



## Regioselective one-step alkoxy-aryloxycarbonylation of alkenes

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### ABSTRACT

The direct alkoxy-aryloxycarbonylation reaction of olefins has been realized for the first time. Under palladium(II) catalysis and with *p*-benzoquinone as oxidant, various olefins (aromatic, aliphatic and 1,2-disubstituted), alcohols (primary, secondary and tertiary) and phenols (with different *para*, *meta* and *ortho* substituents) have been converted in one-step into mixed alkyl aryl succinates in moderate to excellent yields (up to 90%). The reaction is completely regioselective, as the aryl ester moiety was consistently observed on the more substituted carbon of the starting alkene double bond. Based on experimental results and detailed DFT calculations, a plausible catalytic cycle has been proposed, accounting for the observed regioselectivity. Interestingly, from our computation studies, benzoquinone was found to be crucial not only to regenerate the catalytic active species, but also for promoting the final elimination step, leading to the desired succinate. Finally, some reactions were performed to prove the different chemical behavior of the two installed ester groups.

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## 1. Introduction

Since Reppe's pioneering work [1], catalytic carbonylation reactions [2–11] of unsaturated compounds have become a milestone in organic synthesis for the preparation of bulk and fine chemicals containing the carbonyl functionality, such as aldehydes, carboxylic acids, esters, amides, etc. These processes employ CO as an inexpensive C1 building block, which is widely used in both academic laboratories and in industries [12,13], and can also be generated from non-gaseous surrogates [14,15].

In particular, industrially and pharmaceutically useful succinates [16–19] can be easily obtained by the bis-alkoxycarbonylation of olefins [20,21] in the presence of a suitable alcohol under oxidative conditions (Scheme 1a). In oxidative carbonylations, the addition of an oxidant is essential to regenerate the catalytic active species [20–24].

Among metal catalysts developed so far, palladium-based complexes still play a crucial role in carbonylation reactions, including bis-alkoxycarbonylation [2,24]. Various methods have been

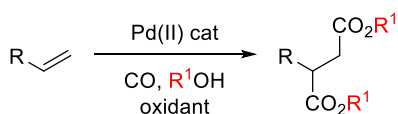
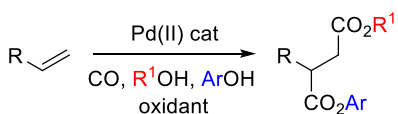
described since the first Pd-catalyzed bis-alkoxycarbonylation of olefins was reported in 1972 by Fenton et al. [25], although stoichiometric processes were already developed by Heck [26] and Yakuwa [27]. PdCl<sub>2</sub> was utilized by Fenton as a catalyst together with molecular oxygen as the final oxidant, in the presence of a mixture of CuCl<sub>2</sub> and FeCl<sub>3</sub> [25]. In 2002, Bianchini and co-workers selectively obtained dimethyl 2-phenylsuccinate by the appropriate choice of the pyridinimine ligand, using benzoquinone as oxidant [28]. They studied the influence of various parameters on the selectivity of the reaction, and, based on the results obtained, proposed the first detailed catalytic cycle for this process. More recently, new ligands and catalysts have been developed to perform the process. As an example, *N*-heterocyclic carbene (NHC) ligands were utilized by Jang and co-workers, again in presence of benzoquinone [29]. Even the asymmetric version of Pd catalyzed bis-alkoxycarbonylation of olefins [20,30,31] has been extensively investigated since the first contribution by Consiglio and collaborators [32].

The main problems that emerge from these examples are represented by the narrow scope of the process, especially regarding the alcohols, and by the usually drastic reaction conditions required, i.e. high temperatures and high CO pressures. Recently, we have reported the bis-alkoxycarbonylation of terminal [33], internal

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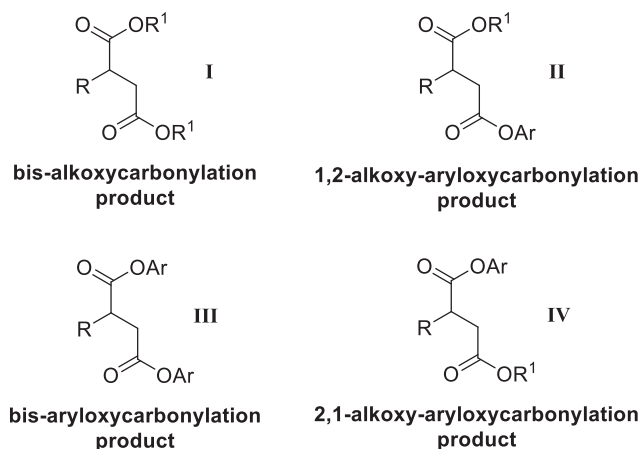
## a. Classical oxidative bis-alkoxycarbonylation of olefins

b. Regioselective alkoxy-aryloxy-carbonylation of olefins (*this work*)

**Scheme 1.** Pd(II)-catalyzed (a) Bis-alkoxycarbonylation of olefins, (b) Alkoxy-aryloxy-carbonylation of olefins (*this work*).

[34], electron-deficient alkenes [35], and of various allyl compounds [36]. Using aryl  $\alpha$ -diimine palladium catalysts, *p*-benzoquinone (*p*-BQ) as oxidant and various types of alcohols as nucleophiles, the reactions proceeded under very mild conditions, producing high yields of the respective carbonylated products. However, despite all the contributions reported in the literature, to the best of our knowledge, no example of intermolecular bis-alkoxycarbonylation that allows the simultaneous addition of two different ester functionalities to the olefin has been described so far. It is worth mentioning that the diversification of the ester functionalities could simplify post-functionalization reactions, possibly facilitating the synthesis of biologically active molecules or drugs in which the succinic scaffold bears two different functional groups (Fig. 1).

In our previous studies on the bis-alkoxycarbonylation reaction of olefins, involving benzoquinone as an oxidant [33–36], we detected the formation of a by-product that contained an aryloxy and an alkoxy substituent on the two different ester groups of the succinate, resulting from the ability of hydroquinone, generated *in situ* from benzoquinone, to act as a nucleophile. Low amounts of the same by-product were also found by others [37]. The formation of this type of product, albeit in minimal amounts, suggests that a direct process for the synthesis of non-homoesteric succinates from low-cost olefins could in principle be developed. The main obstacle in achieving this objective could be the regioselectivity and chemoselectivity of this envisioned process since, in addition to the bis-alkoxycarbonylated (I) and the bis-aryloxy-carbonylated (III) products, a mixture of two alkoxy-aryloxy-carbonylation products, deriving from 1,2-olefin insertion (II) or 2,1-olefin insertion (IV), could be potentially obtained (Fig. 2).

