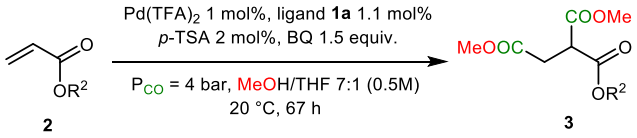
Entry[a]	4	5	Yield [%][b]
8	 **4g**	 **5ga**	88 (90)[c]
9	 **4g**	 **5gb**	93
10[d]	 **4g**	 **5gc**	40 (60)[c]

[a]Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **4a**-**4g** (2 mmol), $Pd(TFA)_2$ (2 mol%), ligand **1a** (2.2 mol%), *p*-TSA (2 mol%) and BQ (1.5 equiv), in 7:1 R^1OH/THF (4 mL), for 67 h. [b]Isolated yields after column chromatography. [c]Incomplete conversions in brackets. [d]Reaction performed with 5 mol% of catalyst loading at 50 °C.

Notably, the hydroxyl group, present in the side chain of the olefin, such as in *N*-(2-hydroxyethyl)acrylamide **4e**, was well tolerated, and the bis-alkoxycarbonylated product **5e** was selectively obtained in nearly quantitative yield (entry 5, Table 4). Products **5f** and **5g**, bearing a dialkyl substituted nitrogen, were obtained in excellent yields. The use of isopropanol or benzyl alcohol as nucleophiles led to excellent yields of the products **5ga** and **5gb** (entries 8 and 9), while in the presence of the more sterically hindered *tert*-butyl alcohol, the corresponding product **5gc** was isolated with a satisfactory selectivity, by rising up the catalyst loading to 5 mol% and increasing the temperature to 50°C (entry 10, Table 4).[32] Unfortunately, acrylates or acrylic amides bearing a methyl or a phenyl group in α- or β-positions were unreactive (Table S4, SI).

Finally, in order to better appreciate the influence of the substituents in acrylic esters and in acrylic amides, some of the reactions described above were tested at 1 mol% of catalyst loading (Table 5 and 6). The results confirmed again the higher reactivity of amides respect to esters in this bis-alkoxycarbonylation reaction. Indeed, while with acrylic esters the conversions range was between 24 % and 56 %, with acrylic amides **4a** and **4c** the conversions are almost complete and resulted to be 90 % and 82 % respectively. Furthermore, it is evident that the size of the substituents negatively affected the reactivity. In particular, as the size of the substituents on the oxygen of acrylic esters or on the nitrogen of acrylic amides increases, the reactivity of the olefin gradually decreases.

Table 5. Bis-methoxycarbonylation of acrylic esters using 1 mol% of catalyst loading.



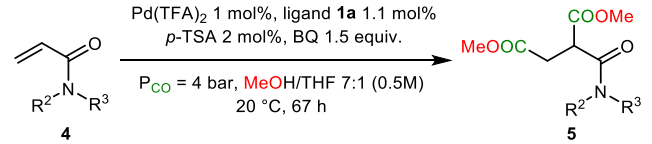
2 3

Entry[a]	Olefin **2**	R^2	Conversion (%)[b]
1	**2a**	Me	56
2	**2c**	Ph	28
3	**2d**	$(CH_2)_{17}CH_3$	47
4	**2e**	^{t}Bu	24

[a]Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **2** (2 mmol), $Pd(TFA)_2$ (1 mol%), ligand **1a** (1.1 mol%), *p*-TSA (2 mol%) and BQ (1.5 equiv.), in 7:1 MeOH/THF (4 mL) as the reaction medium, for 67 h. [b]Determined by ^{1}H NMR analysis of the reaction crude.

However, from the observation of the molecular models based on theoretical calculations, it appears that this trend is not so much dictated by steric effects, but rather derives from an increased inductive effect of the substituents on the esteric or amidic carbonyl. This tends to increase the partial charge on the oxygen, making the coordination to palladium more likely (Table S3), resulting in catalyst partial deactivation.

Table 6. Bis-methoxycarbonylation of acrylic amides using 1 mol% of catalyst loading.



