

Preparation of functional styrenes from biosourced carboxylic acids by copper catalyzed decarboxylation in PEG†

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Stéphane Cadot, Nelly Rameau, Stéphane Mangematin, Catherine Pinel and Laurent Djakovitch*

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A general protocol for the copper-catalyzed decarboxylation of α,β -unsaturated carboxylic acids in PEG, particularly of biosourced cinnamic acid analogues, is reported. Moderate to high isolated yields (31–96%) towards the styrene derivatives were obtained. For the first time, decarboxylation of α -amino acids to the corresponding amines was successfully performed with good to high yields and extended to the decarboxylation of a few condensed heterocyclic compounds. Both the use of PEG as a green solvent and direct separation of the pure product of the reaction by distillation permitted the reuse of the solvent and the Cu-based catalytic system over several cycles without deactivation. This was extended to the synthesis of 4-vinylguaicol on the laboratory scale in an average 92% yield.

Introduction

Functional styrenes, such as vinylphenols, represent a specific class of styrene.¹ They received particular attention due to their widespread applications in polymer, pharmaceutical, agrochemical and food industries.^{2–6} Despite their availability from petrochemical and/or natural sources, the increasing demand from the chemical industries is not fully satisfied. To circumvent this situation many synthetic routes have been described but most of them required either toxic and expensive reagents or harsh reaction conditions.^{7–11} Additionally, when dealing specifically with phenol derivatives, protection/deprotection procedures are often necessary.

A more elegant route to access functional styrene derivatives is the decarboxylation of cinnamic acid derivatives like coumaric, ferulic or sinapic acids. These compounds are readily available from renewables either as extracts from annual plants^{12–15} or as by-products from lignin depolymerization.¹⁶

Decarboxylation of such conjugated acid derivatives is generally conducted by microbial,^{17–19} biocatalytic,²⁰ acid²¹ or base²² (*i.e.* high temperature chemical) pathways. Besides these classical routes, the microwave-assisted base-catalyzed decarboxylation procedures are subject to intensive developments since they can be considered as ecofriendly and rapid

ways to produce at the laboratory scale the required vinyl compounds.^{23–26} Although they have indisputable practical aspects the latter procedures remain limited to gram scale production. A solution can be the development of transition-metal (*i.e.*: TM) catalyzed decarboxylation procedures that can be easily implemented in chemical industries.

Modern TM-catalyzed decarboxylation methodologies were developed under the impulsion of Goossen's group as a part of the Pd/Cu-catalyzed decarboxylative cross-coupling reactions.^{27–30} Limited to the strict protodecarboxylation methodologies, these studies focused particularly on the copper-catalyzed transformation of substituted benzoic acids,^{31–33} and only a few examples related to cinnamic derivatives were reported. Goossen's group initially described a Cu-catalyzed efficient procedure for the protodecarboxylation of various benzoic acids (*i.e.* 5 mol% Cu₂O, 10 mol% 1,10-phenanthroline, 4 equiv. quinoline, NMP, 170 °C).³⁴ However, this procedure failed to convert some *o*-substituted or heterobenzoic acids as well as cinnamic derivatives. Goossen *et al.* developed a silver catalyzed procedure (*i.e.* 5 mol% AgOAc, 15 mol% K₂CO₃, NMP, 120–160 °C) to successfully perform the Cu-catalyzed methodology.³⁵ Under such conditions, cinnamic acid gave the corresponding styrene with good conversion (76%). Interestingly, Zou and co-workers recently reported the protodecarboxylation of various 2,3-diaryl acrylic acids using a CuI/1,10-phenanthroline/PEG-400 system under microwave conditions giving generally good to high yields of the expected stilbene derivatives.³⁶

The field was recently extended to gold catalysis by Nolan and co-workers who described gold-catalyzed decarboxylation of aromatic carboxylic acids using gold(I)-N-heterocyclic

Université de Lyon, CNRS, UMR 5256, IRCÉLYON, Institut de recherches sur la catalyse et l'environnement de Lyon, 2 avenue Albert Einstein, F-69626 Villeurbanne, France. E-mail: Laurent.Djakovitch@ircelyon.univ-lyon1.fr; Fax: +33472445399; Tel: +33472445381

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carbene complexes that led to the corresponding gold(i)-aryl complexes (*i.e.* [Au(IPr)(OH)] (with IPr: (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)), 1,4-dioxane, 110 °C, 1–70 h).³⁷ This catalyst is tolerant to a wide range of aryl and heteroaryl substrates; however, from the first reported data no protodecarboxylation occurred due to the formation of stable gold complexes and the synthetic applications toward the corresponding ArylH were limited. Recently, while revisiting the reaction conditions (*i.e.* 2 mol% [Au(SIPr)(O₂CAd)] (with SIPr: 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) and Ad: adamantyl), anhydrous toluene or DMAc, 120–165 °C, 16–20 h) the authors reported a new procedure for transformation of aromatic carboxylic acids to ArH in moderate to good yields (46–97%) but it was not applied to the transformation of cinnamic derivatives.³⁸

In the field of our ongoing research toward greener synthesis of styrene, stilbene and bibenzyl derivatives,^{3,4,7,8,39–46} we are interested in evaluating the synthesis of various functional styrenes from biosourced substrates. To achieve the procedure in agreement with environmental concerns, studies aiming at decarboxylating selectively cinnamic acids under TM-catalysis and optimizing the reaction conditions were realized.

