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A Highly Efficient Pd/CuI-Catalyzed Oxidative Alkoxycarbonylation

of α -Olefins to Unsaturated Esters

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Dedicated to Prof. Georgiy B. Shul'pin on the occasion of his 70th birthday

Graphical abstract



Highlights

- This is a new protocol for the alkoxycarbonylation of α -olefins to unsaturated esters
- Pd/C, Pd/Al₂O₃ and Pd/CaCO₃, in conjunction with CuI, are the most active catalysts
- A variety of alcohols and olefins were employed as starting materials
- Experimental evidences account for a homogeneous palladium-catalyzed reaction
- Commercial cinnamate derivatives were prepared in good to excellent yields

Abstract

A new protocol for the alkoxycarbonylation of α -olefins to the corresponding unsaturated esters has been developed. Differently substituted styrenes were selectively converted to cinnamate derivatives, via C-H bond functionalization. Various palladium sources, including heterogeneous ones, in combination with CuI exhibited a high catalytic efficiency using oxygen as the most cheap oxidant. Monocarbonylated products were obtained in good yields and high chemoselectivity working with a low CO pressure (2 atm) and an excess of air (35 atm) avoiding in this way explosion risks. Commercial cinnamate derivatives were prepared in good to excellent yields by this very simple onepot procedure.

Keywords: Carbonylation, C-H bond functionalization, Palladium, Cinnamates, Multicomponent reactions

1 Introduction

Carbonylation reactions represent important tools in organic chemistry allowing the synthesis of highvalue molecules, such as pharmaceuticals, agrochemicals, cosmetic ingredients and dyes, from readily available starting materials [1-5]. For instance, alkenes and alkynes can be conveniently transformed into useful carbonylated compounds by metal-catalyzed carbonylation processes that employ carbon monoxide as inexpensive and easily available C1 source [1, 6-10].

Cinnamic acid and its derivatives find application mainly in cosmetic and pharmaceutical industry (Figure 1). The cinnamic acid skeleton is found in a plethora of natural compounds that show a variety of biological activities such as anticancer, antioxidant, antimicrobial, antitubercular and antifungal effects [11-16].

One of the most attractive way for the synthesis of cinnamate esters [16] from readily available feedstocks is the palladium-catalyzed oxidative alkoxycarbonylation of styrenes. In general the oxidative alkoxycarbonylation of terminal olefins with carbon monoxide and alcohols can give rise to three sorts of carbonylated products, β -alkoxy esters **1**, succinate derivatives **2** and α , β -unsaturated esters **3** (Scheme 1) [2]. Nearly all catalytic systems used for oxidative carbonylations are based on Pd^{II} salts and complexes formed from them. They are modified by ligands, promoters as well as different types of co-catalysts. In addition, an appropriate solvent has to be chosen for its great influence on the reaction course. Therefore, depending on the conditions employed, product **1**, **2** or **3** can be obtained selectively in a one-pot fashion. While the formation of compounds **1** and **2** by oxidative carbonylation have been widely investigated [17-22], the straightforward synthesis of α , β -unsaturated esters **3** by oxidative alkoxycarbonylation of alkenes has received less attention [23].

In 1969 Yukawa and Tsutsumi reported the formation of methyl cinnamate from a styrene-palladium complex in the presence of CO and alcohols [24]. Later, methyl cinnamate and phenyl succinate were obtained catalytically at room temperature from styrene, CO and methanol with a polymetallic system such as PdCl₂/CuCl₂/MgCl₂/NaOAc [25]. More recently Bianchini and co-workers reported the oxidative alkoxycarbonylation of styrene to afford methyl cinnamate with 1,1-bis(diphenylphosphino)metallocenes and palladium catalysts [26-27]. Good yields end excellent

selectivity were obtained when a large excess of benzoquinone was employed. Very recently, new interesting protocols for the Pd-catalyzed synthesis of α , β -unsaturated esters from alkenes, CO and alcohols, have been reported independently by Lei [28] and Malkov [29]. Under base- and phosphine-free conditions, only stoichiometric amounts of the alcohol are required for the former, allowing the use of structurally complex alcohols as well [28], while a wide substrate range and good functional-group tolerance feature the latter [29]. High catalyst loading were, however, necessary.

Over the years our research group has developed new and attractive syntheses of carbonylated compounds starting from acetylenic substrates by means of the PdI₂/KI catalytic system [30-38]. Recently, we have reported the PdI₂/KI-catalyzed hydroalkoxycarbonylation of terminal arylacetylenes to branched esters **4** with good selectivity and catalytic efficiency [39]. The reaction is carried out in an easy one-step synthesis under non-oxidative conditions, without other ligands and in the absence of added acids (Scheme 2).

In this paper we report a simple and efficient protocol for the oxidative alkoxycarbonylation of styrenes to cinnamate derivatives **3**, based on Pd/CuI catalytic system and without any base or phosphine ligands. Several homogeneous and heterogeneous palladium sources in combination with copper iodide turned out to be highly active in the oxidative carbonylation of styrenes even at low catalyst loading. The effect of other co-catalyst and other reaction parameters has been studied. Following this method, a variety of alcohols have been used and the corresponding cinnamates were obtained in excellent yields.