4 5

Entry[a]	Olefin **4**	R^2	R^3	Conversion (%)[b]
1	**4a**	H	H	90
2	**4b**	H	^{i}Pr	60
3	**4c**	H	Ph	82
4	**4g**	Me	Me	68

[a]Reaction performed in autoclave at P_{CO} = 4 bar, with olefins **4** (2 mmol), $Pd(TFA)_2$ (1 mol%), ligand **1a** (1.1 mol%), *p*-TSA (2 mol%) and BQ (1.5 equiv.), in 7:1 MeOH/THF (4 mL) as the reaction medium, for 67 h. [b]Determined by ^{1}H NMR analysis of the reaction crude.

Conclusion

Despite the low reactivity of electron-deficient olefins in carbonylation reactions, the first bis-alkoxycarbonylation of acrylic esters and acrylic amides, leading to the synthesis of the respective bis-carbonylated products was successfully developed. The catalytic system is constituted by $Pd(TFA)_2$ as palladium source, the easily affordable aryl α-diimine ligand **1a**, *p*-benzoquinone as oxidant and *p*-toluenesulfonic acid as additive. The reaction proceed under particularly mild conditions (4 bar of CO at 20°C) and different alcohols can be used as nucleophiles. Slight changes on the ligand structure produced a dramatic effect on the performance of the catalytic system. From the screening carried out, the importance of the presence of methyl substituents both on the *ortho*- positions of the aryl rings and on the backbone of the ligand was evidenced, confirming the superiority of ligand **1a**. The resulting blocked conformation of the catalyst with ligand **1a** favors the correct approach of the reagents to the catalytic center, increasing the productivity. On the other hand, the presence of bulky isopropyl groups in *ortho* or of fluorine substituents in *ortho* and *para* positions of the aryls drastically reduces the conversion.

Our catalytic system is able to promote the selective carbonylation of both the β- and the generally non-reactive α-positions of acrylic esters and acrylic amides, leading to the synthesis of 1,1,2-ethanetricarboxylate compounds and 2-carbamoylsuccinates respectively in excellent yields, up to 98%. Remarkably, the reaction can be successfully applied to a wide range of acrylates and acrylamides bearing different types of substituents on the oxygen or on the nitrogen respectively. High productivity has been achieved both with sterically demanding substituents and with substituents showing a different electronic character. Using isopropanol or benzyl alcohol as nucleophiles, instead of methanol, productivity is still very good. To assess the generality of our bis-alkoxycarbonylation process various conjugated polar alkenes, having different electron-withdrawing groups, have been tested.

The resulting trend of reactivity was rationalized on the basis of the proposed catalytic cycle and supported by DFT calculations. These studies suggest that two main factors determine the course of our bis-alkoxycarbonylation: i) the competition between the C-C double bond and the EWG group of the olefins for the coordination to the Pd catalytic center and ii) the transition state energy for the insertion of the second carbonyl group. Finally, to better appreciate the influence of the substituents within the series of acrylic esters and amides, the catalyst loading was lowered to 1%, obtaining a scale that highlights the greater reactivity of the amides. Moreover, although the size of the substituents, on the oxygen or on the nitrogen, negatively influences the reactivity of the olefins, it seems that this is mainly due to the inductive effect of the substituents on the esteric or amidic carbonyl, making it more inclined to coordinate to palladium.

Further studies, including DFT calculations, are in progress in order to get more insights into this remarkable reactivity and to better understand the key steps of the proposed mechanism.