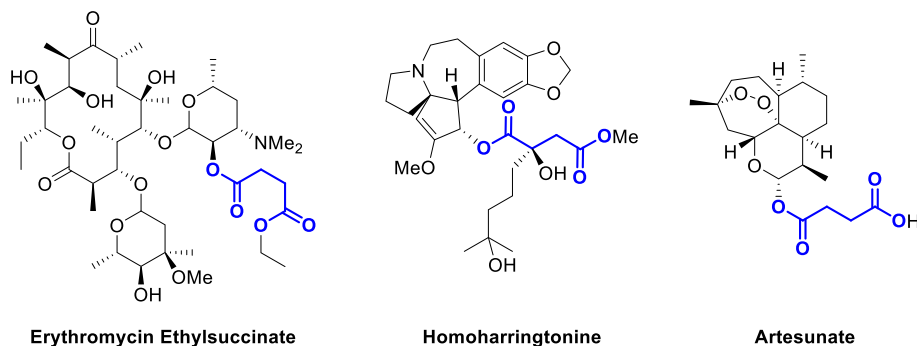


**Fig. 2.** Possible products of the alkoxy-aryloxy-carbonylation reaction for  $\alpha$ -olefins.

In this work, the possibility to realize an unprecedented and regioselective one-step 2,1-alkoxy-aryloxy-carbonylation of alkenes has been investigated (Scheme 1b).

## 2. Results and discussion

During our investigation on the bis-alkoxycarbonylation of internal olefins [34], we noticed that, in the presence of isopropanol and using  $\beta$ -methyl styrenes as substrates, a non-negligible amount of succinate bearing the hydroquinone moiety on the ester bound to the phenyl-substituted carbon was obtained. Therefore, we decided to initiate our study with styrene and isopropanol as model substrates. Using 1 mol% of catalyst, formed *in situ* from Pd(TFA)<sub>2</sub> and the aryl  $\alpha$ -diimine ligand **1a**, *p*-BQ as oxidant (1.5 equiv) and *p*-TSA as additive (2 mol%), in an *i*PrOH:THF 1:1 solution, under 4 bar of CO at 20 °C, the desired 1-(4-hydroxyphenyl) 4-isopropyl 2-phenylsuccinate **3a** was gratifyingly obtained in 68% selectivity over a complete olefin conversion, after 67 h reaction time (Table 1, entry 1). The main by-products detected were the bis-isopropoxycarbonylated product **4a** and the dimeric compound **5a**, which resulted from the reaction of the second hydroxyl group of hydroquinone. Clearly, hydroquinone was generated *in situ* by the reduction of benzoquinone within the catalytic cycle. By adding 30 mol% of external hydroquinone and avoiding the use of *p*-TSA, a drastic drop in conversion was noticed, together with an increase in selectivity toward **3a** (Table 1, entry 2). This is in agreement with literature data, suggesting that the role of the acid is primarily speeding up the reduction of the benzoquinone [38], which is essential to regenerate the catalytic active



**Fig. 1.** Examples of approved drugs containing the succinic scaffold bearing two different carboxylic functionalities.

**Table 1**  
Screening of the conditions for the alkoxy-aryloxycarbonylation of olefins.<sup>[a]</sup>

| Entry               | Catalyst Loading [mol%] | CO pressure [bar] | Hydroquinone [equiv] | iPrOH/THF ratio | Conversion [%] <sup>[b]</sup> | 3a [%] <sup>[b]</sup>  | 4a [%] <sup>[b]</sup> | 5a [%] <sup>[b]</sup> |
|---------------------|-------------------------|-------------------|----------------------|-----------------|-------------------------------|------------------------|-----------------------|-----------------------|
| 1                   | 1                       | 4                 | 0                    | 1:1             | 100                           | 68                     | 20                    | 12                    |
| 2 <sup>[c]</sup>    | 1                       | 4                 | 0.3                  | 1:1             | 25                            | 82                     | 11                    | 7                     |
| 3                   | 0.5                     | 4                 | 0.3                  | 1:1             | 100                           | 68                     | 20                    | 12                    |
| 4                   | 0.5                     | 4                 | 2                    | 1:1             | 90                            | 85 (77) <sup>[d]</sup> | 9                     | 6                     |
| 5 <sup>[e]</sup>    | 0.5                     | 1                 | 2                    | 1:1             | 36                            | 71                     | 14                    | 2                     |
| 6 <sup>[e,f]</sup>  | 1                       | 1                 | 2                    | 1:1             | 45                            | 67                     | 16                    | 2                     |
| 7 <sup>[e,f]</sup>  | 2                       | 1                 | 2                    | 1:1             | 55                            | 65                     | 15                    | 3                     |
| 8 <sup>[e,f]</sup>  | 5                       | 1                 | 2                    | 1:1             | >98                           | 60                     | 12                    | 2                     |
| 9                   | 1                       | 4                 | 2                    | 1:1             | 100                           | 83                     | 11                    | 6                     |
| 10                  | 1                       | 4                 | 2                    | 3:7             | 100                           | 85                     | 9                     | 6                     |
| 11                  | 1                       | 4                 | 2                    | 15:85           | 100                           | 88                     | 6                     | 6                     |
| 12 <sup>[g]</sup>   | 1                       | 4                 | 2                    | 7:93            | 100                           | 92                     | 0                     | 8                     |
| 13 <sup>[g,h]</sup> | 1                       | 4                 | 2                    | 7:93            | < 5                           | N/D                    | N/D                   | N/D                   |

<sup>[a]</sup> Reaction performed in autoclave at indicated CO pressure, with styrene **2a** (1 mmol-scale), Pd(TFA)<sub>2</sub>: ligand **1a** = 1: 1.1 at the indicated catalyst loading, using 1.5 equiv. of *p*-BQ and 2.0 mol% of *p*-TSA in *i*PrOH/THF (0.5 M) as the reaction medium, for 67 h at 20 °C. <sup>[b]</sup> Selectivity, determined by <sup>1</sup>H NMR analysis of the reaction crude. <sup>[c]</sup> No *p*-TSA was utilized. <sup>[d]</sup> Isolated yield in brackets. <sup>[e]</sup> Reaction time = 45 h. <sup>[f]</sup> Isopropyl cinnamate, together with other unidentified by-products, has been detected. <sup>[g]</sup> Olefin concentration = 0.25 M. <sup>[h]</sup> Anhydrous acetone was used in place of THF. N/D = not detected.