2 Experimental section

2.1 Materials and General Methods

All starting alkenes, alcohols and solvents were commercial products. Pd/C (Fluka), Pd/Al₂O₃ (Fluka), and Pd/CaCO₃ (Sigma-Aldrich) were commercial available with 10wt. % of palladium loading. Potassium tetraiodopalladate (K₂PdI₄) was prepared following the reported procedure [39]. Alcohols were distilled and stored under nitrogen over appropriate drying agents. All reactions were carried out in a stainless steel autoclave. GC analyses were performed with a Fisons HRGC Mega 2 Series instrument fitted with a 30 m SE52 capillary column. Merck 60 F_{254} silica gel sheets (0.2 mm thick) were used for TLC analyses. Silica gel 60 (70-230 mesh ASTM) was used for preparative column chromatography. IR spectra were obtained with a Nicolet 5700 FT-IR spectrophotometer. Mass spectra (*m/z*, relative intensity %) were taken with a Hewlett-Packard Mass Selective Detector

HP 5973 Series at 70 eV ionizing voltage interfaced with a Hewlett-Packard 6890 Series GC system fitted with a 30 m DB5 capillary column. Elemental analyses were carried out with a Carlo Erba Elemental Analyzer Model EA 1108. Melting points were determined with a Gallenkamp MPD 350 BM 2.5 apparatus and are uncorrected. NMR spectra were recorded in deuterated chloroform (CDCl₃), using the solvent as internal reference (7.26 and 77.00 ppm, respectively for ¹H and ¹³C), on Bruker AVANCE 300 and 400 spectrometers. Chemical shifts and coupling constants (*J*) are given as δ values (ppm) and in Hz, respectively. Yields and selectivity for products were determined by ¹H NMR spectroscopy and GC-FID analyses using the internal standard method.

2.2 General Procedure for the Alkoxycarbonylation Reaction of Terminal Olefins

The carbonylation reactions were carried out in 120 mL stainless steel high pressure reactors (Parr instruments). The reactors were heated using oil baths and stirred with magnetic stirrer bars. In a general procedure the calculated amount of Pd catalyst, inorganic salts and other additives, if necessary, were charged into a pyrex vessel. A solution of the alkene (5 mmol) and the alcohol (50 mmol) in the solvent of interest (10 mL) was added by a syringe to the vessel that was placed into the autoclave. The reactor was sealed and charged with air (35 atm) and carbon monoxide (2-5 atm, 99.5% Sapio). The reaction mixture was stirred at 120 °C for 24h. After cooling to room temperature, the reactor was carefully depressurized and the reaction crude was recovered with CH_2Cl_2 (25 mL). The mixture was filtered to remove the heterogeneous catalyst and evaporated under vacuum. The residue was dissolved in a volumetric flask. Conversion of the alkene was determined by GC using 1,2,4,5-tetramethylbenzene as an internal standard. Yields reported in Tables 1-3 and 5 were determined by ¹H NMR on the reaction crude using dimethylmaleate as an internal standard.

2.3 General Procedure for Recycling Tests

Run 1 in Table 5 was carried out following the general procedure for the alkoxycarbonylation reaction. The reaction crude was recovered with CH_3CN (10 mL) and the mixture was filtered on a Buchner funnel to separate the solid. Run 2 (Table 5) was carried out using as catalyst the solid recovered from run 1 (Table 5). Following the general procedure methyl cinnamate was formed in 47% yield. To the liquid phase, obtained from the filtration of the reaction crude (run 1), was added one more equivalent of styrene (5 mmol) and allowed to stir under previously defined conditions (run 3, Table 5). After usual treatment compound **3a** was obtained in 61% yield.

2.4 General Procedure for the Alkoxycarbonylation of Styrene Catalyzed by a Solution Prepared from Pd-sponge and CuI under 30 atm of Air

A 120 mL stainless steel autoclave was charged with Pd sponge (0.0053 mg, 0.05 mmol), CuI (0.5 mmol) and CH₃CN (10 mL). The reactor was then pressurized to 30 atm of air and the reaction mixture was stirred at 120 °C for 24 h. To the resulting homogeneous liquid mixture, separated by filtration from the residual solid, was added styrene (5.0 mmol) in MeOH (2.0 mL) and transferred in a second autoclave. CO (2.0 bar) and air (35 bar) were charged and the reaction mixture was stirred at 120 °C for 24 h. Methyl cinnamate **3a** was obtained in 63% yield with a styrene conversion of 67% (run 4, Table 5).

2.5 General Procedure for the Alkoxycarbonylation of Styrene Catalyzed by a Solution Prepared from Pd-sponge and CuI under 1 atm of Air

A 120 mL stainless steel autoclave was charged with Pd sponge (0.0053 mg, 0.05 mmol), CuI (0.5 mmol) and CH₃CN (10 mL). The reaction mixture was stirred under 1 atm of air at 120 °C for 24 h. To the resulting homogeneous liquid mixture, separated by filtration from the residual solid, was added styrene (5.0 mmol) in MeOH (2.0 mL) and transferred in a second autoclave. CO (2.0 bar) and air (35 bar) were charged and the reaction mixture was stirred at 120 °C for 24 h. A 6% yield of methyl cinnamate **3a** was obtained and styrene conversion was 7% (run 5, Table 5).

2.6 Characterization of Products

Methyl (*E*)-3-phenyl-2-propenoate (**3a**) [40]: m.p. (hexane) = 35 °C. ¹H-NMR (CDCl₃): δ 7.87 (d, *J* = 15.9 Hz, 1H), 7.54-7.51 (m, 2H), 7.40-7.38 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H); ¹³C-NMR (CDCl₃): δ 167.4, 144.9, 134.3, 130.3 (2C), 128.9 (2C), 128.1, 117.8, 51.7; IR (v, cm⁻¹): 1728, 1165; MS *m*/*z* 162 (78), 131 (74), 103 (100). Anal. Calcd. for C₁₀H₁₀O₂: C, 74.06; H, 6.21. Found C, 74.14; H, 6.29.