Experimental Section

General methods and materials

All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, in a stainless steel autoclave, by using Schlenk technique. Reactions were monitored by ^{1}H NMR taking a sample of the crude mixture. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 101 MHz), using $CDCl_3$ as solvent. Chemical shifts are reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and to the central line of $CHCl_3$ (77.16 ppm) for ^{13}C NMR. ^{13}C NMR were recorded with ^{1}H broadband decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, dd = double doublets, b = broad. Coupling constants (*J*) are reported in Hertz (Hz). ESI-MS spectra were recorded on Waters Micromass ZQ 4000, using electrospray ionisation techniques, with samples dissolved in MeOH. Carbon monoxide (Cp grade 99.99%) was supplied by Air Liquide. The *p*-benzoquinone was purchased by Sigma-Aldrich and was filtered off a plug of silica gel washing with CH_2Cl_2, obtaining a yellow solid after dried up in vacuum the solution. Olefins **2a-2e**, **4a-4g** and **6, 8-10** were purchased from TCI or Fluorochem. Olefin **2f** was purchased from Sigma-Aldrich. The olefins **2a-2c**, **2e**, **4e-4g**, **6, 8-10** were filtered off a plug of neutral Al_2O_3 and used without further purification. The olefins **2d, 2f** and **4a-4d** were used without further purification. Anhydrous THF was distilled from sodium benzophenone, methanol was distilled from $Mg(OMe)_2$. Isopropanol, benzyl alcohol and *tert*-butyl alcohol were dried over molecular sieves (Alfa Aesar, 4 Å, 1-2 mm, beads). $Pd(TFA)_2$ was purchased by Flurochem, $Pd(PhCN)_2Cl_2$ was purchased by Sigma-Aldrich and both were weighted in an analytical balance without excluding moist and air. All other chemicals were purchased from Sigma-Aldrich and used without further purification. The ligands **1a-b** and **1d-e** were synthesized according to a previously reported procedure,[33] as well as the ligand **1f**.[34] The ligand **1c** was synthesized according to a procedure developed by our group.[11]

Computational Details: DFT calculations have been performed using the ORCA 4.01 suite of quantum chemistry programs.[35] Geometry optimizations and free energy calculations (at 298K) were done with the small def2-TZVP basis[36] and the Becke-Perdew functional.[37] Additional single point energy calculations with the larger def2-QZVPP basis[36] and the M06 functional[38] were performed at the previously optimized geometries. Single point energies were eventually amended by inclusion of solvation effects[39] and dispersion interactions.[40] The final energy of each structure, used to evaluate the relative free energies of the various products and intermediates, was built by summing the difference between the def2-TZVP electronic and free energies to the def2-QZVPP single point electronic energy. Natural Population Analysis[41] (NPA) has been performed using the JAMPA 1.04 package.[42]

General procedure for the bis-alkoxycarbonylation reaction of electron-deficient olefins

In a nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the respective olefin **2**, **3**, **6, 8-10** (2 mmol) and methanol MeOH (3.5 mL) were added. The mixture was left under stirring for 10 min. In another nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the $Pd(TFA)_2$ (13.3 mg, 0.04 mmol or 19.9 mg, 0.06 mmol) and THF (0.5 mL) were added. After the mixture turned in a red/brown color (25 min), the ligand **1a** (12.8 mg, 0.044 mmol or 19.3 mg, 0.066 mmol) was added. The mixture was left under stirring for 20 min, turning in a dark orange color. The olefin solution and the formed catalyst were injected in sequence in a nitrogen flushed autoclave, equipped with a magnetic stirring bar, containing *p*-benzoquinone (325 mg, 3 mmol) and *p*-TSA·H_2O (7.6 mg, 0.04 mmol). After 10 min, the autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at 20 °C for 67 h. The autoclave was vented off, flushed with nitrogen and the reaction mixture was directly analyzed by ^{1}H NMR to determine the conversion of the olefin into the product. The crude was then dried under reduced pressure and filtered off a plug of silica gel eluting with CH_2Cl_2/Et_2O 1:1 and finally the solution was dried up in vacuum. The product was eventually obtained after column chromatography on silica gel.

1-Benzyl 1,2-dimethyl ethane-1,1,2-tricarboxylate (3b): Synthesized following the general procedure, the compound **3b** has been purified by column chromatography using petroleum ether/CH_2Cl_2 50:50 then 30:70, obtaining a colorless oil; isolated yield: 91% (0.510 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 5.22 (d, *J* = 12.3 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 3.91 (t, *J* = 7.4 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.95 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 168.8, 168.2, 135.3, 128.7, 128.5, 128.2, 67.6, 53.0, 52.2, 47.8, 33.0. ESI-MS: m/z = 281 $[M+H]^+$; m/z = 303 $[M+Na]^+$; m/z = 319 $[M+K]^+$.