Results and discussion

The activity of various silver and copper salts used in stoichiometric amounts in the decarboxylation of the cinnamic acid (Scheme 1) was initially evaluated. In the absence of an additional ligand, no reaction was observed in the presence of Cu or Ag salts under neutral conditions. However addition of a base leads to the formation of styrene with up to 23% yield in the presence of Ag₂CO₃. Moreover, Fig. 1 clearly demonstrates that among the TM-salts used, Ag₂CO₃ and Cu(OH)₂ associated with the 1,10-phenanthroline ligand gave the highest yields of the corresponding styrene of 60% and 79%, respectively. Other silver and copper salts, despite the addition of K₂CO₃ and 1,10-phenanthroline, did not give such an activity.

In view of these results, given the highly positive influence on the reaction yields of adding a catalytic amount (0.05 mmol) of 1,10-phenanthroline as a ligand, we next turned to develop a Cu-catalyzed procedure by associating Cu(OH)₂ with various ligands, possibly in the presence of a base (Table 1).

The results show that the Cu(OH)₂/1,10-phenanthroline system can be used catalytically (10 mol%) without any loss of activity reaching 83% yield (Table 1, entry 1) *versus* 79% when Cu(OH)₂ is used in a stoichiometric amount (Fig. 1). The use of 2,2'-bipyridine allowed us to achieve almost a quantitative yield (entry 4), however with an excess of ligand (3 equiv./

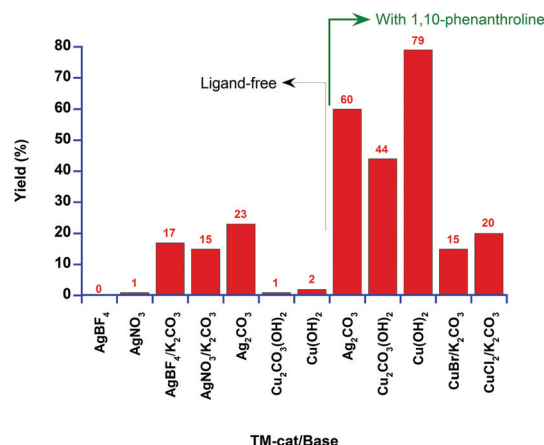


Fig. 1 Evaluating various TM-salts for the protodecarboxylation of cinnamic acid. Reaction conditions: cinnamic acid (0.5 mmol), [Ag]- or [Cu]-catalyst (0.6 mmol), 1,10-phenanthroline (when mentioned, 0.05 mmol), K₂CO₃ (when mentioned, 0.6 mmol), NMP (5 mL), 150 °C, 16 h. The yield is determined by GC using dodecane as an external standard for quantitative determination.

Table 1 Improving the catalytic activity by adding a ligand

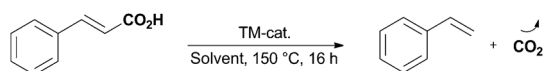
Entry	Ligand (mol%)	Base	Yield ^a (%)
1	1,10-Phenanthroline (10)	—	83
2	2,2'-Bipyridine (10)	—	59
3	2,2'-Bipyridine (20)	—	76
4	2,2'-Bipyridine (30)	—	93
5	1,10-Phenanthroline (10)	Quinoline	74
6	1,10-Phenanthroline (10)	TMEDA	95
7	1,10-Phenanthroline (10)	K ₂ CO ₃	5

Reaction conditions: cinnamic acid (0.5 mmol), [Cu(OH)₂] (10 mol%), ligand (when mentioned, 10–30 mol%), base (when mentioned, 0.5 mmol), NMP (5 mL), 150 °C, 16 h. ^a The yield was determined by GC using dodecane as an external standard for quantitative determination.

Cu(OH)₂ *versus* 1 equiv. with 1,10-phenanthroline). Interestingly, addition of TMEDA as a base to the Cu(OH)₂/1,10-phenanthroline catalytic system allowed us to achieve a quantitative conversion and high yield toward the corresponding styrene (entry 6), a trend already observed by Cahiez and co-workers in a study related to the protodecarboxylation of benzoic acids.³³ Surprisingly, addition of potassium carbonate inhibited the catalytic activity (entry 7), despite the good results observed with Malachite (*i.e.* CuCO₃·Cu(OH)₂, Fig. 1).