Ethyl (*E*)-*3-phenyl-2-propenoate* (**3b**) [40]: Colorless oil. ¹H-NMR (CDCl₃): δ 7.69 (d, *J* = 15.9 Hz, 1H), 7.53-7.50 (m, 2H), 7.39-7.36 (m, 3H), 6.44 (d, *J* = 15.9 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ¹³C-NMR (CDCl₃): δ 167.0, 144.6, 134.5, 130.2, 128.9 (2C), 128.1 (2C), 118.3, 60.5, 14.4; IR (v, cm⁻¹): 1729, 1164; MS *m*/*z* 176 (81), 145 (70), 117 (100). Anal. Calcd. for C₁₁H₁₂O₂: C, 74.98; H, 6.86. Found C, 74.85; H, 6.79.

n-Butyl (*E*)-3-phenyl-2-propenoate (**3c**) [41]: Pale yellow oil. ¹H-NMR (CDCl₃): δ 7.67 (d, *J* = 16.2 Hz, 1H), 7.51-7.30 (m, 5H), 6.43 (d, *J* = 16.2 Hz, 1H), 4.20 (t, *J* = 6.6 Hz, 2H), 1.69 (2H, tt, *J* = 7.2, 6.6 Hz), 1.43 (qt, *J* = 7.2, 6.6 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (CDCl₃): δ 167.2, 144.4, 134.0, 130.4 (2C), 128.3 (2C), 127.2, 118.0, 64.3, 30.8, 19.2, 13.8; IR (v, cm⁻¹): 1725, 1165; MS *m/z*

204 (31), 148 (74), 131 (100), 103 (38). Anal. Calcd. for C₁₃H₁₆O₂: C, 76.44; H, 7.89. Found C, 76.57; H, 7.78.

i-Butyl (*E*)-3-phenyl-2-propenoate (**3d**) [42]: Pale yellow oil. ¹H-NMR (CDCl₃): δ 7.61 (d, *J* = 16.0 Hz, 1H), 7.46-7.41 (m, 2H), 7.30-7.19 (m, 3H), 6.37 (d, *J* = 16.0 Hz, 1H), 3.92 (d, *J* = 6.7 Hz, 2H), 1.97-1.90 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 6H); ¹³C-NMR (CDCl₃): δ 167.0, 144.9, 134.5, 129.4 (2C), 128.0 (2C), 127.8, 118.4, 64.0, 30.8, 19.0 (2C); IR (v, cm⁻¹): 1725, 1166; MS *m*/*z* 204 (4), 148 (55), 131 (100), 103 (42). Anal. Calcd. for C₁₃H₁₆O₂: C, 76.44; H, 7.89. Found C, 76.60; H, 7.83.

Benzyl (E)-3-phenyl-2-propenoate (**3e**) [40]: m.p. (hexane) = 38 °C. ¹H-NMR (CDCl₃): δ 7.74 (d, *J* = 15.9 Hz, 1H), 7.54-7.50 (m, 2H), 7.45-7.34 (m, 8H), 6.49 (d, *J* = 16.0 Hz, 1H), 5.26 (s, 2H); ¹³C-NMR (CDCl₃): δ 166.8, 145.2, 136.1, 136.0, 134.3 (2C), 133.9 (2C), 130.4 (2C), 128.9 (2C), 128.6, 128.3, 117.9, 66.4; IR (v, cm⁻¹): 1725, 1174; MS *m/z* 238 (25), 239 (3), 193 (49), 192 (87), 131 (85), 103 (38), 91 (100), 77 (48), 65 (18). Anal. Calcd. for C₁₆H₁₄O₂: C, 80.65; H, 5.92. Found C, 80.54; H, 6.01.

(*E*)-(2'-Phenylethyl)-3-phenyl-2-propenoate (**3f**) [43]: m.p. (hexane) = 54 °C. ¹H-NMR (CDCl₃): δ 7.68 (d, *J* = 16.1 Hz, 1H), 7.52-7.48 (m, 2H), 7.39-7.36 (m, 3H), 7.34-7.30 (m, 2H), 7.27-7.22 (m, 3H), 6.43 (d, 1H, *J* = 16.1 Hz), 4.43 (t, 2H, *J* = 7.0 Hz), 3.02 (t, 2H, *J* = 7.0 Hz); ¹³C-NMR (CDCl₃): δ 166.9, 144.8, 137.9, 134.4, 130.3 (2C), 128.9 (2C), 128.8 (2C), 128.5 (2C), 127.1, 126.6, 118.1, 65.0, 35.2; IR (v, cm⁻¹): 1729, 1171; MS *m/z* 252 (4), 131 (44), 104 (100), 77 (40); Anal. Calcd. for C₁₇H₁₆O₂: C, 80.93; H, 6.39. Found C, 80.79; H, 6.27.

i-Propyl (*E*)-3-phenyl-2-propenoate (**3g**) [42]: m.p. (hexane) = 40 °C. ¹H-NMR (CDCl₃): δ 7.61 (d, J = 16.0 Hz, 1H), 7.46-7.41 (m, 2H), 7.30-7.26 (m, 3H), 6.37 (d, J = 16.0 Hz, 1H), 1.97-1.90 (m, 1H), 0.91 (d, J = 6.7 Hz, 6H); ¹³C-NMR (CDCl₃): δ 167.0, 144.5, 134.4, 130.1 (2C), 128.0 (2C), 118.3, 70.6, 27.8, 19.1 (2C); IR (v, cm⁻¹): 1723, 1170; MS *m*/*z* 190 (41), 147 (64), 131 (100), 103 (49), 77 (40). Anal. Calcd. for C₁₂H₁₄O₂: C, 75.76; H, 7.42. Found C, 75.83; H, 7.48.

t-Butyl (*E*)-3-phenyl-2-propenoate (**3h**) [29]: Pale yellow oil. ¹H-NMR (CDCl₃): δ 7.43 (d, *J* = 15.7 Hz, 1H), 7.44-7.41 (m, 2H), 7.31-7.28 (m, 3H), 6.29 (d, *J* = 15.7 Hz, 1H), 1.47 (s, 9H); ¹³C-NMR (CDCl₃): δ 166.3, 143.5, 130.0 (2C), 128.8, 128.0 (2C), 120.2, 80.5, 28.2; IR (v, cm⁻¹): 1727, 1173; MS *m*/*z* 204 (8), 148 (65), 131 (100), 103 (36). Anal. Calcd. for C₁₃H₁₆O₂: C, 76.44; H, 7.90. Found C, 76.31; H, 7.98.