species. Reducing the catalyst loading to 0.5 mol%, a higher selectivity in **3a** was achieved by adding 2 equiv of external 1,4-hydroquinone, although no complete conversion was observed (compare entries 3 and 4 of Table 1). Lowering the CO pressure to 1 bar, the substrate conversion increased as the catalyst loading was augmented, while the selectivity in **3a** decreased (Table 1, entries 5–8). This indicates that, under 1 bar of CO, a higher catalyst loading promotes undesired side reactions. Considering these results, we decided to proceed using 1 mol% of catalyst loading, 2 equiv of hydroquinone and 4 bar of CO to investigate the effect of the *i*PrOH/THF solvent ratio (Table 1, entries 9–12). A reduction in the amount of *i*PrOH produced an increased selectivity in **3a**. Indeed, the best result was attained with *i*PrOH/THF = 7:93 (i.e. 4 equiv of *i*PrOH with respect to the olefin) and an olefin concentration of 0.25 M (Table 1, entry 12). Unfortunately, the attempt to replace THF with the greener solvent acetone [39] was unsuccessful (Table 1, entry 13).

When the conditions of Table 1 entry 12 were applied to *p*-methylstyrene **2b**, incomplete conversion of the olefin was observed (Table 2, entry 1). Hence, we decided to raise the catalyst loading to 2 mol%, also enhancing the olefin concentration (0.33 M). Under these conditions, complete conversion and high selectivity were again achieved (Table 2, entry 2). A little survey on aryl  $\alpha$ -diimine ligands was then performed with *p*-methylstyrene, confirming **1a** as the best choice (Table 2, entries 3–6). The high reactivity of the catalytic system obtained with ligand **1a** is probably due to the constrained conformation assumed by the reaction intermediates in which the strong steric interactions, between the methyl groups of the backbone and those in the phenyl *ortho*-positions, force the phenyl rings to arrange almost perpendicular to the palladium coordination plane, thus facilitating the release of the succinic product [34,40,41]. By lowering the amounts of isopropanol and hydroquinone to 1.5 equiv, 87% selectivity was maintained (Table 2, entry 7).

With the optimized conditions in hand (Table 2, entry 7), we proceeded to assess the scope of the reaction (Table 3). Various substituted vinyl arenes bearing different electron-withdrawing and electron-donating groups were successfully employed. In particular, products **3a–3f**, deriving from *para*-substituted styrenes, have been isolated with good to excellent yields, the best ones being attained with styrene **2a** (90%) and *p*-chlorostyrene **2d** (84%) [42]. From these data, however, a reactivity trend based on the properties of the EWG or EDG in *para*-position cannot be deduced.

Concerning *m*-substituted styrenes, a higher yield was obtained with the electron-withdrawing CF<sub>3</sub> group (81%, **3g**) with respect to electron-donating OMe group (64%, **3h**). *Ortho*-substitution with the bromide (olefin **2i**) resulted in low conversion, yielding only 22% isolated yield of compound **3i**, while a good yield can be reached with an *o*-OMe substituent (69%, **3j**). Gratifyingly, the same reaction could also be applied to allylic compounds (allyl benzene **2k**, allyl acetate **2n** and allyl phenyl ether **2o**) and aliphatic olefins (3-butenylbenzene **2l** and 1-heptene **2m**) still with satisfactory isolated yields up to 74%. In particular, especially for the allyl acetate **2n**, it should be noted that in addition to the by-products **4–6**, a  $\beta,\gamma$ -unsaturated ester could also be attained, due to the possible formation of a  $\pi$ -allylpalladium intermediate [43]. Therefore, although the conversion was not complete, obtaining **3n** as the main product proves the good selectivity of our developed method with respect to side reactions.

Interestingly, with 1,2-disubstituted olefins the reaction was diastereospecific as already observed in our investigation on the bis-alkoxycarbonylation of internal olefins [34]. In particular, starting from (*Z*)- $\beta$ -methylstyrene and (*E*)- $\beta$ -methylstyrene, products **3p** and **3q** were obtained respectively with good yields, with a slightly higher reactivity being observed in the case of the *Z* alkene. Unfortunately, using 1,2-disubstituted aliphatic olefins as substrate, under the same reaction conditions, only poor results were achieved [44].

**Table 2**  
Screening of the aryl  $\alpha$ -diimine ligand.<sup>[a]</sup>

**1a**, R<sup>1</sup> = Me, R<sup>2</sup> = Me  
**1b**, R<sup>1</sup> = *i*Pr, R<sup>2</sup> = Me  
**1c**, R<sup>1</sup> = Me, R<sup>2</sup> = H  
**1d**, R<sup>1</sup> = Me, R<sup>2</sup> = Me  
**1e**, R<sup>1</sup> = Me, R<sup>2</sup> = Me

Reaction conditions:  
 2.0 mol% Pd(TFA)<sub>2</sub>  
 2.2 mol% Ligand **1**  
 1.5 equiv *p*-BQ, 2.0 mol% *p*-TSA  
 2 equiv 1,4-hydroquinone  
 4 equiv *i*PrOH  
 P<sub>CO</sub> = 4 bar  
 THF (0.33 M), 20 °C, 67 h

| Entry            | Ligand    | Conversion [%] <sup>[b]</sup> | 3b [%] <sup>[b]</sup> | 4b [%] <sup>[b]</sup> | 5b [%] <sup>[b]</sup> | 6b [%] <sup>[b]</sup> |
|------------------|-----------|-------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| 1 <sup>[c]</sup> | <b>1a</b> | 83                            | 86                    | 4                     | 9                     | 1                     |
| 2                | <b>1a</b> | 100                           | 88                    | 0                     | 8                     | 4                     |
| 3                | <b>1b</b> | 39                            | 84                    | 0                     | 5                     | 11                    |
| 4                | <b>1c</b> | 8                             | 56                    | 0                     | 0                     | 44                    |
| 5                | <b>1d</b> | 100                           | 70                    | 5                     | 10                    | 15                    |
| 6 <sup>[d]</sup> | <b>1e</b> | 87                            | 84                    | 4                     | 5                     | 3                     |
| 7 <sup>[e]</sup> | <b>1a</b> | 100                           | 87                    | 2                     | 8                     | 3                     |

