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Research article

Versatile stereoselective oxidative alkoxycarbonylation of styrenes at room-temperature

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ABSTRACT

Carbonylation reactions carried out at room temperature and at atmospheric pressure of carbon monoxide are highly attractive and extremely rare at the same time. Here, the oxidative alkoxycarbonylation of styrenes to industrially relevant cinnamates has been developed under such a mild conditions (rt, 1 atm of CO) in the presence of a palladium(II) complex bearing a bis(aryl)acenaphthenequinonediimine ligand, benzoquinone and *p*-toluenesulfonic acid. Remarkably, variously substituted styrene derivatives have been efficiently carbonylated using a nearly stoichiometric amount of alcohols, with a dramatic reduction of waste. Even reluctant internal alkenes have shown to be compatible under these carbonylative conditions. In consideration of experimental results and DFT calculations a mechanistic rationale has been proposed. Based on this study, the benzoquinone has been found to promote the final palladium reoxidation, and to boost the reaction under such unprecedent mild conditions. The present methodology has been successfully exploited for the synthesis of high value-added cinnamoyl glycerols and cinnamic acid sugar esters, including the 6-*O*-*p*-coumaroyl-D-glucose natural product.

1. Introduction

Cinnamic acid (3-phenyl-2-propenoic acid) and its derivatives are ubiquitous in biological systems [1]. In particular, cinnamic esters have shown antioxidant [1,2], antimicrobial [1b,2c,3] and antitumoral activities [1,4]. Cinnamates find also applications in the cosmetic industry, especially in sunscreen formulations [5]. Although cinnamic esters can potentially be extracted from plants [2,6], the chemical synthesis still remains the most efficient way to access this class of compounds with high yields and selectivities. Among various established transformations, the carbonylation reaction [7] is probably one of the most versatile methods to achieve cinnamic esters with high atom-economical manner, starting from carbon monoxide, alcohols, and unsaturated compounds such as alkyne or alkene, as largely available and inexpensive reagents [8]. While the branched product (atropate) is generally obtained starting from alkynes [8,9], the inversed regioselectivity with the formation of the linear product is achieved at high pressure of CO, high temperature and/or with a large excess of alcohol (Scheme 1a) [8,10]. Considering the higher availability of styrenes compared with arylacetylenes, the oxidative alkoxycarbonylation of styrenes is a valid alternative for the synthesis of cinnamates (Scheme 1b) [11]. Typically, starting from a styrene derivative, carbon monoxide and an alcohol, the reaction proceeds in the presence of an oxidant, which is necessary to regenerate the active metal species, producing an α,β-unsaturated ester or a succinic acid ester, depending on the reaction conditions. In early works, low selectivity towards the cinnamic product [12] was observed or high CO pressure [13] was required. In 2014, Lei and co-workers reported a palladium-catalyzed oxidative alkoxycarbonylation of alkenes using O_2 as terminal oxidant at 80 °C. Various α,β-unsaturated esters were obtained starting from a stoichiometric amount of alcohol, under 1 atm of CO and 3 mol% of $PdCl_2$ together with 20 mol% of $Cu(OAc)_2$ [14]. A similar catalytic system was also adopted by Malkov and Kočovský, who highlighted the role of acetonitrile both as a ligand and as a solvent, attaining the alkoxycarbonylation of alkenes at 60 °C [15]. More recently, an heterogenous version of this reaction has been reported [16]. Using 1 mol% of Pd/C as the catalyst, a series of *para*-

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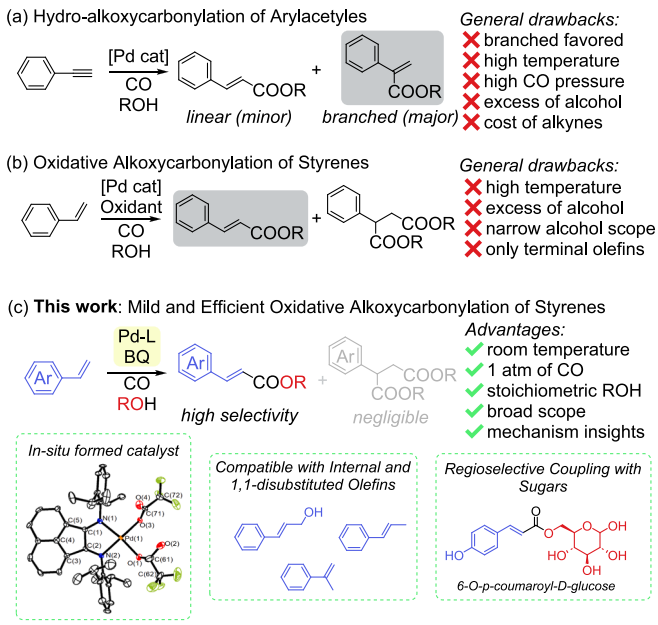


Scheme 1. Cinnamic acid ester synthesis *via* (a) hydro-alkoxycarbonylation of arylacetylenes; (b) oxidative alkoxycarbonylation of styrenes; (c) *This work*.

substituted styrenes have been smoothly converted to cinnamate derivatives under CO/air atmosphere (2 atm of CO and 35 atm of air) at 120 °C. Despite the undisputed value of these works, a versatile alkoxycarbonylation methodology featuring ultra mild conditions (room temperature and 1 atm of CO) is, to the best of our knowledge, totally missing. Current protocols are often limited by a narrow scope regarding the olefins, the use of an excess of alcohol, and sporadic mechanistic investigations [13a,17]. Other methods, which aim to replace CO with surrogates, such as formates, deserve mention [18]. However, in these cases, depending on the desired ester substituent, formate has to be previously synthesized, clearly reducing the synthetic versatility of the method and, compared to the oxidative alkoxycarbonylation using CO, lower yields are generally reached. In this work, we have developed a new palladium-catalyzed alkoxycarbonylation process aimed at the synthesis of cinnamate esters, overcoming the previously identified limitations (Scheme 1c). In fact, our method features general applicability, broad styrenes and alcohols scope, the use of nearly stoichiometric amount of alcohols, and very mild conditions (room temperature and atmospheric pressure of CO). A detailed mechanistic study of the catalytic cycle has been performed and, to demonstrate the versatility of this newly developed methodology, synthetic applications are described.