Methyl (*E*)-*3*-(*4*'-*tolyl*)-2-*propenoate* (**3i**) [44]: m.p. (hexane) = 59-60 °C. ¹H-NMR (CDCl₃): δ 7.89 (d, *J* = 16.0 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.42 (d, *J* = 16.0 Hz, 1H),

3.80 (s, 3H), 2.37 (s, 3H); ¹³C-NMR (CDCl₃): δ 167.5, 144.8, 140.6, 136.0, 131.6 (2C), 129.5 (2C), 116.6, 51.57, 21.40; IR (v, cm⁻¹): 1725, 1170; MS *m*/*z* 176 (51), 145 (100), 115 (62), 91 (32). Anal. Calcd. for C₁₁H₁₂O₂: C, 74.98; H, 6.86. Found C, 75.07; H, 6.99.

Methyl (*E*)-3-(4'-t-Butylphenyl)-2-propenoate (**3j**) [45]: m.p. (hexane) = 32-33 °C. ¹H-NMR (CDCl₃): δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 6.41 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 1.33 (s, 9H); ¹³C-NMR (CDCl₃): δ 167.4, 153.7, 144.6, 131.5, 127.8 (2C), 125.7 (2C), 116.7, 51.4, 34.7, 31 (3C); IR (v, cm¹): 1724, 1170; MS *m*/*z* 218 (31), 161 (63), 146 (100), 115 (32). Anal. Calcd. for C₁₄H₁₈O₂: C, 77.03; H, 8.31. Found C, 77.17; H, 8.14.

Methyl (*E*)-*3*-(*4*'-*methoxyphenyl*)-2-*propenoate* (**3k**) [29]: m.p. (hexane) = 88 °C. ¹H-NMR (CDCl₃): δ 7.60 (d, *J* =15.9 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.29 (d, *J* = 15.9 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H); ¹³C-NMR (CDCl₃): δ 169.8, 161.4, 144.5, 129.7 (2C), 127.2, 115.3 (2C), 55.43, 51.6; IR (v, cm¹): 1724, 1170, 1159; MS *m*/*z* 192 (65), 161 (100), 133 (41), 89 (30). Anal. Calcd. for C₁₁H₁₂O₃: C, 68.74; H, 6.29. Found C, 68.89; H, 6.39.

Methyl (*E*)-*3*-(*4*'-*chlorophenyl*)-2-*propenoate* (**3l**) [45]: m.p. (hexane) = 74-75 °C. ¹H-NMR (CDCl₃): δ 7.64 (d, *J* = 15.9 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.41 (d, *J* = 15.9 Hz, 1H), 3.81 (s, 3H); ¹³C-NMR (CDCl₃): δ 166.9, 147.0, 136.0, 132.7, 129.1 (2C), 126.7 (2C), 118.3, 51.6; IR (v, cm¹): 1720, 1167; MS *m*/*z* 196 (74), 176 (100), 137 (51), 102 (45). Anal. Calcd. for C₁₀H₉O₂Cl: C, 61.08; H, 4.61. Found C, 60.89; H, 4.49.

Methyl (*E*)-*3*-(*4*'-*bromophenyl*)-2-*propenoate* (**3m**) [46]: m.p. (hexane) = 81 °C. ¹H-NMR (CDCl₃): δ 7.62 (d, *J* = 16.1 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.42 (d, *J* = 16.1 Hz, 1H), 3.81 (s, 3H); ¹³C-NMR (CDCl₃): δ 167.1, 143.5, 133.3, 132.2, 129.5 (2C), 124.6 (2C), 118.6, 51.79; IR (v, cm¹): 1722, 1167; MS *m*/*z* 242, 240 (88), 111, 109 (100). Anal. Calcd. for C₁₀H₉O₂Br: C, 49.82; H, 3.76. Found C, 49.99; H, 3.89.

Methyl (*E*)-4-*phenylbut*-2-*enoate* (**3n**) [47] in 1:2 mixture with **3n**': Colorless oil. ¹H-NMR (CDCl₃): δ 7.39-7.03 (m, 6H), 5.81 (dt, *J* =15.7, 1.3 Hz, 1H), 3.73 (s, 3H), 3.53 (dd, *J* = 6.7, 1.3 Hz, 2H); ¹³C-NMR (CDCl₃): δ 166.6, 147.3, 137.0, 128.5 (2C), 128.4 (2C), 126.4, 121.8, 51.2, 38.3.

Methyl (*E*)-4-*phenylbut-3-enoate* (**3n**') [48] in 2:1 mixture with **3n**: Colorless oil. ¹H-NMR (CDCl₃): δ ¹H NMR (CDCl₃) δ 7.29-7.11 (m, 5H), 6.39 (dt, *J* = 16.0, 1.4 Hz, 1H), 6.20 (dt, *J* = 16.0, 6.9 Hz, 1H), 3.61 (s, 3H), 3.16 (dd, J= 6.9, 1.4 Hz, 2H); ¹³C-NMR (CDCl₃): δ 172.1, 136.9, 133.6, 128.7, 128.6 (2C), 127.7,126.4 (2C), 121.8, 52.0, 38.3.

Methyl (E)-non-2-enoate (**3o**) [49] in 2:1 mixture with **3o**': Pale yellow oil. ¹H-NMR (CDCl₃): δ 7.04-6.95 (m, 1H), 5.84-5.78 (m, 1H), 3.74 (s, 3H), 2.24-2.17 (m, 2H), 1.48-1.42 (m, 2H), 1.37-1.25 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ¹³C-NMR (CDCl₃): δ 167.2, 149.8, 120.7, 51.2, 32.1, 31.5, 28.7, 27.9, 22.4, 13.9.