<sup>[a]</sup>Reaction performed in autoclave at P<sub>CO</sub> = 4 bar, with *p*-methylstyrene **2b** (1 mmol-scale), Pd(TFA)<sub>2</sub> 2.0 mol%, Ligand **1** 2.2 mol%, using 2.0 equiv. of 1,4-hydroquinone, 4.0 equiv. of isopropanol, 1.5 equiv. of *p*-BQ and 2.0 mol% of *p*-TSA in THF (0.25 M) as the reaction medium, for 67 h at 20 °C. <sup>[b]</sup> Selectivity, determined by <sup>1</sup>H NMR analysis of the reaction crude. <sup>[c]</sup> 1 mol% of catalyst loading and olefin concentration = 0.25 M. <sup>[d]</sup> Up to 5% of other unidentified products. <sup>[e]</sup> 1.5 equiv of 1,4-hydroquinone and 1.5 equiv of *i*PrOH have been utilized.

In addition to *i*PrOH, various alcohols were well tolerated. Even with unbulky MeOH, the selectivity of the reaction remained high (yield of 1-(4-hydroxyphenyl) 4-methyl 2-phenylsuccinate **3r**, 82%). White single crystals of **3r** were obtained by slow evaporation of the solvent, after dissolving the compound in a small amount of CH<sub>2</sub>Cl<sub>2</sub>, and XRD analysis confirmed the product structure (see [Supporting Information](#)). A long-chain alcohol, such as 1-dodecanol, could be successfully used, as well as benzyl alcohol and isobutanol without affecting the product yields (**3s–3u**). Remarkably, even with bulky *t*-BuOH and secondary cyclic alcohols, such as cyclopentanol, the corresponding products could be isolated in moderate to high yields (**3v** and **3w**, [Table 3](#)).

We then explored the scope of phenolic derivatives. Since hydroquinone is always formed *in situ* from benzoquinone, we investigated the possibility of changing the oxidant with the aim of reducing undesired competitive reactions arising from the different phenolic derivatives. However, of all the oxidizing agents tested, none gave satisfactory results, and overall no conversion of the styrene was observed (see [Supporting Information](#)). Therefore, using 4-methoxyphenol as a model substrate, together with styrene and isopropanol, we finally found that with 6 equivalents of the phenolic derivative it was possible to obtain a 95:5 selectivity of the desired product with respect to that deriving from hydroquinone (see [Supporting information](#)). It is worth mentioning that the unreacted excess of the phenol derivative could be easily recovered by chromatographic column. In addition to *p*-methoxyphenol, phenol and *p*-nitrophenol could be successfully employed (**3x–3z**). With *meta*-substituted phenols, satisfactory yields were obtained (**3aa** and **3ab**), while only a poor yield was found when substituents in *ortho* position were present (**3ac** and

**3ad**) and the main product attained was **3a** deriving from the *in situ* generated hydroquinone. From this screening on phenols, it appears that lower yields are obtained when EWGs are present on the aromatic ring, probably indicating that the electron-withdrawing effect renders the phenolic oxygen less nucleophilic.

It is important to underline that all the reported examples proceed in a regioselective manner, since the aryl ester is always bonded to the more substituted carbon of the starting olefin (or to the phenyl-substituted carbon, in the case of the  $\beta$ -methylstyrenes). Under our optimized conditions, the bis-aryloxycarbonylated compound (**III**, [Fig. 2](#)) and the succinic product bearing the alkyl ester bonded to the more substituted carbon (**II**, [Fig. 2](#)) have never been detected [45].

In order to clarify the observed selectivity, we then decided to investigate in detail the mechanism involved in the process, by means of DFT calculations. Mechanistic studies concerning the “classical” bis-alkoxycarbonylation reaction ([Scheme 1a](#)) have already been carried out [28,40,41,46–51], and recently some of us have proposed a catalytic cycle describing the main steps of the process ([Scheme 2](#)) [36,52]. In particular, starting from the complex (NN)Pd(TFA)<sub>2</sub> **A**, in the presence of carbon monoxide and an alcohol molecule, the alkoxy carbonylpalladium complex **B** is formed. At this point, a 2,1-insertion of the olefin could be expected, as widely reported by the literature when nitrogen ligands are employed [20,40,41,46–59], accounting for the formation of five-membered intermediate **C**. Subsequent CO insertion leads to the 6-membered complex **D**. Then, the phenol derivative coordinates the palladium to give product **3** and Pd(0) after reductive elimination. The active Pd(II) species is then restored by benzoquinone.

**Table 3**  
Scope of the alkoxy-aryloxy-carbonylation of alkenes.<sup>[a]</sup>

$R^1 = \text{aryl, alkyl}$   
 $R^2 = \text{H, Me}$

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Olefin Scope

|   |   |
|---|---|
| <p> <b>3a</b>, X = H, y = 90%<br/> <b>3b</b>, X = Me, y = 75%<br/> <b>3c</b>, X = Br, y = 56% (86%)<sup>[b]</sup><br/> <b>3d</b>, X = Cl, y = 84%<br/> <b>3e</b>, X = CN, y = 62%<br/> <b>3f</b>, X = OMe, y = 66%         </p> <p> <b>3g</b>, X = CF<sub>3</sub>, y = 81%<br/> <b>3h</b>, X = OMe, y = 64% (80%)<sup>[b]</sup> </p> <p> <b>3i</b>, X = Br, y = 22% (31%)<sup>[b]</sup><br/> <b>3j</b>, X = OMe, y = 69% (88%)<sup>[b]</sup> </p> | <p> <b>3k</b>, R<sup>1</sup> = CH<sub>2</sub>Ph, y = 42% (57%)<sup>[b,c]</sup><br/> <b>3l</b>, R<sup>1</sup> = CH<sub>2</sub>CH<sub>2</sub>Ph, y = 65% (86%)<sup>[b]</sup><br/> <b>3m</b>, R<sup>1</sup> = <i>n</i>-C<sub>5</sub>H<sub>11</sub>, y = 60%<br/> <b>3n</b>, R<sup>1</sup> = CH<sub>2</sub>OAc, y = 36% (60%)<sup>[b,c]</sup><br/> <b>3o</b>, R<sup>1</sup> = CH<sub>2</sub>OPh, y = 74% (84%)<sup>[b,c]</sup> </p> <p> <b>3p</b>, y = 76%<sup>[d]</sup> </p> <p> <b>3q</b>, y = 67%<sup>[d]</sup> </p> |
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Alcohol Scope<sup>[e]</sup>