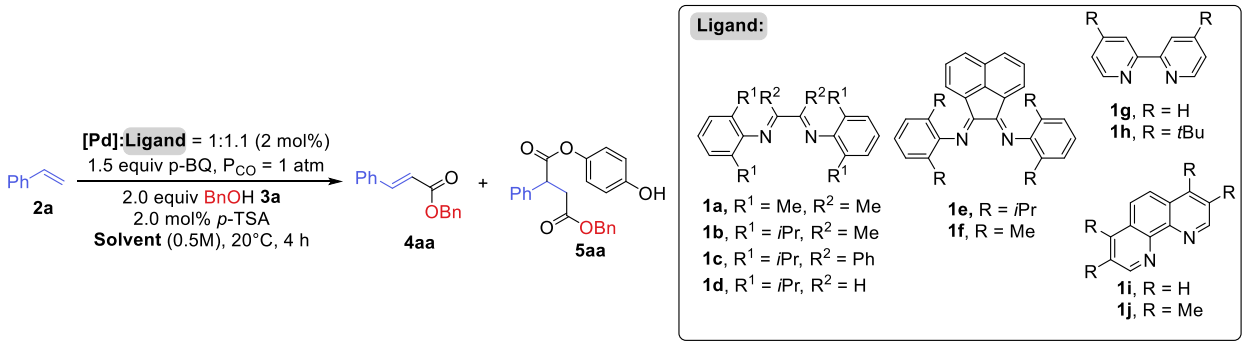
2. Results and discussion

We started our investigation using styrene **2a** and benzyl alcohol **3a** (2 equiv) as model substrates. Based on our expertise with palladium-catalyzed bis-alkoxycarbonylation reactions [19], *p*-benzoquinone (*p*-BQ) has been selected as the oxidant and the reactions have been conducted at room temperature under atmospheric pressure of carbon monoxide, in the presence of 2 mol% of *p*-toluenesulfonic acid (*p*-TSA), which is known to facilitate both the formation of a free-coordination site at the metal centre [13a] and the final *p*-BQ-mediated oxidation step [20]. When $Pd(TFA)_2$ was employed without additional ligands, a poor conversion was obtained and only traces of the desired cinnamic product **4aa** were detected (Table 1, entry 1). Then, several nitrogen ligands were evaluated. Using the aryl α-diimine ligand **1a**, which has been previously applied in bis-alkoxycarbonylation processes [19a,c-d], and displaying methyl substituents in the *ortho* positions of the aryls and on the backbone, compound **4aa** and the alkoxy-aryloxycarbonylated compound **5aa** [19a] were formed, although with moderate conversion (33 %) and limited selectivity (entry 2). Replacing the *ortho* substituents of the aromatic rings in the ligand **1a** with isopropyl groups (ligand **1b**), still very low conversion was observed (entry 3). Then, the substituents on the diimine skeleton were modified (entries 4–6). If the introduction of phenyl rings or hydrogens in the backbone did not lead to any improvement (entries 4–5), using the bis(imino)acenaphthene (BIAN) ligand **1e**, 60 % of conversion, with complete selectivity towards the desired product **4aa**, was obtained after 4 h (entry 6). A slightly less satisfying selectivity was reached with the BIAN ligand **1f**, having methyl substituents on the *ortho* positions of the aromatic rings (entry 7). Variously substituted bipyridine or phenanthroline ligands were found unsuitable for this transformation (entries 8–11).

The higher reactivity observed with BIAN-based diimine ligands is likely ascribed to various parameters. Firstly, these are known to possess both better σ-donating and π-accepting properties with respect to bipyridine and phenanthroline ligands, allowing the stabilization of the metal center in both high and low oxidation states [21]. Secondly, since BIAN derivatives are more chemically stable and more rigid than related acyclic diimine ligands (i.e., ligands **1a**-**1d**), more stable complexes are generally formed with BIAN-based diimine ligands [21]. Furthermore, the aromatic backbone, by imposing a precise coordination geometry, positively influences the reactivity of the complexes, promoting strong chelation of the metal [21]. It has been also observed that the nearly perpendicular position of the *N*-aryl rings with respect to the palladium coordination plane in aryl α-diimine ligands, induced by *ortho* substitutions, can favour the release of carbonylated products, enhancing the efficiency of the reaction [19]. On the other hand, bulkier *ortho* substituents can hinder the coordination of the reagents, reducing the productivity, but possibly enhancing the selectivity, as observed with ligand **1e**, which presents sterically cumbersome isopropyl groups (compare entries 6 and 7). Ligand **1e** was also tested in association with other Pd sources. A conversion of 55 % was observed with $Pd(OAc)_2$ (entry 12) while no reaction occurred with $PdCl_2$ (entry 13). Surprisingly, a Pd(0) source, such as Pd_2dba_3, could be efficiently employed (entry 14), achieving the same results obtained with $Pd(TFA)_2$ (compare entry 6 and entry 14). Reasonably, in this case *p*-BQ is responsible for the initial *in situ* oxidation of the palladium(0). A solvent screening did not lead to any improvement (entries 15–17) and THF was selected as the best solvent for this reaction. Delightedly, the combination $Pd(TFA)_2$/ligand **1e** enabled the complete conversion of the starting material to cinnamate **4aa** after 18 h (entry 18), and, remarkably, the reaction occurred in the presence of a nearly stoichiometric amount of alcohol. It should be noted that using ligand **1f** allowed to obtain a high yield of **4aa** (entry 19), although with a reduced selectivity (compare entries 18 and 19). An excellent result was still achieved decreasing the catalyst loading to 1 mol% (entry 20). Noteworthy, only the *trans* isomer **4aa** was observed. Pleasingly, reaction times can be significantly reduced by increasing the temperature, maintaining good yields and selectivities (see Supporting Information).

The scope of this transformation was next explored using the optimized conditions (Table 1, entry 18), starting from several vinyl arenes **2** [22] and benzyl alcohol **3a** (Table 2). Simple styrene **2a** led to benzyl cinnamate **4aa** in excellent yield (94 %) after column chromatography. Carbonylated compounds **4ba**-**4sa**, bearing different electron-donating (ED) and electron-withdrawing (EW) groups in *para* position, were isolated with good to excellent yields (54–100 %). *N*-(4-vinylphenyl) benzamide **2i** [23] afforded the lowest yield of the expected carbonylated product (**4ia**, 54 %), however with remarkable complete selectivity. Excellent results were generally obtained with both EDGs (Me, OMe, OAc, NC(O)R) and EWGs (F, Cl, CF_3, CO_2Me, CO_2H, CN, BPin [24]), demonstrating high functional group tolerance. Notably, groups such as CO_2H and BPin, suitable for useful derivatizations, have been found to be compatible with the present alkoxycarbonylation reaction. Similarly, starting from *meta*-substituted styrenes, the corresponding alkoxycarbonylated compounds bearing a nitro (**4ra**), a formyl (**4qa**), a