Methyl (E)-non-3-enoate (**30'**) [50] in 1:2 mixture with **30**: Pale yellow oil. ¹H-NMR (CDCl₃): δ 5.59-5.48 (m, 2H), 3.72 (s, 3H), 3.07-2.98 (m, 2H), 2.11-1.95 (m, 2H), 1.38-1.28 (m, 6H), 0.87 (t, *J* = 6.6 Hz, 3H), ¹³C-NMR (CDCl₃) δ 172.6, 134.9, 121.2, 51.6, 37.8, 32.3, 31.2, 27.9, 22.4, 13.9.

Dimethyl 2-phenylsuccinate (**2a**) [51]: m.p. (hexane) = 55 °C. ¹H-NMR (CDCl₃): δ 7.31-7.21 (m, 5H), 4.31 (t, *J* = 7.0 Hz, 1H), 3.60, 3.57 (2s, 6H), 3.02, 2.83 (2 dd, *J* = 7.0, 6.7 Hz, 2H); ¹³C-NMR (CDCl₃): δ 169.7, 169.0, 140.9, 129.9 (2C), 127.8 (2C), 126.9, 52.7, 51.9, 47.0, 37.8; IR (v, cm⁻¹): 1727, 1725, 1165; MS *m*/*z* 222 (67), 205 (21), 105 (100).

Dimethyl 2-benzylsuccinate (**2n**) [52]: Colorless oil. ¹H-NMR (CDCl₃): δ 7.34-7.25 (m, 5H), 3.65, 3.60 (2s, 6H), 3.31 (m, 1H), 3.27, 3.12 (2 dd, 2H, *J* = 6.8, 6.6 Hz), 2.96, 2.80 (2 dd, 2H, *J* = 7.0, 6.7 Hz); ¹³C-NMR (CDCl₃): δ 168.7, 168.6, 140.0, 129.5 (2C), 127.0 (2C), 126.9, 53.7, 51.7, 42.0, 36.1, 35.9; IR (v, cm⁻¹): 1726, 1725, 1162; MS *m/z* 236 (79), 219 (12), 119 (65), 105 (100).

Dimethyl 2-hexylsuccinate (**2o**): Pale yellow oil. ¹H-NMR (CDCl₃): δ 3.69, 3.66 (2s, 6H), 3.97-2.72 (m, 2H), 2.43 (2 dd, *J* = 15.8, 4.6 Hz, 1H), 1.71–1.53 (m, 2H) 1.39–1.13 (m, 8H), 0.92-0.77 (m, 3H); ¹³C-NMR (CDCl₃): δ 175.6, 172.5, 51.7, 51.6, 41.0, 35.5, 31.5, 31.2, 26.4, 22.4, 22.1, 13.9; IR (v, cm⁻¹): 1726, 1724, 1160; MS *m*/*z* 230 (5), 199 (32), 157 (65), 146 (89), 114 (100).

Methyl 3-phenylpropanoate [53]: m.p. (hexane) = 143 °C. ¹H-NMR (CDCl₃): δ 7.28-7.20 (m, 5H), 3.64 (s, 3H), 2.82, 2.54 (2t, *J* = 6.8 Hz, 4H); ¹³C-NMR (CDCl₃): δ 169.4, 142.9, 128.9 (2C), 128.1 (2C), 126.0, 51.7, 34.0, 31.8; IR (v, cm⁻¹): 1729, 1161; MS *m*/*z* 164 (42), 133 (87), 105 (100).

Methyl 2-phenylpropanoate [54]: Colorless oil. ¹H-NMR (CDCl₃): δ 7.26-7.17 (m, 5H), 3.67 (q, *J* = 6.5 Hz, 1H), 3.60 (s, 3H), 1.64 (d, 3H, *J* = 6.6 Hz); ¹³C-NMR (CDCl₃): δ 169.0, 142.9, 129.9 (2C), 127.8 (2C), 126.9, 52.7, 40.0, 13.8; IR (v, cm⁻¹): 1727, 1165; MS *m*/*z* 164 (21), 133 (32), 105 (100).

3 Results and Discussion

Our first experiments on the use of palladium-based catalysts for the oxidative alkoxycarbonylation of olefins were carried out on styrene as model substrate, employing different palladium source with additional iodide salts as co-catalysts (Table 1), in a 1:5 mixture of MeOH/MeCN as reaction medium

and oxygen as oxidizing agent [29]. Pressure of CO was initially kept at 5 atm, and, consequently, 35 atm of air were necessary in order to avoid explosion risks.

3.1 Activities of Palladium-based Catalytic Systems

Under the reported conditions, poor conversions were observed using PdI₂, K₂PdI₄ or the heterogeneous Pd/C as the sole catalytic species (run 1-3, table 1). The addition of a source of iodide anions such as KI (10 mol%), increased the reaction rate, even though the selectivity to methyl cinnamate 3 remained rather low (run 4). A dramatic effect on the 3a/2a molar ratio was exerted by CO pressure. In fact, reducing the pressure of CO from 5 to 2 atm selectivity to compound 3a raised to 81% when PdI_2 was used (run 5). Since it is likely that an excess of I⁻ promoted the Pd(0)/Pd(II)oxidation step [28, 55] thus improving the yield of **3a**, we decided to use CuI for its putative double role when it is used in combination with palladium catalysts. Both copper and iodide ligand would contribute, together with O₂, in the re-oxidation of palladium, which seems to be critical in this process. The use of CuI (10 mol%) instead of KI with homogeneous palladium source did not really improve the yield of cinnamate (run 7 and 8). Unexpectedly, the heterogeneous Pd/C (1 mol%) in conjunction with CuI gave the best result in term of efficiency without altering the selectivity (run 9). Pd and Cu-based species are active catalysts in aerobic oxidation of alkenes [56,57], and under our reaction conditions oxidized compounds, such as benzaldeyde, acetophenone, benzoic acid and methyl benzoate were formed in a limited amount (<10%). Only when a 10% of KI was added to this system (Pd/C and CuI) a considerable amount of styrene oxidation products, at the expense of the yield of **3a**, were observed (run 10). Probably a too large excess of I^{-} can make more difficult the coordination of styrene on palladium, slowing down the rate of the alkoxycarbonylation reaction. Small amount of linear and branched methyl phenylpropanoates, originated from a different mechanism that involves a palladium hydride species (see the mechanistic discussion, Schemes 3 and 4), were also detected [58]. Other metal iodide, such as FeI₂, NiI₂, and CoI₂, failed as co-catalyst, yielding mainly oxidized derivatives. Only the Pd/C-MnI₂ catalytic system provided methyl cinnamate in good selectivity but was less effective (run 11).