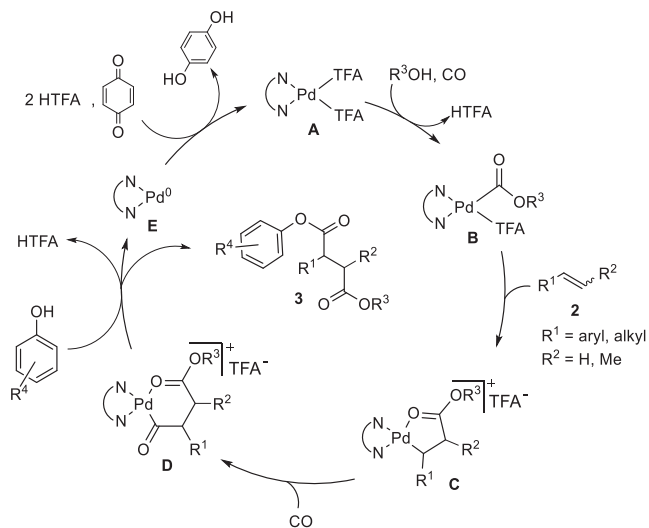
|  |   |  |
|--|---|--|
| <p> <b>3r</b>, R<sup>3</sup> = Me, y = 82%<br/> <b>3s</b>, R<sup>3</sup> = <i>n</i>-C<sub>12</sub>H<sub>25</sub>, y = 79%         </p> | <p> <b>3t</b>, R<sup>3</sup> = Bn, y = 74%<br/> <b>3u</b>, R<sup>3</sup> = <i>t</i>Bu, y = 80%         </p> | <p> <b>3v</b>, R<sup>3</sup> = <i>t</i>Bu, y = 60%<sup>[f]</sup><br/> <b>3w</b>, R<sup>3</sup> = cyclopentyl, y = 83%         </p> |
|--|---|--|

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Phenol Scope<sup>[g]</sup>

|   |  |
|---|--|
| <p>Ar =</p> <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> <p><b>3x</b>, Z = OMe, y = 89%<sup>[h]</sup></p> </div> <div style="text-align: center;"> <p><b>3aa</b>, y = 51%<sup>[i]</sup></p> </div> <div style="text-align: center;"> <p><b>3ac</b>, Z = Cl, y = 23%<sup>[j]</sup></p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: flex-start; margin-top: 10px;"> <div style="text-align: center;"> <p><b>3y</b>, Z = H, y = 67%</p> </div> <div style="text-align: center;"> <p><b>3ad</b>, Z = NO<sub>2</sub>, y = 14%<sup>[j]</sup></p> </div> <div style="text-align: center;"> <p><b>3ab</b>, y = 56%</p> </div> </div> | <p> <b>3ae</b>, y = 84%<sup>[h]</sup> </p> |
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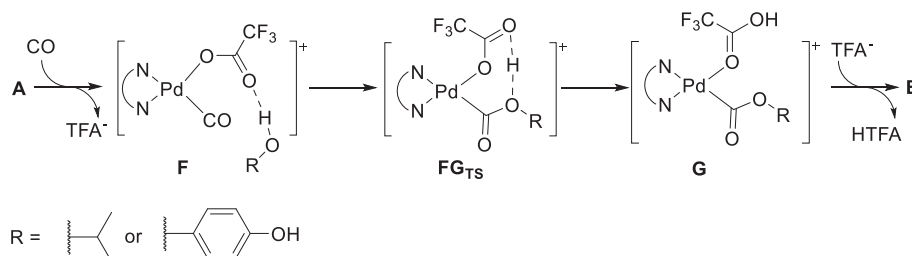
<sup>[a]</sup>Reaction performed in autoclave at P<sub>CO</sub> = 4 bar, with alkene **2** (1 mmol-scale), Pd(TFA)<sub>2</sub> 2.0 mol%, ligand **1a** 2.2 mol%, using 1.5 equiv. of ArOH, 1.5 equiv. of alcohol, 1.5 equiv. of *p*-BQ and 2.0 mol% of *p*-TSA in THF (0.33 M) as the reaction medium, for 67 h at 20 °C. Isolated yields are reported. <sup>[b]</sup>If incomplete, olefin conversion is reported in parenthesis. <sup>[c]</sup>5 mol% of catalyst loading was utilized with olefin concentration = 0.5 M. <sup>[d]</sup>2 equiv of hydroquinone was utilized in *i*PrOH:THF = 1:1 (0.5 M) as reaction medium. <sup>[e]</sup>1 mol% of catalyst loading was utilized. <sup>[f]</sup>Reaction performed using 5 mol% of catalyst loading with 4 equiv of *t*BuOH and olefin concentration = 0.5 M, at 50 °C. <sup>[g]</sup>1 mol% of catalyst loading and 6 equiv of ArOH were utilized. <sup>[h]</sup>2 mol% of catalyst loading was utilized. <sup>[i]</sup>3 mol% of catalyst loading was utilized with olefin concentration = 0.5 M. <sup>[j]</sup>NMR yield. Evaluated using 1,3,5-trimethoxybenzene as standard.



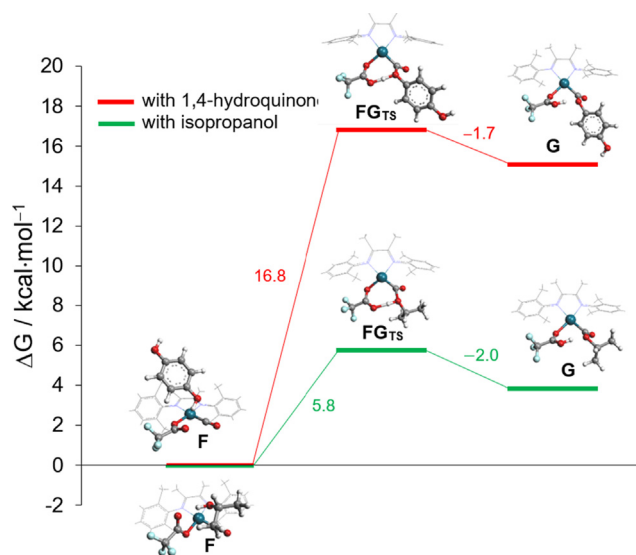
**Scheme 2.** Proposed catalytic cycle.