Table 1
Optimization study for the oxidative alkoxycarbonylation of styrenes.[a]



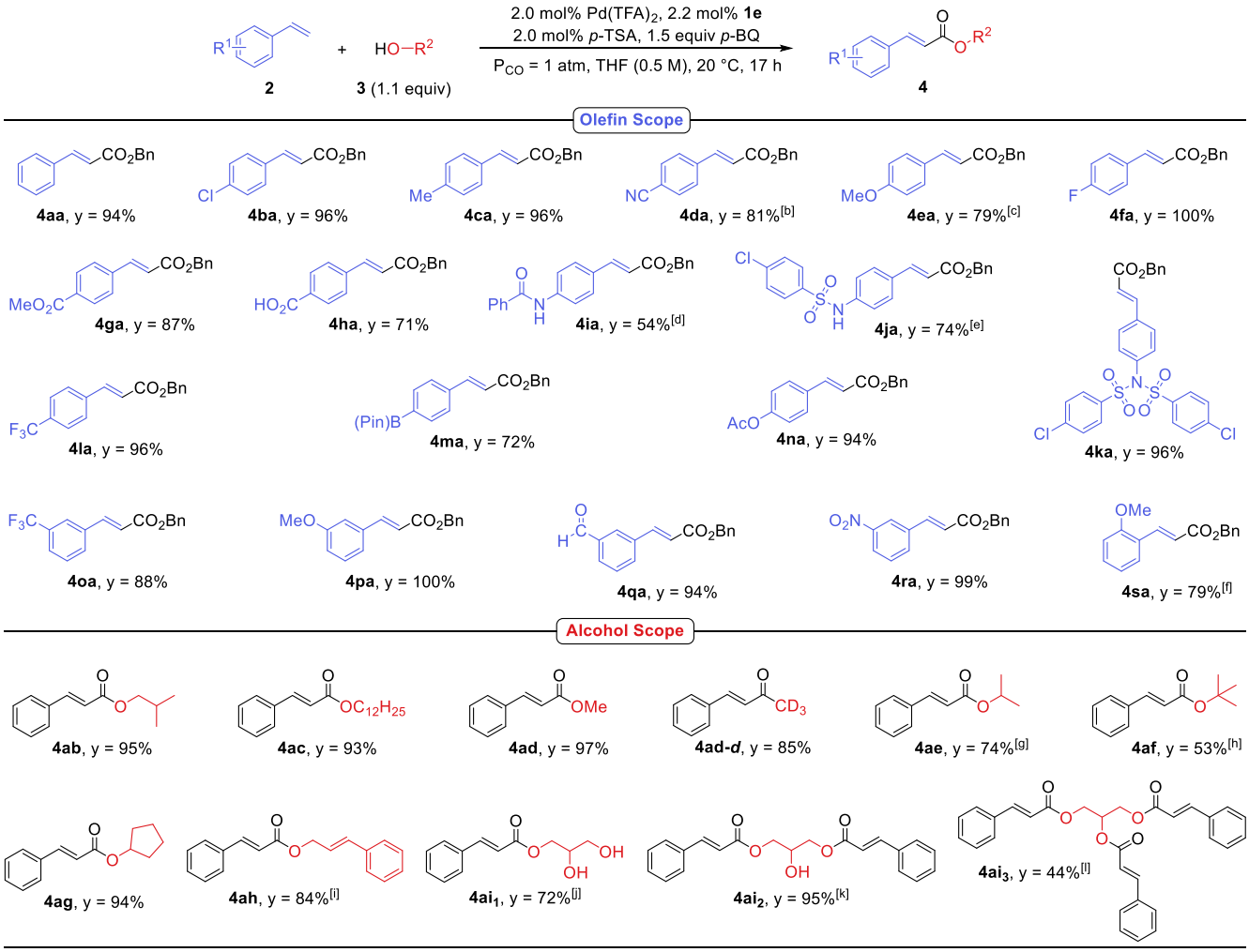
Entry	[Pd]	Ligand	Solvent[b]	Conv. (%)[c]	Yield **4aa** (%)[c]	Yield **5aa** (%)[c]
1[d]	$Pd(TFA)_2$	–	THF	6	3	0
2[d,e]	$Pd(TFA)_2$	**1a**	THF	33	13	13
3	$Pd(TFA)_2$	**1b**	THF	<5	2	0
4	$Pd(TFA)_2$	**1c**	THF	<5	1	0
5	$Pd(TFA)_2$	**1d**	THF	<5	3	0
6	$Pd(TFA)_2$	**1e**	THF	60	60	0
7[e]	$Pd(TFA)_2$	**1f**	THF	80	71	6
8	$Pd(TFA)_2$	**1g**	THF	NR	0	0
9	$Pd(TFA)_2$	**1h**	THF	NR	0	0
10[d]	$Pd(TFA)_2$	**1i**	THF	8	4	2
11[d]	$Pd(TFA)_2$	**1j**	THF	7	5	0
12	$Pd(OAc)_2$	**1e**	THF	55	55	0
13	$Pd(Cl)_2$	**1e**	THF	NR	0	0
14[f]	Pd_2dba_3	**1e**	THF	60	59	0
15[g]	$Pd(TFA)_2$	**1e**	CH_2Cl_2	10	6	0
16	$Pd(TFA)_2$	**1e**	CH_3CN	NR	0	0
17[g]	$Pd(TFA)_2$	**1e**	Acetone	17	13	0
18[h]	$Pd(TFA)_2$	**1e**	THF	100	99	0
19[e,h]	$Pd(TFA)_2$	**1f**	THF	100	92	5
20[h,i]	$Pd(TFA)_2$	**1e**	THF	93	91	0

[a] Reaction performed at 1 atm of CO pressure, with styrene **2a** (0.25 mmol scale), [Pd]: ligand = 1: 1.1 at 2 mol% of catalyst loading, using 2.0 equiv. of BnOH **3a**, 1.5 equiv. of *p*-BQ and 2.0 mol% of *p*-TSA in the indicated solvent (0.5 M), for 4 h at 20 °C.
[b] Anhydrous solvents were used.
[c] Determined by ^{1}H NMR analysis of the reaction crude.
[d] Up to 3 % of dibenzyl 2-phenylsuccinate was detected.
[e] Up to 3 % of benzyl (*E*)-4-oxo-3,6-diphenylhex-5-enoate was detected.
[f] 1 mol% of Pd_2dba_3 was used.
[g] Up to 4 % of unidentified products were detected.
[h] 1.1 equiv of BnOH **3a** was used, with a reaction time of 18 h.
[i] 1 mol% of catalyst loading was used. NR = No Reaction (the starting material was completely recovered).