With these preliminary data in hand, further experiments were carried out on other palladium supported catalysts used in combinations with different copper-based co-catalysts (Table 2). After having verified that the Pd/Cu molar ratio 1:10 is optimal under our reaction conditions (compare run 9 in Table 1 with run 1 and 2 in Table 2), we first tried commercial 10% Pd/Al₂O₃ and 10% Pd/CaCO₃ in place of Pd/C. As shown in Table 2 these palladium precursor proved to be as active as Pd/C and

slightly more selective towards compound **3a** (run 3 and 4, Table 2). The basic character of supports employed could in part justify the improve selectivity observed [25]. Continuing the study of the catalytic system, we also tested various copper salts as co-catalyst in conjunction with Pd/CaCO₃ (run 5-11, Table 2). While CuO did not demonstrate any activity (run 5, Table 2), Cu(OAc)₂, which was the additive of choice in a recent palladium-catalyzed alkoxycarbonylation of alkenes [29], under our conditions was detrimental to the reaction outcome (run 6, Table 2). Remarkably, the process was totally site-selective when Cu(acac)₂ was used (run 7, Table 2), even though its activity was rather limited. Copper chlorides and bromides led to satisfactory results in term of yield of methyl cinnamate (run 8-11, Table 2), however the best outcome was achieved using CuI.

3.2 Influence of the Reaction Media

Having established the suitable reaction conditions and studied the influence of parameters and additives on the methoxycarbonylation of styrene in MeOH/MeCN mixture, we next investigated the influence of various reaction media, consisting of mixtures of methanol and a co-solvent, in the presence of Pd/CaCO₃ and CuI (Table 3).

Solvents such as acetonitrile and benzonitrile gave the best results in term of yield and selectivity (run 1 and 2, Table 3). Very poor conversions were observed when DMA (*N*,*N*-dimethylacetamide) or NMP (*N*-methylpyrrolidone) were employed (run 3 and 4, Table 3). On the other hand, low polar solvents such as DME (dimethoxyethane) or 1,4-dioxane led to satisfactory conversion values but lower selectivities (run 5 and 6, Table 3). In this case, a not negligible amount of 2- and 3-phenylpropanoates was formed. As expected, a good conversion was attained when MeOH was employed as the sole reaction medium, but dimethylsuccinate **2a** was in this case the preferred product (run 7, Table 3). Although it is quite difficult to rationalize the solvent effects, it may be speculated that a polar solvent can stabilize ionic versus neutral species modifying the selectivity of the process. Moreover, in our case, the solubility of CO and CuI can account for the observed behavior. Aprotic polar MeCN of high coordinating ability [59], is able to dissolve CuI and CO in an appropriate amount, giving the best results as also reported by Malkov et al. [29].

3.3 Scope and Limitations of the Pd/C-CuI-catalyzed Alkoxycarbonylation Reaction

We next investigated the generality of this oxidative alkoxycarbonylation reaction catalyzed by the most common source of supported palladium such as 10% Pd/C (Table 4). α,β-Unsaturated esters, mainly cinnamate derivatives, were obtained in good to excellent yields. Primary and secondary alcohols reacted readily with styrene providing the corresponding cinnamates in high isolated yield (run 1-7, Table 5). In particular, *i*-butyl cinnamate **3d**, which it is known to exhibit a strong antibacterial activity [60], was obtained in almost quantitative yield (run 4, Table 5). A sterically hindered alcohol, such as the *t*-butyl one, exhibited poor reactivity (25%), resulting in a low isolated yield of the corresponding cinnamate **3h** (16%, run 8, table 5). Styrenes bearing an alkyl group in para position of the aromatic ring, such as methyl or t-butyl, gave satisfactory results, affording 63 and 60% yield of the corresponding esters **3i** and **3j** (run 9 and 10, Table 5). The methoxy group, ubiquitous in natural and pharmaceutical compounds, is well tolerated (run 11, Table 5) as well as halogen atoms, such as chloro and bromo (run 12 and 13, Table 5), which can be further functionalized by palladium chemistry. Notably, halogenated cinnamic acid derivatives showed a very high CNS depressant activity [61]. Under the same reaction conditions, allylbenzene and 1octene showed good reactivity even if monocarbonylated products were obtained as isomeric mixture in 45 and 65% total yield, respectively. Dicarbonylated compounds 2n and 20 were also formed in 16 and 23% (run 14 and 15, Table 5).

3.4 Recycling tests

Since $Pd/CaCO_3$ could be easily separated from the reaction mixture by simple filtration, we initially examined the alkoxycarbonylation of styrene using the recycled solid (see recycling procedure in section 2.3, run 2, Table 5) coming from a first cycle of $Pd/CaCO_3$ -CuI-catalyzed carbonylation reaction (run 1, Table 5). The yield of cinnamate **3a** amounted to 47% and this result prompted us to believe that a considerable palladium-leaching was occurring [62]. In fact, when to the filtered solution was added an extra equivalent of styrene, and the resulting mixture was subjected to our carbonylation conditions, the yield of compound **3a** reached 61%, confirming that a catalyst leaching took place. Notably, the total catalytic activity, sum of those of recycled solid and solution, was even better than one obtained in the first run.