To date, the full cycle has been studied computationally [52] using only model catalysts and substrates, and it proved to be suitable to explain recent experimental findings [34–36]. However, when applied to the present reaction it became quickly clear that it fails to account for the observed reactivity. Therefore, more accurate methods, considering the true structure of the catalyst, were applied.

First of all, the 2,1-insertion of the olefin leading to **C** has been compared, by calculations, with the 1,2-insertion. As expected, the observed 2,1-insertion results more advantageous both from kinetic (by 9.9 kcal/mol) and thermodynamic (by 5.3 kcal/mol) point of views. These data, together with the atom-connectivity in products **3**, support the order of addition of the nucleophiles, since the preferential entry of the alkyl alcohol over the phenol must occur at the beginning of the cycle (from **A** to **B**) while, the opposite order is expected at the end of the process (from **D** to **E**). Therefore, these two crucial steps have been investigated in detail.



**Scheme 3.** Proposed mechanism for the formation of complex **B** using isopropanol or 1,4-hydroquinone.

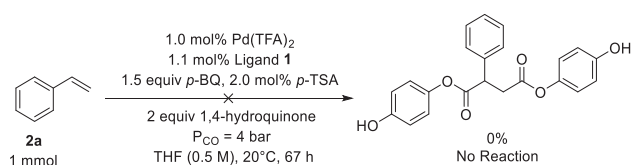


**Fig. 3.** Energy profile (kcal/mol) for the first ROH nucleophilic attack (from intermediates **F** to **G**) with isopropanol (green line) and 1,4-hydroquinone (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Regarding the formation of **B** (Scheme 3), it starts with the substitution of a TFA ligand with a CO molecule in complex **A** to form the (NN)Pd(CO)(TFA) intermediate. Subsequently, an alcohol molecule coordinates, *via* hydrogen bond, the trifluoroacetate ligand (complex **F**), placing the alcohol in a position suitable for the formation of a new C–O bond. Complex **F** evolves, through the transition state **FG<sub>TS</sub>**, into **G**, still bearing the HTFA coordinated. Finally, the release of the trifluoroacetic acid molecule leads to complex **B**.

When the alcohol is isopropanol, the **FG<sub>TS</sub>** energy barrier is +5.8 kcal/mol, which increases to +16.8 kcal/mol when the 1,4-hydroquinone is employed (Fig. 3). Therefore, the formation of the alkoxy carbonyl complex **G** is kinetically favored in the first case.

Accordingly, when the reaction was performed using only hydroquinone, no conversion of the olefin was detected (Scheme 4). Our computational study confirms that this nucleophile is not able



**Scheme 4.** Unsuccessful bis-aryloxycarbonylation of styrene using 1,4-hydroquinone.

to initiate the catalytic cycle and explains why no bis-aryloxycarbonylated (**III**, Fig. 2) and 1,2-alkoxy-aryloxycarbonylated (**II**, Fig. 2) products were ever observed.

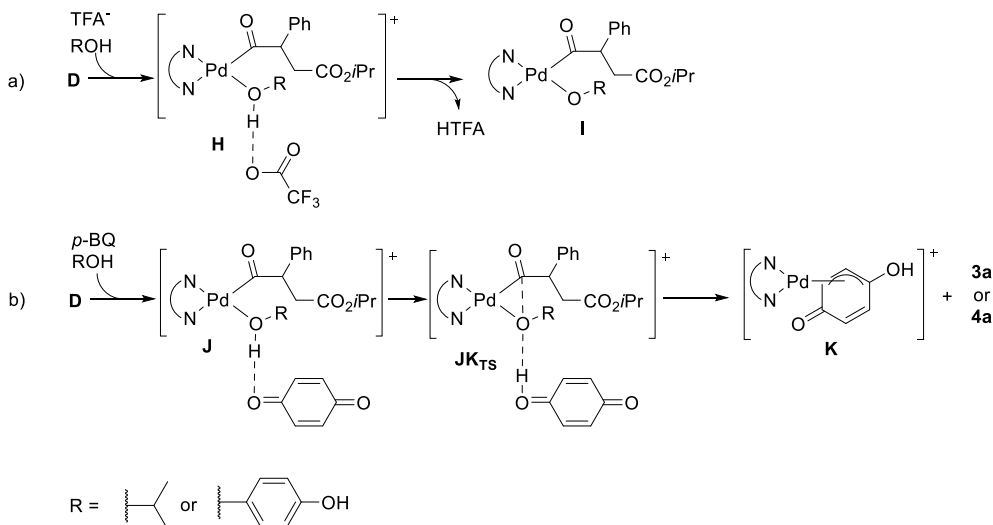
Regarding the final part of the catalytic cycle, we have previously proposed [52] that, after the opening of the six-membered palladacycle **D** by an alcohol molecule, the deprotonation of the latter was assisted by the trifluoroacetate anion (intermediate **H**), generating HTFA and the acyl-alkoxy-Pd(II) complex **I** (Scheme 5a). However, the present study proves that this path is viable only for isopropanol, because the hydrogen transfer to  $\text{CF}_3\text{COO}^-$ , to form HTFA, is energetically unfavorable for 1,4-hydroquinone.

By exploring several different reaction pathways, we finally concluded that the concomitant and competitive formation of products **3** and **4** is allowed only when the deprotonation of hydroquinone/isopropanol is directly assisted by *p*-benzoquinone. The crucial role of benzoquinone as hydrogen acceptor may also explain the difficulties encountered in substituting it with other oxidants, as it appears to be essential not only for the final oxidation of the Pd(0) complex, but also in the previous steps of the cycle. Scheme 5b illustrates the steps which can explain the formation of products **3a** or **4a** using styrene as olefin.