trifluoromethyl (**4oa**) or a methoxy (**4pa**) group, were successfully synthesized with yields ranging from 88 % to 100 %. Finally, 2-vinylanisole **2s**, bearing a OMe substituent at the *ortho* position, was converted into the corresponding benzyl cinnamate **4sa** in 79 % isolated yield. Subsequently, several alcohols were evaluated in combination with styrene **2a** (Table 2). [22] Primary alcohols (i.e. isobutanol **3b**, dodecanol **3c**, methanol **3d**) gave nearly quantitative yields of the desired cinnamic products **4ab**-**4ad**. Using CD_3OD as alcohol, the respective deuterated product **4ad-*d*** was isolated in 85 % yield. Less satisfactory results were obtained with isopropanol **3e** (**4ae**, y = 74 %) as the olefin conversion was incomplete, while very high yields were reached using cyclopentanol **3g** (**4ag**, y = 94 %). The sterically demanding *tert*-butanol **3f** led to the expected **4af** in 53 % isolated yield with 5 mol% of catalyst loading. Interestingly, in the presence of styrene **2a**, cinnamyl alcohol **3h** acted exclusively as external nucleophile, affording product **4ah** in 84 % yield. With the aim to achieve high value-added cinnamoyl glycerol derivatives [25,26], we studied the reaction of **2a** with glycerol **3i**, a largely available feedstock obtained as a byproduct of biodiesel production [27]. As glycerol bears three hydroxyl groups, the reaction was studied by varying the **2a**:**3i** molar ratio. When an equimolar amount of glycerol and styrene was utilized, only one of the primary hydroxyl groups was involved in the reaction, and monocinnamoyl glycerol **4ai$_1$** was isolated in 72 % yield. By doubling the amount of styrene, both the primary OH groups reacted to give the dicarbonylated product **4ai$_2$** in nearly quantitatively yield. Finally, with a styrene:glycerol ratio = 3.1:1, all the hydroxyl groups took part in the carbonylation, achieving 44 % isolated yield of **4ai$_3$**, together with 54 % of **4ai$_2$**, corroborating that primary alcohols are more reactive than secondary ones. It is worth noting that the exclusive formation of the *E* stereoisomer was observed in all the reported examples.

This evidence was confirmed by ^{1}H NMR spectra, as well as by X-ray analysis of **4ba**, **4ca** and **4ga** (see Supporting Information). In addition to terminal aromatic olefins [28], we also tested substituted olefins (Scheme 2). Substituted alkenes are usually less reactive in carbonylation reactions, as they are less prone to coordinate palladium mainly for steric reasons [29]. Using cinnamyl alcohol **3h**, without other alcohols or olefins, afforded γ-lactone **6** in 72 % isolated yield under standard conditions (Scheme 2a). Product **6** results from an initial cycloalkoxycarbonylation reaction and a subsequent intermolecular alkoxycarbonylation, in which another molecule of **3h** acts as an external

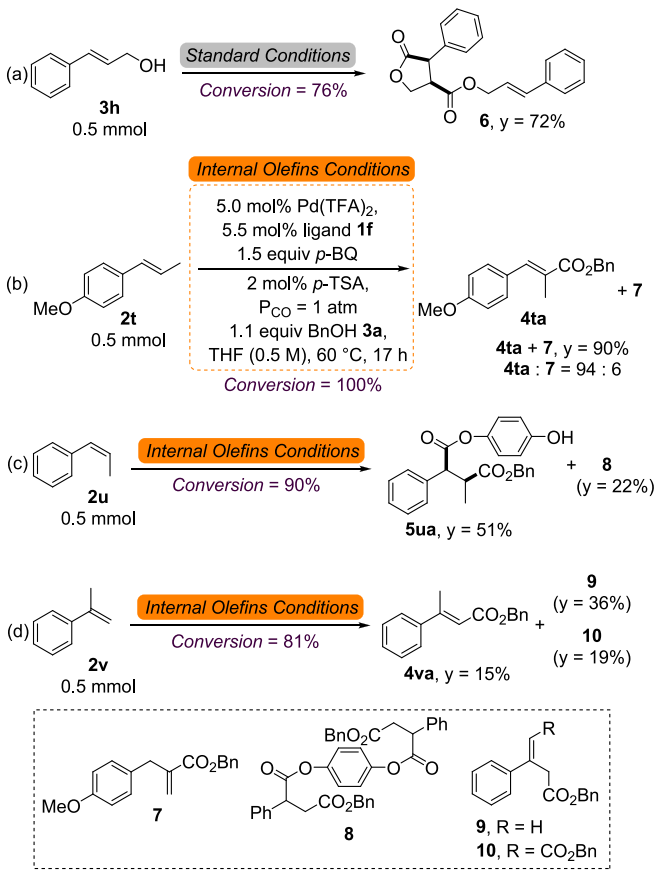
Table 2
Scope of the oxidative alkoxycarbonylation of styrenes.[a]



[a]Reaction performed at 1 atm of CO pressure, with olefin **2** (0.5 mmol-scale), 2.0 mol% $Pd(TFA)_2$, 2.2 mol% ligand **1e**, using 1.1 equiv of alcohol R^2OH **3**, 1.5 equiv of *p*-BQ, 2.0 mol% of *p*-TSA in THF (0.5 M), for 17 h at 20 °C. Isolated yields are reported.
[b]Conversion = 86 %.
[c]Conversion = 89 %.
[d]Conversion = 56 %.
[e]Conversion = 75 %.
[f]Conversion = 84 %.
[g]Conversion = 78 %.
[h]5 mol% of catalyst loading is utilized. Conversion = 68 %.
[i]Conversion = 90 %.
[j]Ratio styrene: glycerol = 1:1. 14 % of compound **4ai$_2$** has been detected.
[k]Ratio styrene: glycerol (0.5 mmol) = 2:1.
[l]Reaction performed with a ratio styrene: glycerol (0.5 mmol) = 3.1:1 and 5 mol% of catalyst loading for 60 h. 54 % of compound **4ai$_2$** has been detected.

alcohol. The relative observed stereochemistry comes from a concerted *syn* addition of the alkoxycarbonylpalladium moiety to the double bond [19d]. In this case, the α,β-unsaturated cyclic ester is not observed since the formation of the four-membered Pd-H complex **F** (*vide infra*) is not favored. The formation of the reported γ-lactone was confirmed by HMBC analysis (see Supporting Information). Under the standard conditions, the 1,2-disubstituted olefin **2t**, used in combination with benzyl alcohol **3a**, was totally unreactive. On the other hand, a complete conversion could be reached at 60 °C with ligand **1f** and 5 mol% of catalyst loading (see Supporting Information). The main product obtained was the benzyl (*E*)-3-(4-methoxyphenyl)-2-methylacrylate **4ta**, in which the aryl group and the installed ester functionality are *trans* to each other [30]. While no traces of the (*Z*)-isomer were detected, 6 % of the constitutional isomer benzyl 2-(4-methoxybenzyl)acrylate **7** was observed. The inseparable mixture **4ta** and **7** was isolated with 90 % yield (Scheme 2b, **4ta**: **7** = 94: 6). To the best of our knowledge, this is the first example of oxidative alkoxycarbonylation of internal olefins to cinnamates in the presence of CO.