Further optimizations were achieved by evaluating the influence of the solvent. While good results were observed in NMP, other solvents were evaluated due to greener characteristics (Fig. 2a and 2b). Two catalytic systems were evaluated: Cu(OH)₂/1,10-phenanthroline (1 : 1; 10 mol%) and Cu(OH)₂/2,2'-bipyridine (1 : 2; 10 mol%).

Among “classical” solvents used (Fig. 2a), regardless of the catalytic system, NMP and DMAc gave the highest yields of styrene of 97% and 89%, respectively. Water completely inhibits the catalytic activity and acetonitrile or benzonitrile gave poor results (*resp. ca.* 15% and *ca.* 10%) with both systems.



Scheme 1

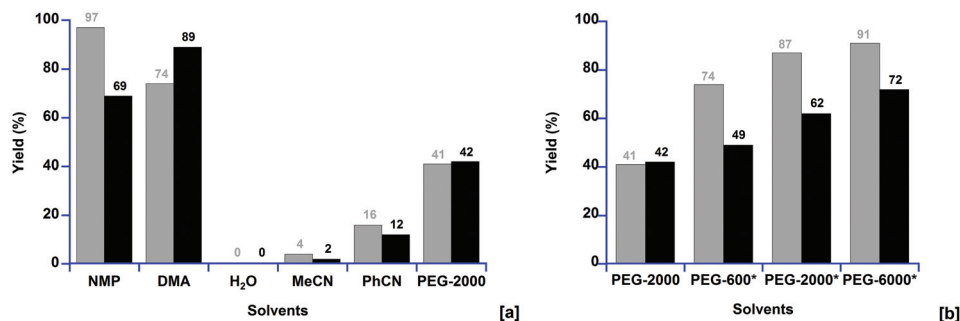


Fig. 2 Optimisation of the solvent in the decarboxylation of cinnamic acid. Reaction conditions: cinnamic acid (0.5 mmol), $\text{Cu}(\text{OH})_2$ (10 mol%), ligand: (■) 1,10-phenanthroline (10 mmol%) or (■) 2,2'-bipyridine (20 mol), solvent (5 mL or 5 g for PEGs), 150 °C, 16 h. The yield is determined by GC using dodecane as an external standard for quantitative determination. * PEG BioUltra grade was used.

The different yields observed between the two catalytic systems (*i.e.* $\text{Cu}(\text{OH})_2/1,10\text{-phenanthroline}$ (1:1; 10 mol%_{Cu}) or $\text{Cu}(\text{OH})_2/2,2'\text{-bipyridine}$ (1:2; 10 mol%_{Cu}) could be related to the relative stability of the intermediate {Cu/ligand} complexes in the chelating solvent.

Interestingly, while the yield of styrene is clearly lower, PEG-2000 used as the solvent gave useful results regarding the environmentally friendly features. This encourages us to evaluate different PEG-solvents varying their molecular mass or purity grade (Table 2, Fig. 2b). The results showed that higher purity (*i.e.* PEG-2000 BioUltra grade for molecular biology *versus* “standard” PEG-2000; Fig. 2) as well as higher molecular mass (*i.e.* PEG BioUltra grade with M_w varying from 2000 to 6000 g mol⁻¹) allowed us to increase considerably the catalyst activity. Thus, in PEG-6000 BioUltra grade, 91% yield of styrene using the $\text{Cu}(\text{OH})_2/1,10\text{-phenanthroline}$ (1:1; 10 mol%) was obtained. The differences observed can be correlated both with the presence of protic impurities as water traces and the number of terminal hydroxy groups (that is related to the average molecular mass for each PEG) that are detrimental to the catalytic activity or stability. This conclusion is supported by further experiments in which a controlled amount of water was added in the reaction mixture (Table 3). These results clearly indicate that an increase of the water content results in decreased reaction yields.

We were next interested in comparing more deeply the activity of the $\text{Cu}(\text{OH})_2/1,10\text{-phenanthroline}$ (1:1; 10 mol%) catalytic system in both NMP and PEG-6000*, the two solvents

Table 3 Influence of adding water to the reaction mixture on the yield of styrene

Entry	Amount of added water (μL)	Water content		Yield (%) ^a
		mg	mmol	
1	0	12.5	0.7	87
2	50	62.5	3.5	44
3	113	125	6.9	32

Reaction conditions: cinnamic acid (0.5 mmol), $\text{Cu}(\text{OH})_2$ (10 mol%), 1,10-phenanthroline (10 mmol%), PEG-2000* (5 g), 150 °C, 16 h. ^a The yield was determined by GC using dodecane as an external standard for quantitative determination.