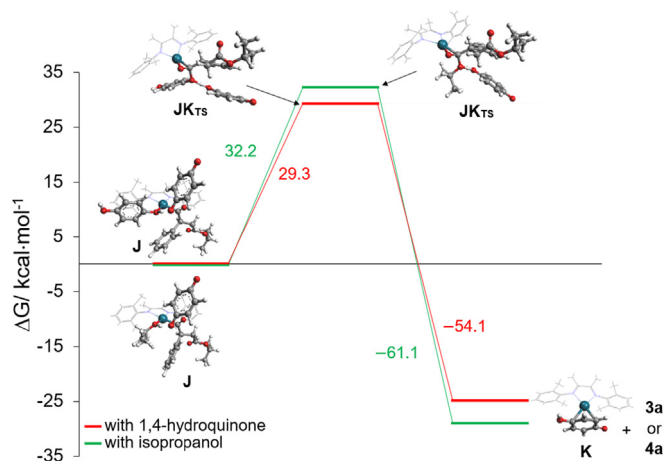
Also in this case, the coordination of the isopropanol or 1,4-hydroquinone forces the opening of the 6-membered palladacycle intermediate **D**. Successively, a hydrogen bond takes place between an oxygen of the benzoquinone and the coordinated alcohol/phenol, forming intermediate **J**. Passing through the transition state **JK<sub>TS</sub>**, a new bond between the acyl and the alkoxy/aryloxy ligand is formed, with a concomitant transfer of hydrogen from ROH to benzoquinone, eventually leading to complex **K** together with products **3a** or **4a**, depending on the R substituent. The regeneration of active palladium species from **K** then may occur according to the previously suggested pathway [52].

In Fig. 4 is reported the energy profile calculated from **J** to **K** both for isopropanol and for hydroquinone.

Interestingly, the formation of product **4a** is thermodynamically favored over **3a**. However, looking at the transition state energies, a lower energy barrier needs to be overcome when hydroquinone acts as a nucleophile (29.3 kcal/mol) instead of *i*PrOH (32.3 kcal/mol). Therefore, the path to products **3** (i.e. from **J** to **K** with hydroquinone) is kinetically favored by about 3 kcal/mol. It should be again underlined that, among all the possible pathways investigated by calculations, the formation of **3** resulted to be possible only when benzoquinone acts as a hydrogen acceptor. Notably, the small difference between the transition state energies for hydroquinone and isopropanol in the second ROH entry accounts for the possibility of obtaining also the classical bis-alkoxy carbonylation [33–36]. Indeed, when a high amount of the alcohol (i.e. using the alcohol as the solvent) is employed, the probability of achieving the bis-alkoxy carbonylated product is enhanced. In the present case, being phenol and alcohol present in the same amount, the kinetic 2,1-alkoxy-aryloxycarbonylated product **3** is favored. This finding confirms what has already been



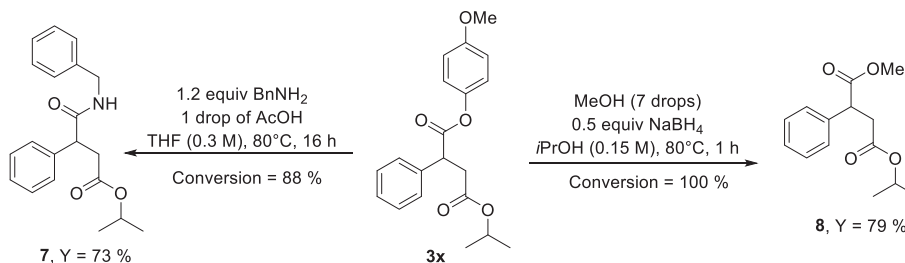
**Scheme 5.** Proposed mechanistic pathways for the final part of the catalytic cycle assisted by a) TFA<sup>-</sup> or b) benzoquinone.



**Fig. 4.** Energy profile (kcal/mol) for the second ROH nucleophilic attack (from intermediates J to K) utilizing isopropanol (green line) and 1,4-hydroquinone (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

noted in Table 1: the selectivity of the reaction can be basically shifted towards the desired product by modifying the quantity of the alcohol.

Finally, to evaluate the reactivity of the two different ester functionalities, the succinate **3x** was allowed to react with benzylamine or with MeOH (Scheme 6). In both cases, only the aryl ester was



**Scheme 6.** Selective aryl ester functionalization for the synthesis of the amide **7** and the methyl ester **8**.

selectively replaced by the nucleophile, obtaining the amide **7** and the succinic ester **8**, in high yields. This result confirms the possibility for regioselective manipulation of the succinic diesters synthesized in this work, thus opening the way to further synthetic diversification.

### 3. Conclusions

In conclusion, the first regioselective one-step alkoxy-aryloxycarbonylation reaction of olefins has been realized. Aryl  $\alpha$ -diimine palladium (II) catalysts, different olefins, alcohols, and phenols have been successfully employed, under mild reaction conditions (4 bar of CO and room temperature), for the synthesis of mixed alkyl aryl succinates.

The reaction proved to be completely regioselective, since the aryl ester is always formed on the more substituted carbon of the double bond of the starting olefin. Through a detailed computational study of the catalytic cycle, utilizing the real structure of the catalyst, the observed regioselectivity has been rationalized. In particular, the role of the benzoquinone, acting not only as oxidant, but also as a base for the deprotonation of the alcohol coordinated to the palladium, has been identified. We believe that these observations can be useful for the implementation of other carbonylation processes involving benzoquinone as an oxidant.

Finally, in order to assess the different chemical reactivity of the two succinic ester functionalities, selective post-functionalization reactions have been performed, thus improving the synthetic utility of the described methodology.

## 4. Experimental section

### 4.1. General experimental methods

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  $^1\text{H}$  NMR taking a direct sample of the crude mixture.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were recorded on a Bruker Avance 400 spectrometer ( $^1\text{H}$ : 400 MHz,  $^{13}\text{C}$ : 101 MHz), using  $\text{CDCl}_3$  as solvent. Chemical shifts are reported in the  $\delta$  scale relative to residual  $\text{CHCl}_3$  (7.26 ppm) for  $^1\text{H}$  NMR and to the central line of  $\text{CDCl}_3$  (77.16 ppm) for  $^{13}\text{C}$  NMR.  $^{13}\text{C}$  NMR were recorded with  $^1\text{H}$  broadband decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, br = broad, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, app dq = apparent as doublet of quartets, m = multiplet. 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. Caution: carbon monoxide is a toxic gas with potentially lethal action, therefore adequate precautions must be observed. The *p*-benzoquinone was purchased by Alfa Aesar and was filtered off a plug of silica gel washing with  $\text{CH}_2\text{Cl}_2$ , obtaining a yellow solid after drying the solution under vacuum. Pure compounds **3** were isolated through flash column chromatography on silica gel 60 (40–60  $\mu\text{m}$ , 230–400 mesh). Olefins were purchased from Merck Sigma-Aldrich. The purchased olefins were filtered off a plug of neutral  $\text{Al}_2\text{O}_3$  and used without further purification. Anhydrous THF was distilled from sodium-benzophenone and methanol was distilled from  $\text{Mg}(\text{OMe})_2$ . Isopropanol was dried over molecular sieves (Alfa Aesar, 4 Å, 1–2 mm, beads). All the other alcohol and phenols derivatives were utilized as purchased.  $\text{Pd}(\text{TFA})_2$  was purchased by Flurochem. All other chemicals were purchased from Merck Sigma-Aldrich and used without further purification. The ligands **1a–1d** were synthesized according to literature procedures [60], while the ligand **1e** was synthesized according to a procedure developed by our group [41]. All solid reagents were weighed in an analytical balance without excluding moisture and air.