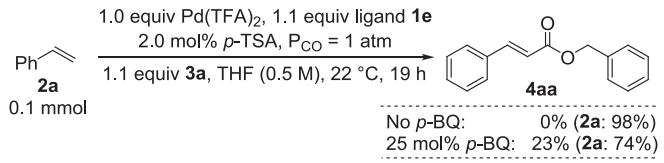
A completely different outcome was observed with *cis*-β-methylstyrene **2u**, as the alkoxy-aryloxycarbonylation product **5ua** was generated with the involvement of the *in-situ* generated hydroquinone (Scheme 2c). Compound **5ua** was isolated in 51 % yield together with 22 % of the dimeric O'^1,O^1-(1,4-phenylene) 4-dibenzyl bis(2-phenylsuccinate) **8** [31]. The different reactivity between *cis* and *trans*



Scheme 2. Oxidative alkoxycarbonylation of substituted olefins a) cinnamyl alcohol, b) *trans*-anethole, c) *cis*-β-methylstyrene, and d) α-methylstyrene.

internal olefins can be explained considering that with a *cis*-olefin, the formation of the corresponding (*Z*)-cinnamate is unfavorable, as suggested by the DFT calculations (*vide infra*), therefore allowing the preferential alkoxy-aryloxycarbonylation pathway to take place [19a].

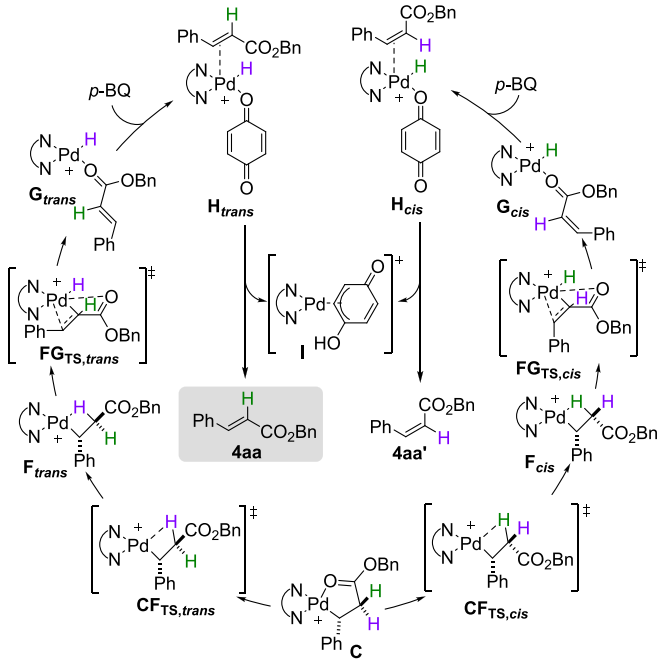
Finally, we tested the 1,1-disubstituted olefin α-methylstyrene **2v**. In this case, an incomplete conversion of the olefin was observed, and three carbonylated products were formed. In addition to the desired product **4va** (y = 15 %) and its isomer **9** (y = 36 %), compound **10**, deriving from a second carbonylation on **9**, was isolated in 19 % yield (Scheme 2d). Unfortunately, using 1,2-disubstituted aliphatic olefins, such as *cis*-4-



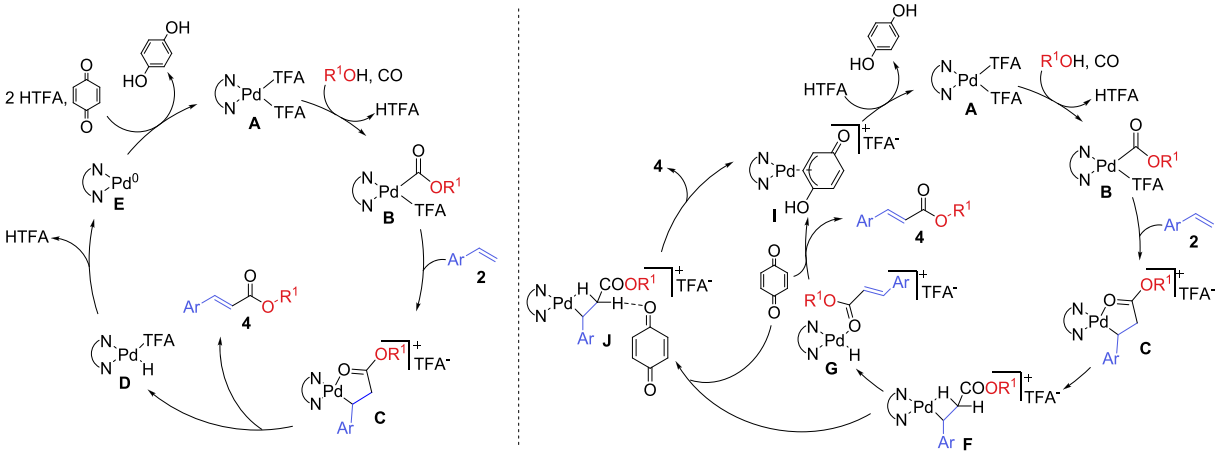
Scheme 4. Effect of the *p*-benzoquinone on the oxidative alkoxycarbonylation of styrene with a stoichiometric amount of catalyst. NMR yields of **4aa** and the remaining **2a** are given.

octene, *trans*-4-octene or methyl oleate, no reactions occurred, and the starting alkenes have been completely recovered.