1,2-dimethyl 1-phenyl ethane-1,1,2-tricarboxylate (3c): Following the general procedure, the olefin **2c** was converted for 94%. The compound **3c** has been purified by column chromatography petroleum ether/CH_2Cl_2 20:80, obtaining a pale yellow oil; isolated yield: 90% (0.479 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 1H), 7.28 – 7.22 (m, 1H), 7.14 – 7.09 (m, 1H), 4.10 (dd, *J* = 7.8, 7.0 Hz, 1H), 3.83 (s, 1H), 3.74 (s, 1H), 3.10 (dd, *J* = 17.4, 7.9 Hz, 1H), 3.04 (dd, *J* = 17.4, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 168.6, 167.2, 150.6, 129.6, 126.4, 121.4, 53.2, 52.4, 47.9, 33.1. ESI-MS: m/z = 267 $[M+H]^+$; m/z = 289 $[M+Na]^+$; m/z = 305 $[M+K]^+$.

1,2-Dimethyl 1-octadecyl ethane-1,1,2-tricarboxylate (3d): Synthesized following the general procedure, but adding the solid olefin **2d** directly into the autoclave together with *p*-benzoquinone and *p*-TSA. The compound **3d** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 20:80, obtaining a white powder; isolated yield: 92% (0.814 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 – 4.08 (m, 2H), 3.85 (t, *J* = 7.4 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.94 (d, *J* = 7.4 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.36 – 1.18 (m, 30H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 169.1, 168.5, 66.2, 52.9, 52.2, 47.8, 33.1, 32.1, 29.8 (8C), 29.72, 29.67, 29.5, 29.3, 28.6, 25.9, 22.8, 14.3. ESI-MS: m/z = 443 $[M+H]^+$; m/z = 465 $[M+Na]^+$; m/z = 481 $[M+K]^+$.

1-(*tert*-butyl) 1,2-Dimethyl ethane-1,1,2-tricarboxylate (3e): Following the general procedure, but using 5 mol% of catalyst loading, olefin **2e** was converted for 97%. The compound **3e** has been purified by column chromatography petroleum ether/CH_2Cl_2 30:70, obtaining a colorless oil; isolated yield: 93% (0.460 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (t, *J* = 7.4 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 2.89 (d, *J* = 7.4 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 169.5, 167.4, 82.6, 52.8, 52.2, 48.8, 33.1, 28.0. ESI-MS: m/z = 269 $[M+Na]^+$; m/z = 285 $[M+K]^+$.

1,2-Diisopropyl 1-methyl ethane-1,1,2-tricarboxylate (3aa): Following the general procedure, but using 5 mol% of catalyst loading and ^{i}PrOH as nucleophile, olefin **2a** was

converted for 40%. The compound **3aa** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 30:70, obtaining a yellow oil; isolated yield: 32% (0.166 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 – 4.94 (m, 2H), 3.80 (t, J = 7.5 Hz, 1H), 3.75 (s, 3H), 2.88 (d, J = 7.5 Hz, 2H), 1.27 – 1.18 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.2, 168.0, 69.6, 68.7, 52.8, 48.1, 33.6, 21.9 (2C), 21.7, 21.6. ESI-MS: m/z = 261 $[M+H]^+$; m/z = 283 $[M+Na]^+$; m/z = 299 $[M+K]^+$.

1,2-Dibenzyl 1-methyl ethane-1,1,2-tricarboxylate (3ab): Synthesized following the general procedure and using BnOH as nucleophile. The compound **3ab** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 20:80, obtaining a colorless oil; isolated yield: 88% (0.627 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 10H), 5.20 (d, J = 12.3 Hz, 1H), 5.15 (d, J = 12.3 Hz, 1H), 5.11 (s, 2H), 3.93 (t, J = 7.4 Hz, 1H), 3.70 (s, 3H), 3.01 (d, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 168.8, 168.2, 135.5, 135.3, 128.7 (2C), 128.54, 128.50, 128.4, 128.3, 67.6, 67.0, 52.9, 47.8, 33.3. ESI-MS: m/z = 379 $[M+Na]^+$; m/z = 395 $[M+K]^+$.