CCDC.2242825 (compound **3r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [https://www.ccdc.cam.ac.uk/data\\_request/cif](https://www.ccdc.cam.ac.uk/data_request/cif).

### 4.2. Computational details

All DFT calculations have been performed using the ORCA 4.2.1 suite of quantum chemistry programs [61,62]. For a limited set of computations (thermochemical properties) version 5.0.2 of the same code was used. Geometries were optimized in vacuum using the M06L functional [63] and the def2-TZVP basis [64]. Dispersion corrections were also accounted for, following the DFT-D3 procedure (with zero damping functions) as suggested by Grimme et al. [65]. Vibrational frequencies were calculated at the optimized geometries to check the stability of the stationary points. Free energies at 298 K were evaluated by applying a scale factor of 0.9824 to the vibrational frequencies, adequate for the present combination of DFT functional and basis set [66] and a fictitious pressure of 302 atm for the THF solvent [67], in order to correct the overestimation of entropic contributions. Final single point energy calculations at the previously optimized geometries were performed with the large def2-QZVPP basis [64] and the M06 functional [68], with the inclusion of solvation effects through the SMD

model [69] and of dispersion interactions [65]. 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.

### 4.3. Typical procedure for the alkoxy-aryloxyacylation of olefins

in a nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the olefin **2** (1 mmol) and the alcohol ROH (1.5 mmol) were dissolved in THF (2 mL). The mixture was left under stirring for 10 min. In another nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, the  $\text{Pd}(\text{TFA})_2$  (6.6 mg, 0.02 mmol) and THF (1 mL) were added in sequence. After the mixture turned into a red/brown color (20 min), ligand **1a** (6.4 mg, 0.022 mmol) was added. The mixture was left under stirring for 15 min, turning into a orange color with a precipitate. 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 (162.3 mg, 1.5 mmol), the 1,4-hydroquinone (165 mg, 1.5 mmol) and *p*-TSA· $\text{H}_2\text{O}$  (3.8 mg, 0.02 mmol). After 5 min of stirring, the autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at room temperature (20 °C) for 67 h.

The autoclave was vented off, flushed with nitrogen and the crude was dried under reduced pressure and filtered off a plug of silica gel, washing with  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$  1:1.

The solution was dried up in vacuum and the product was eventually obtained after column chromatography on silica gel. Product characterization data are reported in the Supporting Information.

**Alcohol Scope:** Otherwise differently stated, following the general procedure, for the synthesis of compounds **3r** – **3w**, 1 mol% of catalyst loading has been utilized.

**Phenol Scope:** Otherwise differently stated, following the general procedure, for the synthesis of compounds **3x** – **3ae**, 1 mol% of catalyst loading and 6 equiv of the phenol derivate have been utilized.

### 4.4. Synthesis of amide **7**

In a vial equipped with a magnetic stirring bar, containing the succinate **3x** (0.15 mmol, 51 mg) in THF (0.5 mL), benzylamide (0.18 mmol, 20  $\mu\text{L}$ ) was added dropwise. The mixture was left under stirring for 5 min and 1 drop of glacial acetic acid was added. The vial was tightly capped, parafilm and the reaction was left under stirring at 80 °C for 16 h. The solution was dried up in vacuum and product **7** was eventually obtained after column chromatography on silica gel (petroleum ether/EtOAc 90:10 to 80:20) as white solid; yield: 73% (35.7 mg).  $R_f$  = 0.17 (petroleum ether/EtOAc = 80:20).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 – 7.18 (m, 8H), 7.15 – 7.10 (m, 2H), 5.89 (br s, 1H), 4.95 (hept,  $J$  = 6.3 Hz, 1H), 4.42 (dd,  $J$  = 15.0, 5.8 Hz, 1H), 4.35 (dd,  $J$  = 15.0, 5.8 Hz, 1H), 3.95 (dd,  $J$  = 8.7, 6.2 Hz, 1H), 3.27 (dd,  $J$  = 16.6, 8.7 Hz, 1H), 2.64 (dd,  $J$  = 16.6, 6.2 Hz, 1H), 1.19 (d,  $J$  = 6.3 Hz, 3H), 1.14 (d,  $J$  = 6.3 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3, 171.6, 139.0, 138.3, 129.1, 128.7, 128.1, 127.7, 127.5, 127.4, 68.2, 48.9, 43.8, 38.3, 21.84, 21.80. ESI-MS:  $m/z$  = 326 [M + H] $^+$ .

### 4.5. Synthesis of succinic diester **8**

In a vial equipped with a magnetic stirring bar containing the succinate **3x** (0.15 mmol, 51 mg) in *i*PrOH (1 mL), 7 drop of MeOH and  $\text{NaBH}_4$  (0.075 mmol, 2.8 mg) were added in sequences. The vial was capped and the reaction was left under stirring at 80 °C for 1 h. The reaction was quenched with  $\text{H}_2\text{O}$  (2 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (5  $\times$  5 mL). The combined organic layers were dried



over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed in vacuo. Product **8** was obtained after column chromatography on silica gel (petroleum ether/CH<sub>2</sub>Cl<sub>2</sub> 50:50 to 80:20) as colorless oil; yield: 79% (29.7 mg). *R*<sub>f</sub> = 0.68 (CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35 – 7.24 (m, 5H), 4.99 (hept, *J* = 6.3 Hz, 1H), 4.07 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.67 (s, 3H), 3.15 (dd, *J* = 16.7, 10.0 Hz, 1H), 2.65 (dd, *J* = 16.7, 5.5 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 173.6, 171.1, 137.9, 129.0, 127.9, 127.8, 68.4, 52.4, 47.4, 38.4, 21.90, 21.85. ESI-MS: *m/z* = 251 [M + H]<sup>+</sup>.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcat.2023.03.008>.

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