With all these data in hand, we decided to get insights into the reaction mechanism. To start with, complex **A**, which is formed *in situ* by mixing $Pd(TFA)_2$ and ligand **1e**, was isolated and fully characterized by NMR analyses (see Supporting Information). Moreover, orange single crystals suitable for XRD analysis, have been obtained by slow evaporation of a dichloromethane solution of **A**. The structure displays the expected square-planar geometry, with two coordination sites of the Pd



Scheme 5. Proposed mechanism for the formation of the products **4aa** and **4aa'** *via* palladium-hydride complex formation.



Scheme 3. Generally accepted mechanism (*left*) and revisited mechanism (*right*) for the oxidative alkoxycarbonylation of styrenes.

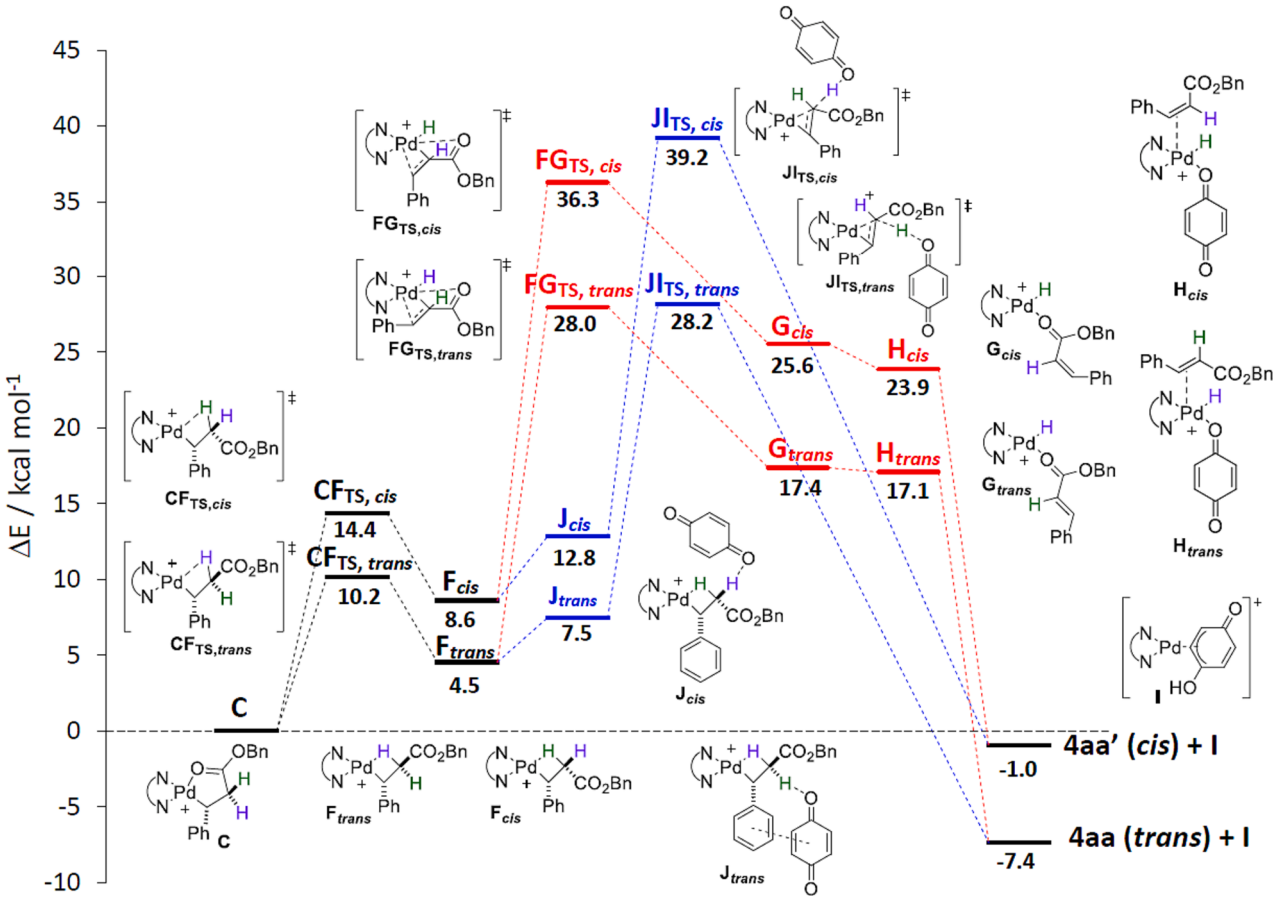
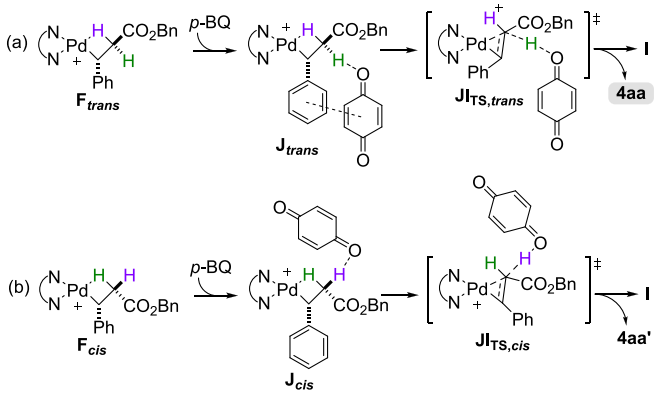


Fig. 1. Energy profile (kcal/mol) of the final steps of the cycle leading to the synthesis of the *cis* or *trans* cinnamic products. The palladium-hydride mechanism is shown in red; the benzoquinone-assisted deprotonation mechanism is shown in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



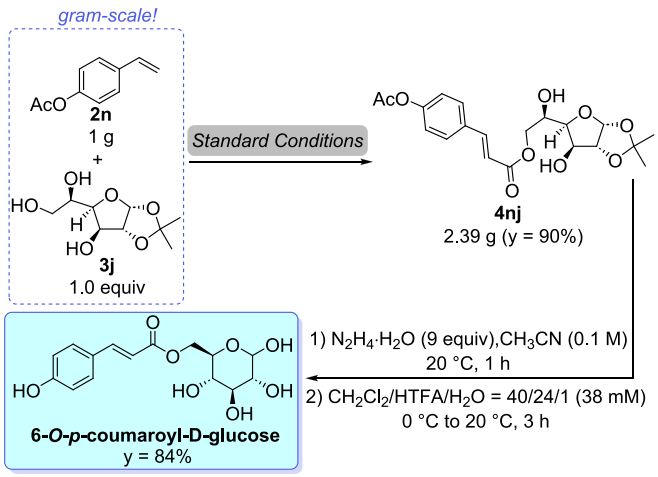
Scheme 6. Proposed mechanism for the formation of the (a) *trans* **4aa** or (b) *cis* **4aa'** products *via* benzoquinone-assisted deprotonation.