Dimethyl 2-carbamoylsuccinate (5a): Synthesized following the general procedure, but adding the solid olefin **4a** directly into the autoclave together with *p*-benzoquinone and *p*-TSA and without filtering on a plug of silica gel. The compound **5a** has been purified by column chromatography petroleum ether/ethyl acetate 50:50 then 30:70, obtaining a white powder; isolated yield: 91% (0.344 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (bs, 1H), 5.77 (bs, 1H), 3.77 (s, 3H), 3.74 (t, J = 6.8 Hz, 1H), 3.69 (s, 3H), 3.00 (d, J = 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 170.1, 169.0, 53.1, 52.2, 47.8, 32.5. ESI-MS: m/z = 190 $[M+H]^+$; m/z = 212 $[M+Na]^+$; m/z = 228 $[M+K]^+$.

Dimethyl 2-(isopropylcarbamoyl)succinate (5b): Synthesized following the general procedure, but adding the solid olefin **4b** directly into the autoclave together with *p*-benzoquinone and *p*-TSA. The compound **5b** has been purified by column chromatography petroleum ether/ethyl acetate 30:70, obtaining a white powder; isolated yield: 92% (0.428 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (bs, 1H), 4.05 (m, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.62 (t, J = 6.9 Hz, 1H), 2.98 (d, J = 6.9 Hz, 2H), 1.16 (d, J = 6.6 Hz, 2H), 1.15 (d, J = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 170.5, 165.7, 52.9, 52.1, 48.4, 42.1, 32.7, 22.64, 22.59. ESI-MS: m/z = 232 $[M+H]^+$; m/z = 254 $[M+Na]^+$; m/z = 270 $[M+K]^+$.

Dimethyl 2-(*tert*-butylcarbamoyl)succinate (5d): Following the general procedure, but adding the solid olefin **4d** directly into the autoclave together with *p*-benzoquinone and *p*-TSA, a conversion of 85% has been achieved. The compound **5d** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 30:70, obtaining a white powder; isolated yield: 78% (0.383 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (bs, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.58 (t, J = 6.9 Hz, 1H), 2.95 (d, J = 6.9 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 170.6, 165.6, 52.9, 52.1, 51.8, 49.0, 32.6, 28.7. ESI-MS: m/z = 246 $[M+H]^+$; m/z = 268 $[M+Na]^+$; m/z = 284 $[M+K]^+$.

Dimethyl 2-((2-hydroxyethyl)carbamoyl)succinate (5e): Synthesized following the general procedure, without filtering on a plug of silica gel. The compound **5e** has been purified by column chromatography petroleum ether/ethyl acetate 20:80, obtaining a pale yellow oil; isolated yield: 98% (0.457 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (bs, 1H), 3.75 (s, 3H), 3.72 – 3.66 (m, 3H), 3.68 (s, 3H), 3.50 – 3.35 (m, 2H), 3.00 (d, J = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 170.2, 167.9, 61.8, 53.1, 52.3, 48.1, 42.8, 32.7. ESI-MS: m/z = 234 $[M+H]^+$; m/z = 256 $[M+Na]^+$; m/z = 272 $[M+K]^+$.

Dimethyl 2-(morpholine-4-carbonyl)succinate (5f): Synthesized following the general procedure, the compound **5f** has been purified by column chromatography petroleum ether/ethyl acetate 50:50 then 40:60, obtaining a yellow oil; isolated yield: 98% (0.508 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (dd, J = 8.3, 5.8 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.80 – 3.52 (m, 8H), 3.08 (dd, J = 17.5, 8.4 Hz, 1H), 2.97 (dd, J = 17.5, 5.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 169.1, 166.3, 66.8, 66.6, 53.0, 52.2, 46.9, 44.1, 43.0, 33.3. ESI-MS: m/z = 260 $[M+H]^+$; m/z = 282 $[M+Na]^+$; m/z = 298 $[M+K]^+$.