To further confirm the homogeneous character of this palladium-catalyzed process and to gain more insights about the active catalytic species, a different heterogeneous source of palladium(0), that is, palladium sponge, was treated with CuI in MeCN under 30 atm of air in autoclave at 120 °C for 24h (see section 2.4). The resulting solution, separated by filtration from the residual solid, was used as "catalyst" in our conventional reaction conditions, and the desired ester **3a** was obtained in 63% yield and excellent selectivity (run 4, Table 5). Almost no activity was observed (run 5, Table 5) when the solution was obtained treating the Pd-sponge at atmospheric pressure of air (see section 2.5). Only a 45% of palladium (0.0225 mmol) was transferred in the homogeneous phase, giving 140 as turnover number. The treatment of Pd-sponge with CuI and oxygen (30 atm) generated an oxidized Pd species catalytically active in the oxidative alkoxycarbonylation of styrene in homogeneous phase. The nature of this active catalytic species and the exact role of copper in the catalytic reaction are currently unknown. Further investigations are in progress trying to increase TON and recyclability of this simple catalytic system.

3.5 Proposed Reaction Pathways

According to the literature [1,2,17-20,23] we propose a reaction mechanism (Scheme 3) that starts from the supported Pd⁰, which is initially oxidized to Pd^{II} by means of Cu^{II}. This seems to be plausible, since the activity of Pd catalyst is very low in the absence of CuX. The active species **I** reacts with the alcohol leading to complex **II**, which after insertion of CO, affords an alkoxycarbonylpalladium complex **III**. The subsequent coordination and insertion of the olefin on **III** yields intermediate **V**, which undergoes β -hydride elimination with formation of compound **3** and the unstable palladium hydride complex **VI**. The latter then easily decomposes to the Pd⁰ species **VII**. Re-oxidation of Pd⁰ to Pd^{II} is realized by Cu^{II}, which in its turn is regenerated by O₂, or directly by O₂, which, in the presence of an excess of I⁻ anions, is able to restore the Pd^{II} species [31,32].

Succinate derivatives 2 results from CO insertion on intermediate V and subsequent nucleophilic displacement by the alcohol (Scheme 4). Saturated 2- and 3-phenyl propanoates, observed in small amount under our reaction conditions (Table 1), are generated by reaction of styrene with Pd-H species according to Scheme 4.

4 Conclusions

In conclusion, we have found that a very simple catalytic system, consisting of a heterogeneous palladium source such as Pd/C, Pd/Al₂O₃ and Pd/CaCO₃ in conjunction with CuI, is a highly effective

catalyst for the oxidative alkoxycarbonylation of α -olefins to unsaturated esters. The reaction conditions, featuring only 1 mol% of palladium and 10 mol% of CuI, the use of oxygen as the most cheap oxidant, and the absence of any base or phosphorous ligands, represent a valuable alternative protocol for the synthesis of α , β -unsaturated esters. Experimental evidences account for a homogeneous palladium-catalyzed alkoxycarbonylation reaction. Further studies, in order to gain insight the active catalytic species, are in progress and will be reported in due course.

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Ö MeO

Ö MeO

Octyl 4-methoxycinnamate (Sunscreen)

0 MeO

2-Ethoxyethyl 4-methoxycinnamate (Sunscreen)

Isoamyl 4-methoxycinnamate (Sunscreen)

ö ŞO2 `Me С N

Piroxicam Cinnamate (Anti-inflammatory agent)

Figure 1. Active ingredients in approved drugs.



Scheme 1. Oxidative alkoxycarbonylation of terminal olefins with CO and alcohols.



Scheme 2. PdI₂/KI-catalyzed hydroalkoxycarbonylation of terminal arylacetylenes to branched esters 4.



L = I⁻, CO, Solvent, Olefin





Scheme 4. Proposed reaction pathway to compound 2 and propanoate derivatives.

=	/	<u>^</u>	co-cat	MeO ₂ C	CO ₂ Me	CO₂Me ∕
) MeOH	LO I CC Ai 12	0 (2-5 atı r (35 atıı MeCN 20 °C, 24	m) n)	2a ⁺	3a
Run	Pd cat	co-cat	CO	Styrene	2a	3a
			(atm)	conversion (%) ^a	yield (%) ^b	yield (%) ^{b,c}
1	PdI ₂	-	5	5	<1	3
2	K ₂ PdI ₄	-	5	8	2	5
3	Pd/C	-	5	<1	_	traces
4	PdI ₂	KI	5	59	31	23 (39)
5	PdI ₂	KI	2	57	5	46 (81)
6	Pd/C	KI	2	22	2	13 (59)
7	PdI ₂	CuI	2	56	1	43 (77)
8	K ₂ PdI ₄	CuI	2	49	1	37 (75)
9 ^d	Pd/C	CuI	2	96	6	77 (80)
10 ^e	Pd/C	CuI+KI ^f	2	81	4	48 (59)
11	Pd/C	MnI ₂	2	48	2	38 (79)

Table 1. Activities of Palladium Catalysts in the Oxidative Alkoxycarbonylation of Styrene.

Pd cat

Reaction conditions: styrene (5.0 mmol), MeOH (50 mmol, 2.0 mL), Pd-cat (1 mol%), co-catalyst (10 mol%), MeCN (10 mL), air (35 atm), CO, 120 °C, 24h. ^a Determined by GC using 1,2,4,5-tetramethylbenzene as an internal standard. ^b Determined from ¹H NMR of the reaction crude using dimethylmaleate as an internal standard. ^c Selectivity to **3a** are in brackets. ^d By-products are mainly formed by acetophenone and methyl benzoate (8%) and methyl 2-phenylpropanoate and 3-phenylpropanoate (2%). ^e Benzaldehyde, acetophenone, benzoic acid and methyl benzoate (22%). ^f 10 mol% of CuI and 10 mol% of KI.