(II) centre occupied by the ligand **1e** and the others by two trifluoroacetate ligands. The Pd(II) centre displays a slightly distorted square planar coordination. The N-Pd-N bite angle in the rigid five-membered palladacycle [81.6(4)°] is significantly smaller than 90°, as found in related Pd(II) complexes [32]. All the atoms of ligand **1e**, the Pd center and the two coordinated O-atoms are perfectly planar (mean deviation from the least-squares plane 0.0525 Å). The angles between the planes of the two aromatic rings and these least-squares plane are 78.7° and 76.5°, respectively (see Supporting Information). In the presence of CO and alcohol **3**, complex **A** evolves into the palladium-alkoxycarbonyl intermediate **B** [33] (Scheme 3, left). The successive 2,1-insertion of the styrene derivative **2**, which is known to be preferential when nitrogen ligands are utilized [34], affords the five-membered palladacycle **C** [35], which can be in equilibrium with its open form, in which the vacant Pd-coordination site can be occupied by a trifluoroacetate ligand or a CO molecule, or with the respective η^3-allylic complex [34a]. At this point, a β-H-elimination with the concomitant formation of the palladium-hydride intermediate **D** and product **4** is expected [13a,14,15,17]. A subsequent reductive elimination from **D** leads to trifluoroacetic acid and Pd(0), which is eventually oxidized by the benzoquinone [20,36], thus closing the catalytic cycle (Scheme 3, left). According to the proposed cycle, if a stoichiometric amount of catalyst is present, the reaction would proceed quantitatively even in the absence of oxidant.

However, running a stoichiometric reaction, no product was observed, unless benzoquinone was present (Scheme 4). Moreover, from our theoretical calculations, both the formation of the (NN)Pd(H)TFA complex **D** and the successive reductive elimination to form **E** and HTFA are thermodynamically disfavored.

These results suggest that benzoquinone participates in the catalytic cycle not only as an oxidant but also in a different way [37], allowing the formation of **4** under such mild reaction conditions. We therefore used DFT calculations to discover the role of benzoquinone in the final steps of the process, utilizing styrene **2a** and benzyl alcohol **3a** as model substrates and the actual structure of the best catalyst [38] (see Supporting Information).

Starting from the 5-membered palladacycle **C** [35], a stable 4-membered cycle (**F**) with a Pd-H-C bridge, is formed [39]. The 5-membered cycle may open in two possible ways, which eventually



Scheme 7. Total synthesis of 6-*O*-*p*-coumaroyl-D-glucose.

lead to the *cis* and the *trans* carbonylated products **4aa'** and **4aa**, respectively. These two routes have been investigated and we found that the formation of intermediate $\mathbf{F}_{trans}$ is favored both kinetically (4.2 kcal/mol) and thermodynamically (4.1 kcal/mol) over $\mathbf{F}_{cis}$ (Scheme 5 and Fig. 1, black line). Successively, the **F** complexes evolve (Fig. 1, red line), through the transition state $\mathbf{FG}_{TS}$, to the complexes **G**, where the palladium is still bound to a hydrogen atom and to the products **4** through the carboxyl oxygen. Again, the energy barrier of the *trans* route (23.5 kcal/mol) is lower than the *cis* route (27.7 kcal/mol). The successive barrierless reaction of complexes **G** with benzoquinone leads to intermediates **H**, which evolves to give to the complex **I** and products **4** in *cis* (**4aa'**) or *trans* (**4aa**) configuration (Scheme 5 and Fig. 1, red line). The restoration of the active species **A** from intermediate **I** can eventually occur by following the steps already reported in the literature [40].

The proposed mechanism explains why the production of compound **4aa**, having the *E* configuration, is highly favored both from the kinetic and the thermodynamic point of view, in strict agreement with the experimental results. It is also notable that the driving force of the whole process is the formation of the low-energy complex **I**, confirming the importance of benzoquinone in promoting this reaction under unprecedently mild reaction conditions and explaining the results reported in Scheme 4. The mechanism described above is perfectly compatible with the experimental findings and it is valid both for terminal and internal olefins. However, we devised and investigated another possible pathway that merits to be considered, even if it can occur only with terminal olefins. In particular, in the case of styrene, the Mulliken charge for the hydrogen not involved in the H-bridged four-atom palladacycle **F** is + 0.14 for $\mathbf{F}_{trans}$ and + 0.16 for $\mathbf{F}_{cis}$. Therefore, it can weakly bond, *via* a dipole–dipole interaction, with the carbonyl of benzoquinone, forming intermediates **J** (Scheme 6 and Fig. 1, blue line). The formation of these intermediates is slightly endergonic due to the unfavorable entropic contribution, but complex $\mathbf{J}_{trans}$ is stabilized by a π-π interaction between the benzoquinone and the aromatic ring of the styrene, making its formation more favored by about 5 kcal/mol with respect to the *cis* one.

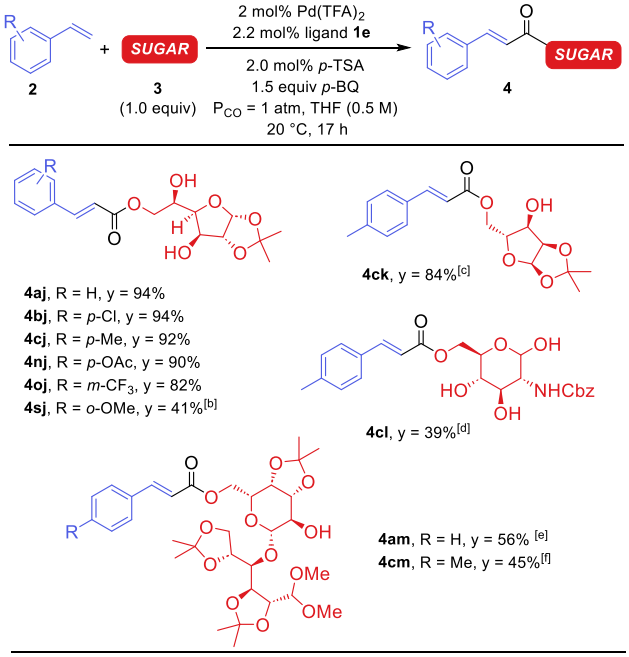
Afterward, the hydrogen is transferred to the benzoquinone through the transition state $\mathbf{JI}_{TS}$, with an energy barrier of + 20.7 kcal/mol for the *trans* form and + 26.4 kcal/mol for the *cis*, directly evolving into the final product **4** and the complex **I** (Scheme 6 and Fig. 1, blue line) [41]. Gratifyingly, even in this case the formation of the *trans* product is kinetically and thermodynamically favored. The possible interaction of the solvent THF with the hydrogens in the palladacycles $\mathbf{F}_{cis}$ and $\mathbf{F}_{trans}$ was also explored, with the conclusion that no proton extraction can occur due to the low basicity of the THF oxygen. This second mechanism, which envisages that the benzoquinone acts both as a proton extractor as well as oxidant, can clearly work only when terminal (or 1,1-disubstituted) olefins are employed. Probably both mechanisms may operate concurrently (Scheme 3, right), making the synthesis of cinnamates possible under these mild conditions.