Dimethyl 2-(dimethylcarbamoyl)succinate (5g): Synthesized following the general procedure, the compound **5g** has been purified by column chromatography petroleum ether/ethyl acetate 70:30 then 50:50, obtaining a yellow oil; isolated yield: 95% (0.414 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (dd, J = 8.3, 5.9 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.17 (s, 3H), 3.05 (dd, J = 17.5, 8.3 Hz, 1H), 3.00 (s, 3H), 2.95 (dd, J = 17.5, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 169.4, 167.8, 52.8, 52.0, 44.4, 37.8, 36.2, 33.4. ESI-MS: m/z = 218 $[M+H]^+$; m/z = 240 $[M+Na]^+$; m/z = 256 $[M+K]^+$.

Diisopropyl 2-(dimethylcarbamoyl)succinate (5ga): Following the general procedure and using *i*-PrOH as nucleophile, olefin **4g** was converted for 90%. The compound **5ga** has been purified by column chromatography petroleum ether/ethyl acetate 70:30 then 50:50, obtaining a yellow oil; isolated yield: 88% (0.481 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (hept, J = 6.3 Hz, 1H), 4.97 (hept, J = 6.3 Hz, 1H), 4.08 (dd, J = 8.3, 5.9 Hz, 1H), 3.15 (s, 3H), 2.98 (dd, J = 17.3, 8.4 Hz, 1H), 2.98 (s, 3H), 2.88 (dd, J = 17.4, 5.9 Hz, 1H), 1.24 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 168.5, 168.0, 69.4, 68.4, 45.0, 37.9, 36.2, 34.0, 21.9 (2C), 21.8, 21.7. ESI-MS: m/z = 274 $[M+H]^+$; m/z = 296 $[M+Na]^+$; m/z = 312 $[M+K]^+$.

Dibenzyl 2-(dimethylcarbamoyl)succinate (5gb): Synthesized following the general procedure and using BnOH as nucleophile. The compound **5gb** has been purified by column chromatography petroleum ether/CH_2Cl_2 50:50 then 20:80, obtaining a yellow oil; isolated yield: 93% (0.686 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H), 5.18 – 5.03 (m, 4H), 4.19 (dd, J = 8.6, 5.7 Hz, 1H), 3.15 (dd, J = 17.5, 8.6 Hz, 1H), 3.06 (s, 3H), 3.01 (dd, J = 17.5, 5.7 Hz, 1H), 2.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 168.7, 167.6, 135.7, 135.4, 128.71, 128.67, 128.5, 128.4, 128.3, 128.2, 67.4, 66.9, 44.7, 37.8, 36.2, 33.7. ESI-MS: m/z = 370 $[M+H]^+$; m/z = 392 $[M+Na]^+$; m/z = 408 $[M+K]^+$.

Di-*tert*-butyl 2-(dimethylcarbamoyl)succinate (5gc): Following the general procedure, but using *t*-BuOH as nucleophile and 5 mol% of catalyst loading at 50°C, olefin **4g** was converted for 60%. The compound **5gc** has been purified by column chromatography (petroleum

ether/CH_2Cl_2 20:80 then pure CH_2Cl_2), obtaining a pale orange oil; isolated yield: 40% (0.241 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (dd, J = 8.2, 6.0 Hz, 1H), 3.14 (s, 3H), 2.98 (s, 3H), 2.90 (dd, J = 17.3, 8.2 Hz, 1H), 2.80 (dd, J = 17.3, 6.0 Hz, 1H), 1.43 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 168.4, 168.3, 82.2, 81.0, 45.9, 37.8, 36.2, 34.8, 28.2, 28.0. ESI-MS: m/z = 302 $[M+H]^+$; m/z = 324 $[M+Na]^+$; m/z = 340 $[M+K]^+$.

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[18] Pd(II) complexes bearing bisoxazoline or diphosphine ligands resulted to be inactive in our bis-alkoxycarbonylation reaction of α-olefins, therefore were not tested with the less reactive electron-deficient olefins. See ref. [4e].

[19] The bis-methoxycarbonylated dimethyl 2-(diethoxyphosphoryl)succinate product **7**, deriving from olefin **6**, has been isolated and fully characterized (page S10, SI).

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