leading to the highest chemical yields (Fig. 3). In both NMP and PEG-6000*, an induction period of *ca.* 1 hour was observed and attributed to the complexation of $\text{Cu}(\text{OH})_2$ by the 1,10-phenanthroline ligand and to the dissolution of the copper salt. It was observed experimentally that insoluble copper species initially present were solubilized in the reaction medium (*i.e.* after 1 hour at 150 °C only 8% of introduced

Table 2 Analytical data for PEGs (from suppliers, see the ESI for more details)

Solvent	Number of hydroxyl ^a (mg KOH g ⁻¹)		Water content ^b (wt%)
	Theoretical	Experimental	
PEG-2000	56	51–62	0.5
PEG-600*	187	172–204	Not provided
PEG-2000*	56	51–62	0.25
PEG-6000*	19	17–22	0.16

^a Test method: ASTM D – 4252. ^b Test method: ASTM D – 1744.

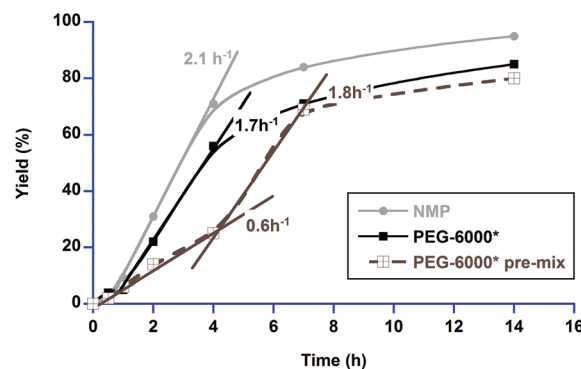


Fig. 3 Yield of styrene *versus* the time for the { $\text{Cu}(\text{OH})_2/1,10\text{-phenanthroline}$ (1:1)} catalytic system. Reaction conditions: cinnamic acid (0.5 mmol), $\text{Cu}(\text{OH})_2$ (10 mol%), 1,10-phenanthroline (10 mol%), solvent (5 mL for NMP or 5 g for PEG-6000*), 150 °C. For the “PEG-6000* pre-mix” experiment, $\text{Cu}(\text{OH})_2$ and 1,10-phenanthroline were mixed together in PEG-6000* at 150 °C for 1 h before adding the cinnamic acid. The yield is determined by GC using dodecane as an external standard for quantitative determination.

$\text{Cu}(\text{OH})_2$ was solubilized in the absence of ligand, *versus* >99% in the presence of 1,10-phenanthroline). Then, the reaction rate increased to give finally 95% and 85% yield after 24 h, respectively. Interestingly, the TOF of the catalytic system was slightly affected by the solvent raising $1.9 \pm 0.2 \text{ h}^{-1}$ in both NMP and PEG-6000* (Fig. 3) making PEG particularly interesting given its non-toxicity compared to NMP. Under these conditions, we were able to develop a procedure allowing separation of styrene directly under low vacuum, giving the pure compound in 59% isolated yield.

In order to gain deeper insights concerning the induction period observed in previous experiments, we conducted a test in PEG-6000* in which the catalytic system ($\text{Cu}(\text{OH})_2$ /1,10-phenanthroline (1 : 1; 10 mol%)) was pre-mixed for 1 hour at 150 °C before adding the cinnamic acid, setting at this time the reaction time to $t = 0$ (Fig. 3, PEG-6000* pre-mix). During the pre-mixing time, formation of metallic copper in the form of copper mirror was observed. After addition of cinnamic acid, the first period was observed during which the reaction rate remains limited to $0.6 \pm 0.1 \text{ h}^{-1}$. This rate closely corresponds to the one observed during the induction period for the reactions conducted in NMP or PEG-6000* without pre-mixing. After this time, dissolution of the metallic copper was observed and the reaction rate increased to reach finally $1.8 \pm 0.2 \text{ h}^{-1}$ like in the experiment performed in PEG-6000* without pre-mixing.

These results suggest that the induction period observed in these experiments is not only due to the dissolution of the original $\text{Cu}(\text{OH})_2$ to give with 1,10-phenanthroline a soluble copper complex, but also to the reduction of $\text{Cu}(\text{II})$ - to active $\text{Cu}(\text{I})$ -species, these being suspected from the pre-mix experiment. To support this hypothesis, an experiment with Cu_2O as the $\text{Cu}(\text{I})$ -source was carried out (Fig. 4). In that case, no induction period was observed and the initial reaction rate reached $1.3 \pm 0.1 \text{ h}^{-1}$ in the same range as in previous experiments.