Finally, we decided to apply our efficient alkoxycarbonylation process to the synthesis of Cinnamic Acid Sugar Ester Derivatives (CASEDs). These compounds feature a phenylacrylic moiety linked, *via* an ester bond, to a carbohydrate molecule. CASEDs have been identified and extracted from various plants [42], showing a wide range of biological activities, including anti-oxidant, anti-inflammatory, anti-viral antidepressive and anti-cancer [43]. Despite their interesting properties, their synthesis is still poorly studied and especially enzymatic esterification strategies have shown several limitations (i.e., low yields with long reaction times and high costs of enzymes) [44]. Selectivity problems, due to the high number of hydroxyl groups present in the starting sugar, have also been pointed out. Therefore, we decided to proceed with synthesizing 6-*O*-*p*-coumaroyl-D-glucose, a natural monosaccharide ester present in several plants [45], which has shown interesting pharmacological activities [46].

Unfortunately, D-glucose cannot be used directly, due to its poor solubility in THF. However, when the unexpensive and commercially available 1,2-*O*-isopropyliden-α-D-glucofuranose **3j** was employed, together with 4-acetoxystyrene **2n** as substrate, the gram-scale alkoxycarbonylation reaction proceeded with a total conversion, and 2.39 g of the respective cinnamate **4nj** was obtained in 90 % isolated yield (Scheme 7).

Moreover, the reaction is completely stereoselective (only the (*E*)-isomer is formed) and regioselective (involving the primary hydroxyl group exclusively), in accordance with the results reported in Table 2. Deprotection of **4nj** allowed the synthesis of the desired natural product 6-*O*-*p*-coumaroyl-D-glucose with an overall yield of 76 % (see

Table 3
Oxidative alkoxycarbonylation of olefins utilizing sugar derivatives.[a]



[a]Reaction performed at 1 atm of CO pressure, with olefin **2** (0.5 mmol-scale), 2.0 mol% $Pd(TFA)_2$, 2.2 mol% ligand **1e**, using 1.0 equiv of sugar **3**, 1.5 equiv of *p*-benzoquinone, 2.0 mol% of *p*-TSA in THF (0.5 M), for 17 h at 20 °C. Isolated yields are reported.
[b]Conversion = 46 %.
[c]Conversion = 88 %.
[d]Conversion = 45 %.
[e]Conversion = 63 %.
[f]Conversion = 76 %.

Supporting Information). Our reaction can be successfully applied to different sugars employing various olefins (Table 3). In the presence of glucofuranose **3j**, yields greater than 90 % have been achieved with styrene (**4aj**), *p*-chlorostyrene (**4bj**), *p*-methylstyrene (**4cj**) and 4-acetoxystyrene (**4nj**). With *m*-trifluoromethylstyrene **2o**, 82 % of **4oj** was obtained while slightly less satisfactory results were found with the *o*-methoxystyrene **2 s**, probably due to steric hindrance. *p*-Methylstyrene **2c** in combination with 1,2-*O*-isopropyliden-α-D-ribose (**3k**) gave the cinnamic ester **4ck** with 84 % isolated yield. The alkoxycarbonylation of *p*-methylstyrene with *N*-benzyloxycarbonyl-D-glucosamine (**3l**), despite the presence of four hydroxyl groups, proceeds regioselectively at the primary OH group. The modest yield (39 %) of **4cl** can be mainly ascribed to the low solubility of the protected D-glucosamine sugar in THF, which led to a poor conversion. Lastly, the reaction was extended to the disaccharide LTA (lactose tetraacetal, **3m**) which afforded the corresponding cinnamates **4am** and **4cm** in 56 % and 45 % isolated yields, respectively using styrene **2a** and *p*-methylstyrene **2c**. All these reactions showed complete regioselectivity and stereoselectivity towards the desired 6-*O*-*trans*-sugar cinnamic ester.

3. Conclusion

In conclusion, the first room temperature palladium-catalyzed oxidative alkoxycarbonylation of styrene derivatives under atmospheric pressure of CO has been realized. The methods allow the stereoselective synthesis of various *trans* cinnamic ester derivatives in good to excellent yields. Various *para*, *meta* and *ortho* substituted styrenes and alcohols of different nature, including polyols, have been successfully employed. Even substituted olefins (i.e., 1,2-disubstituted or 1,1-disubstituted) turned out to be reactive under our conditions, although in these cases the nature of the carbonylated product obtained is strictly correlated with the particular structure of the starting olefinic substrate. The catalyst, isolated and fully characterized by NMR and X-ray analyses, is formed *in situ* by mixing $Pd(TFA)_2$ and the bis(aryl)acenaphthenequinonediimine ligand **1e**, bearing *ortho* isopropyl groups on the aromatic rings. The effect of the oxidant *p*-benzoquinone in this transformation has been investigated through DFT calculations, and its additional role in promoting the last steps of the alkoxycarbonylation process has been highlighted, thus explaining the mild reaction conditions required with the developed catalytic system. Finally, the reaction has been exploited for the stereo- and regioselective synthesis of various 6-*O* cinnamic acid sugar ester derivatives, including the natural compound 6-*O*-*p*-coumaroyl-D-glucose.

CRediT authorship contribution statement

Diego Olivieri: Writing – original draft, Methodology, Investigation, Conceptualization. **Michele Verboni:** Investigation. **Riccardo Tarroni:** Formal analysis, Data curation. **Stefano Zacchini:** Investigation. **Simone Lucarini:** Writing – review & editing, Conceptualization. **Nicola Della Ca':** Writing – review & editing, Validation. **Raffaella Mancuso:** Writing – review & editing, Validation. **Bartolo Gabriele:** Writing – review & editing, Validation. **Carla Carfagna:** Writing – original draft, Supervision.

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.

Data availability

Data will be made available on request.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2024.115397.

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