Table 2. Improvement of the Activity and Selectivity of Pd supported – CuX Catalytic Species.

	/== + CO	Pd supp CuX	MeO ₂ C	_CO ₂ Me	CO ₂ Me
	MeOH	CO (2 a Air (35 a MeC 120 °C,	atm) atm) N 24h	+ 2a 〈	3 a
Run	Pd	CuX	Styrene	2a	3a
	supported		conversion (%) ^a	yield (%) ^b	yield (%) ^{b,c}
1	Pd/C	CuI ^d	80	7	63 (79)
2	Pd/C	CuI ^e	91	5	72 (79)
3	Pd/Al ₂ O ₃	CuI	96	5	82 (85)
4	Pd/CaCO ₃	CuI	99	8	83 (84)
5	Pd/CaCO ₃	CuO	1	-	<1
6	Pd/CaCO ₃	Cu(OAc) ₂	50	2	5
7	Pd/CaCO ₃	Cu(acac) ₂	19	-	19 (100)
8	Pd/CaCO ₃	CuCl	98	9	65 (66) ^f
9	Pd/CaCO ₃	CuCl ₂	98	4	72 (73) ^f
10	Pd/CaCO ₃	CuBr	97	10	71 (73) ^f
11	Pd/CaCO ₃	CuBr ₂	98	3	63 (64) ^f

Reaction conditions: styrene (5.0 mmol), MeOH (50 mmol, 2.0 mL), Pd-supported (1 mol%), CuX (10 mol%), MeCN (10 mL), air (35 atm), CO (2 atm), 120 °C, 24h. ^a Determined by GC. ^b Determined from ¹H NMR of the reaction crude using dimethylmaleate as an internal standard. ^c Selectivity to **3a** are in brackets. ^d 1 mol% of CuI. ^e 100 mol% of CuI. ^f 15-21% of a mixture of phenylpropanoate isomers was observed.

а
u

Table 3. Reaction Media Influence under Optimized Reaction Conditions.

Reaction conditions: styrene (5.0 mmol), MeOH (50 mmol, 2.0 mL), Pd/CaCO₃ (1 mol%), CuI (10 mol%), Solvent (10 mL), air (35 atm), CO (2 atm), 120 °C, 24h. ^a Determined by GC. ^b Determined from ¹H NMR of the reaction crude using dimethylmaleate as an internal standard. ^c Selectivity to **3a** are in brackets. ^d *N*,*N*-Dimethylacetamide. ^e *N*-Methylpyrrolidone. ^f Dimethoxyethane. ^g 14% of a mixture of 2- and 3-phenylpropanoates. ^h 13% of a mixture of 2- and 3-phenylpropanoates.

Table 4. Pd/C-CuI-Catalyzed Alkoxycarbonylation Reaction of α -Olefins.



Run	R ¹	\mathbb{R}^2	Product	3
				yield (%) ^a
1	Ph	Ме	0 0 0	3a 74
2	Ph	Et		3b 83
3	Ph	<i>n</i> Bu		3c 79
4	Ph	<i>i</i> Bu		3d 95
5	Ph	PhCH ₂		3e 81
6	Ph	PhCH ₂ CH ₂		3f 80
7	Ph	<i>i</i> Pr		3 g 79
8	Ph	<i>t</i> Bu	0 0 0	3h 16 ^b

9	4-MeC ₆ H ₄	Me		3i 63
			· · · · · · · · · · · · · · · · · · ·	
10	$4-tBuC_6H_4$	Me		3j 60
			0	
11	4-OMeC ₆ H ₄	Me	0	3k 82
12	4-ClC ₆ H ₄	Me		3l 90
			CI	
13	4-BrC ₆ H ₄	Me	0	3m 80
			Br	
14	PhCH ₂	Me		3n+3n' 45°
				1:2
1.7			3n 3n'	2 . 2 . c . c . d
15	C_6H_{13}	Ме		30+30 ⁷ 65 ^u
			30	2.1
			3o'	

Reaction conditions: Olefin (5.0 mmol), R²OH (50 mmol, 2.0 mL), Pd/C (1 mol%), CuI (10 mol%), MeCN (10 mL), air (35 atm), CO (2 atm), 120 °C, 24h. ^a Isolated yield. ^b Conversion of styrene was 25%. ^c 16% of dicarbonylated compound **2n** was isolated. ^d 23% of dicarbonylated compound **2o** was isolated.

Run	Pd source	Styrene	3 a
		conversion (%) ^a	yield (%) ^{b,c}
1	Pd/CaCO ₃	99	83 (84)
2	Recycle of Solid from 1	56	47 (81)
3	Recycle of Solution from 1	72	61 (85)
4	Solution from Pd sponge ^d	67	63 (94)
5	Solution from Pd sponge ^e	7	6

Table 5. Recycling Experiments on the Pd/CaCO₃-Catalyzed Alkoxycarbonylation.

Reaction conditions: styrene (5.0 mmol), MeOH (50 mmol, 2.0 mL), Pd source (1 mol%), CuI (10 mol%), MeCN (10 mL), air (35 atm), CO (2 atm), 120 °C, 24h. ^a Determined by GC. ^b Determined from ¹H NMR of the reaction crude. ^c Selectivity to **3a** are in brackets. ^d Solution was obtained treating Pd sponge with CuI in MeCN under 30 atm of air at 120 °C for 24 h. ^e Solution was obtained treating Pd sponge with CuI in MeCN under 1 atm of air at 120 °C for 24 h.