A reaction mechanism is proposed (Fig. 5) to explain the observed results and is in agreement with previous reports in the literature.^{36,38} Initially, the mixture of $\text{Cu}(\text{OH})_2$ and

1,10-phenanthroline in PEG gave, after reduction of $\text{Cu}(\text{II})$ - to $\text{Cu}(\text{I})$ species, probably by some of the remaining hydroxyl groups of the solvent, a $\{\text{Cu}(\text{I})(1,10\text{-phenanthroline})(\text{OH})\}$ -complex **A**. This complex **A** reacts with the cinnamic acid to give a carboxylate intermediate **B** releasing water in the reaction medium before leading to decarboxylation under the reaction conditions to provide an organo-copper derivative **C**. Either upon hydrolysis, or by reaction with a new molecule of cinnamic acid, **C** forms the expected styrene regenerating either the initially active complex **A** (cycle I) or carboxylate intermediate **B** (cycle II) engaging thus a new catalytic cycle (Fig. 4). This proposed mechanism can also explain the inhibitory effect observed in the presence of water, assuming that cycle II is more efficient than cycle I.

This preliminary work validates the catalytic decarboxylation of cinnamic acid in the presence of the copper complex. Then, we evaluated the scope and limitations of the procedure involving continuous distillation of the product from the reaction medium. We engaged in the reaction various substituted cinnamic and benzoic acids working on a 15 mmol scale in the presence of only 5 mol% catalytic metal (*i.e.* carboxylic acid (15 mmol), $\text{Cu}(\text{OH})_2$ /1,10-phenanthroline (1 : 1; 5 mol%), PEG-6000 (20 g)). To face with the difference in reactivity of the various carboxylic acids involved in this set of experiments, the reaction mixture was heated up to the effective reaction temperature (*i.e.* 130–230 °C) as attested by CO_2 release and carried out under vacuum (*i.e.* 0.5–1 mbar) until no more product is collected in the collecting flask, corresponding to complete conversion of the substrate. The results are summarized in Table 4.

Considering cinnamic derivatives (entries 1–9), except for *p*-coumaric acid and caffeic acid that did not give the expected compounds under the reaction conditions due to rapid polymerization (entries 6 and 5, respectively), useful to good yields were achieved for all evaluated substrates. The main difficulty remains the effective and rapid separation of the pure substituted styrene derivative prior to its polymerization in the reaction flask.

The decarboxylation methodology was found to be efficient to convert nitrobenzoic acids (entries 10–12) in shorter reaction time compared to the reported procedure using Cu_2O or AgOAc in the case of the *ortho* derivative (entry 10 *versus* 13³⁴ and 14,³⁵ respectively). Interestingly, the procedure gave encouraging results when engaging sorbic acid that gave the corresponding 1,3-pentadiene, however in a non-optimized limited 14% yield despite its direct separation, mainly due to its loss under vacuum (entry 15). For the first time, we report here the direct Cu-catalyzed decarboxylation of α -amino acids. DL-Phenylalanine and DL-tyrosine gave the corresponding amines, respectively the 2-phenylethylamine and the 4-(2-aminoethyl)phenol both in 68% yields (entries 16 and 17). L-Valine, D-leucine and DL-methionine gave reaction mixtures. In the case of L-valine, the distillate contains a mixture of three compounds that were quantified through ^1H NMR and GC-MS: the starting L-valine (*ca.* 45%), the expected 2-methylpropan-1-amine⁴⁷ (*ca.* 45%) and the third product identified as 2-amino-1-(isobutylamino)-3-methylbut-1-en-1-ol⁴⁸ resulting

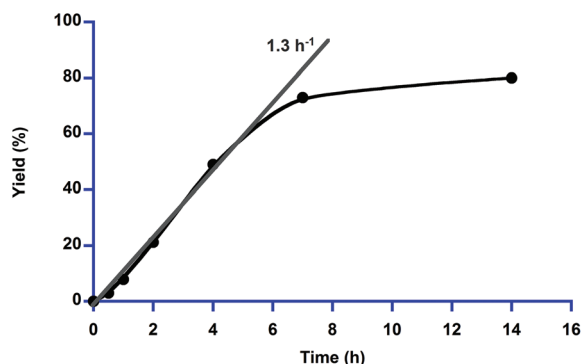


Fig. 4 Yield of styrene *versus* the time for the $\{\text{Cu}(\text{OH})_2\}$ /1,10-phenanthroline (1 : 1) catalytic system. Reaction conditions: cinnamic acid (0.5 mmol), Cu_2O (10 mol%), 1,10-phenanthroline (10 mol%), PEG-6000* (5 g), 150 °C. The yield determined by GC using dodecane as an external standard for quantitative determination.

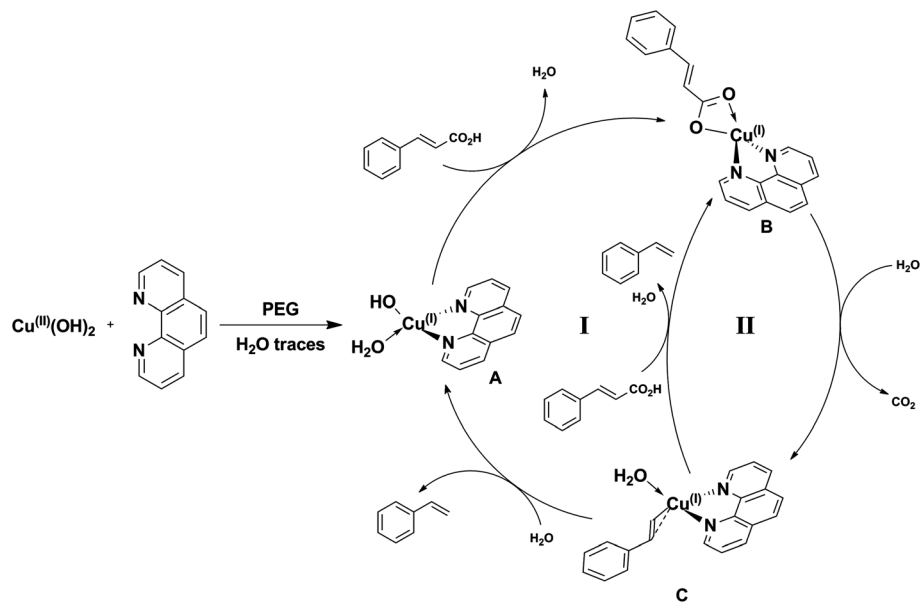
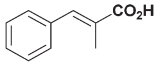
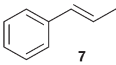
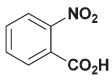
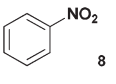
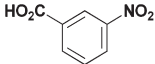
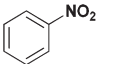
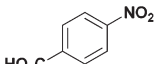
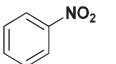
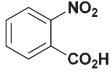
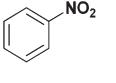
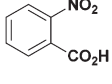
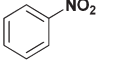
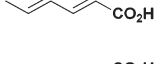
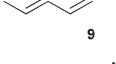
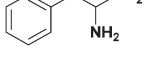
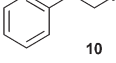
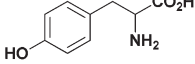
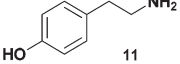
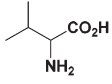
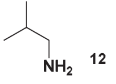
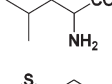
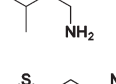
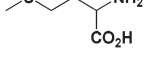
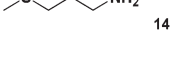
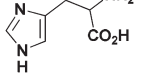
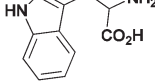
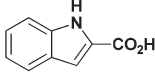
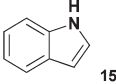
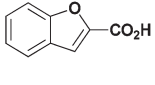
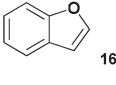
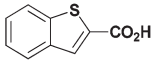
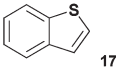


Fig. 5 Proposed reaction mechanism.

Table 4 Scope and limitation of the decarboxylation procedure with various carboxylic acid derivatives

Entry	Substrate	T °C	Time	Product	Yield (%)
1		210	1h00		68
2		210	1h45		52
3		200	2h30		73
4		140	1h00		96
5		130	0h30		— ^a
6		130	1h30		— ^a
7		130	1h10		31
8		195	2h30		59

Table 4 (Contd.)

Entry	Substrate	<i>T</i> °C	Time	Product	Yield (%)
9		180	5h00	 7	54
10		165	1h00	 8	90
11		210	3h00		55
12		220	3h30		46
13 ³⁴		170	12h		87
14 ³⁵		120	16h		92
15		180	5h00	 9	14
16		210	2h00	 10	68
17		210	5h00	 11	68
18		180	3h00	 12	Mixture
19		185	3h00	 13	Mixture
20		210	4h00	 14	Mixture
21		Up to 230	15h	Decomposition	—
22		Up to 230	15h	Decomposition	—
23		195	2h30	 15	75
24		190	4h00	 16	82
25		190	4h00	 17	75
26	CH ₃ (CH ₂) ₁₀ CO ₂ H	230	5h00	No reaction	—

Reaction conditions: carboxylic acid (15 mmol), Cu(OH)₂ (10 mol%), 1,10-phenanthroline (10 mmol%), PEG-6000 BioUltra grade (20 g), *T* (°C), time. All reported yields are isolated yields of the pure compound obtained by direct distillation. ^a Despite the observed decarboxylation (CO₂ bubbling) no product could be isolated due to the polymerization.

from the reaction between L-valine and the obtained amine (*ca.* 10%) (entry 19). D-Leucine and DL-methionine gave a complex reaction mixture of compounds that could not be fully identified despite the presence of the expected amine observed by GC-MS in both cases (entries 19 and 20). L-Histidine and L-tryptophan led to decomposition (entries 21 and 22). Suspecting an inhibiting effect due to the presence of heterocycles in the two last examples, we evaluated the decarboxylation of the 1*H*-indole-2-carboxylic acid, the benzofurane-2-carboxylic acid and the benzo[*b*]thiophene-2-carboxylic acid; all gave good to high isolated yields toward the expected heterocycles, respectively, the 1*H*-indole (68%), the benzofurane (82%) and the benzo[*b*]thiophene (68%) demonstrating thus that the presence of heterocycles in the structure did not affect the performances of the Cu(OH)₂/1,10-phenanthroline catalytic system (entries 23–25). Finally, decarboxylation of aliphatic acids like lauric acid failed (entry 26). Together with the examples of L-histidine and L-tryptophan, this result shows a limitation to the procedure.

Finally, in order to improve the beneficial impact on the environment of this new procedure we evaluated the possibility to reuse both the catalytic system and the PEG-solvent for several runs. This was evaluated for the decarboxylation of relatively cheap ferulic acid to the 4-vinylguaiacol, a high added-value compound finding numerous applications in pharmaceutical and food industries, like for synthesizing vanillin.⁴⁹ The procedure corresponds to the following: an initial catalytic run was conducted under the standard reaction conditions using a fresh copper catalyst (10 mol%) and PEG-6000 solvent (50 g) on a 30 mmol scale (5.8 g). Once the 4-vinylguaiacol production ends as attested by the absence of both CO₂ bubbling and product distillation, a new charge of

Table 5 Reuse of the catalytic system (*i.e.* Cu(OH)₂/1,10-phenanthroline/PEG-6000-Fig. 6) for several runs in the protodecarboxylation of ferulic acid

<chem>COc1ccc(cc1O)/C=C/C(=O)O</chem> $\xrightarrow[\text{PEG-6000 BioUltra grade, 140 } ^\circ\text{C}]{\text{Cu(OH)}_2 \text{ (10 mol\%)} \atop \text{1,10-phenanthroline (10 mol\%)}}$ <chem>COc1ccc(cc1O)/C=C/C</chem> + CO ₂				
Run	Time (min)	Gram yield	Yield (%)	TOF (min ⁻¹)
1	55	3.80	84	0.15
2	50	4.36	97	0.19
3	50	4.07	90	0.18
4	55	4.34	96	0.18

ferulic acid was added after cooling in the boiler and a new run is performed. The procedure was then repeated twice (Fig. 6). The results reported in Table 5 show that the catalytic system (*i.e.*: Cu-catalyst and solvent) remains stable upon reuse without deactivation. On each run, full conversion was achieved giving a high isolated yield of the 4-vinylguaiacol target that corresponds to an average TON of 9.2 per run, and a cumulative TON of 37 over the 4 runs. Small differences in yield were observed between the first run and the following runs due to condensation on the glassware apparatus of 4-vinylguaiacol during the first run. That was not the case during successive runs.

Conclusion

In summary, a new protocol for the copper-catalyzed decarboxylation of cinnamic acid derivatives in PEG has been developed. The procedure gave generally moderate to high isolated yields of the target molecules. It was found that our procedure can be used to transform aromatic acids, heterocycle-2-carboxylic acids and more generally α,β-unsaturated acids, and for the first time α-amino acids. The use of the more environmentally friendly PEG solvent allowed to perform the transformation under reduce pressure to isolate directly the product by continuous distillation, preventing therefore its possible rapid polymerization. Furthermore, it allowed the reuse of both the solvent and catalytic system (*i.e.* Cu/ligand) to perform several cycles without observing any deactivation. Thus, the high added-value 4-vinylguaiacol could be prepared in relatively short reaction time (50 min) at an interesting laboratory large scale (*ca.* 4 g).

This protocol, additionally to be practical, is thus suitable for easily synthesizing a variety of molecules derived from bio-sourced carboxylic acids including styrene derivatives from cinnamic compounds, olefins from the acrylic moiety or amines from amino acids.

Experimental

General information

All glassware was base-, acid- and water-washed and oven dried. The catalytic reactions were carried out under low

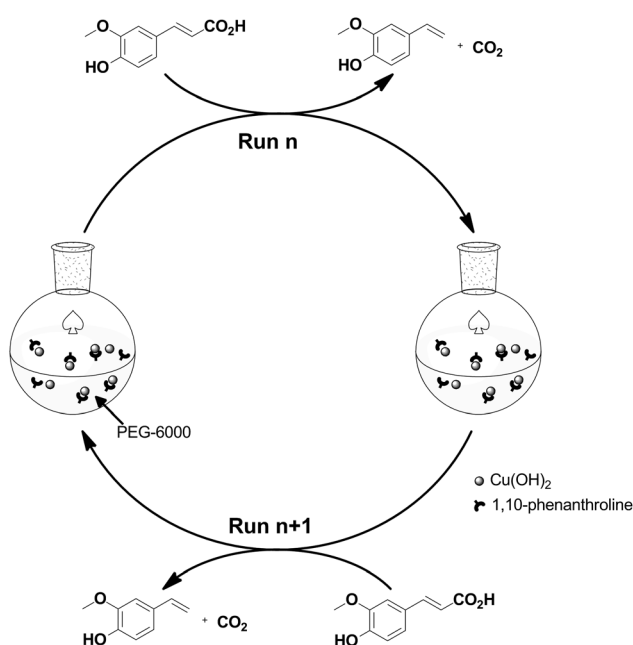


Fig. 6 Recycling the {Cu(OH)₂/1,10-phenanthroline/PEG-6000} catalytic system in the protodecarboxylation of ferulic acid (Table 1).

vacuum in distillation apparatus consisting of a two-necked flask equipped with a condenser, a vacuum adapter and a collecting flask.

The qualitative and quantitative analysis of the reactants and the products was made by Gas Phase Chromatography using dodecane as an external standard.

All chemicals were purchased from Acros and Aldrich Chemicals in their highest purity. All solvents were used as supplied without further purification.

Liquid-state NMR spectra were recorded on a BRUKER AC-250 or BRUKER DRX300 spectrometer. All chemical shifts were measured relative to the residual ^1H NMR resonances in the deuterated solvents: CDCl_3 , δ 7.26 ppm for ^1H NMR; D_2O , 4.79 ppm for ^1H NMR. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad) and coupling constants (in Hz), integration and assignments in that order.

Thin layer chromatography was performed on a Fluka Silica Gel 60 F₂₅₄. GC analyses were performed on a Shimadzu GC-2010 chromatograph equipped with a FID detector, a AOC-20i+ autosampler and a Phenomenex Zebron ZB-5HT column (cross-linked 5% phenyl-methylsiloxane, 30 m \times 0.25 mm i.d. \times 0.25 μm film thickness). Nitrogen is used as a carrier gas. The mass spectra were obtained on a Shimadzu GC-MS-QP2010S equipped with a AOC-20i+ autosampler and a Sulpelco SLB-5MS column (95% methylpolysiloxane + 5% phenylpolysiloxane, 30 m \times 0.25 mm \times 0.25 μm) with He as carrier gas. The experimental error was estimated to be $\Delta_{\text{rel}} = \pm 5\%$.

Procedures

General procedures for the decarboxylation of carboxylic acids. 15 mmol of carboxylic acid, 0.75 mmol (73 mg) of $\text{Cu}(\text{OH})_2$, 0.75 mmol (135 mg) of 1,10-phenanthroline and 20 g of PEG-6000 BioUltra are introduced into a two-necked flask. After adapting a condenser, a vacuum adapter and a receiving flask, the reaction mixture was degassed by a series of vacuum-argon under stirring. Then it is heated up to the effective reaction temperature (*i.e.* 130–230 $^\circ\text{C}$) as attested by CO_2 release under low vacuum (*i.e.* 0.5–1 mbar) until complete conversion. The pure decarboxylated compound is obtained directly in the receiving flask.

All compounds gave analytical data in agreement with that reported in the literature; (**1**;¹¹ **2**;⁵⁰ **3**;⁵¹ **4**;²⁴ **5**;²⁴ **7**⁵²) or available data for commercially available compounds (**6**[CAS 100-42-5]; **8**[CAS 98-95-3]; **9**[CAS 2004-70-8]; **10**[CAS 64-04-0]; **11**[CAS 51-67-2]; **12**[78-81-9] **13**[CAS 541-23-1]; **14**[4104-45-4]; **15**[CAS 120-72-9]; **16**[CAS 271-89-6]; **17**[CAS 95-15-8]) from the National Institute of Advanced Industrial Science and Technology (AIST).

General procedure for recycling studies. The same distillation installation as for a classical run is used in these experiments. 30 mmol (5.8 g) of ferulic acid, 1.5 mmol (146 mg) of $\text{Cu}(\text{OH})_2$, 1.6 mmol (288 mg) of 1,10-phenanthroline and 50 g PEG-6000 BioUltra are introduced into a two-necked flask. After degassing the reaction mixture by a series of vacuum-argon under stirring, it is heated up to 140 $^\circ\text{C}$ under low

vacuum (*i.e.* 0.5–1 mbar) until quantitative conversion. After collecting the pure 4-vinylguaiaicol from the receiving flask, a new charge of ferulic acid (30 mmol; 5.8 g) is added in the boiling flask and the decarboxylation procedure was repeated, constituting thus a new run of the catalytic mixture (*i.e.* catalyst and solvent). The overall cycle is repeated twice.

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