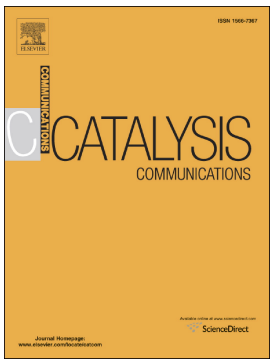

A sustainable access to ynones through laccase/TEMPO-catalyzed metal- and halogen-free aerobic oxidation of propargylic alcohols in aqueous medium

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Short communication

A sustainable access to Ynones through Laccase/TEMPO-catalyzed metal- and halogen-free aerobic oxidation of propargylic alcohols in aqueous medium

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ABSTRACT

Tuning laccase/TEMPO-catalyzed aerobic oxidation of secondary propargylic alcohols in aqueous media was accomplished in order to efficiently synthesize ynones. This study led to the formulation of an effective and sustainable catalytic method for the preparation of mono- and bis-substituted ynones compared with traditional oxidative methods .

1. Introduction

Ynones are challenging and useful building blocks in organic synthesis mainly due to their versatility to be readily converted into other functional groups. They are also useful intermediates in the preparation of pharmacologically relevant compounds examples such as diazepines[1], strychnos Alkaloids[2], and pyridine containing heterocycles[3–6]. Furthermore the ynone subunit is frequently found in bioactive acetylenic natural products[7,8]. Thus, significant attention has been given to the preparation of this class of compounds.

Among available general methods for ynone access, the oxidation of propargylic alcohols retains its prominence as the most common protocol employed. Indeed, oxidation is a pivotal transformation in organic chemistry where one of the actual challenges is the development of general catalytic methods, which minimize the use of hazardous and toxic reagents. Oxidation of propargylic alcohol involves the use of stoichiometric amounts, or even large excess of oxidants such as chromium reagents PCC/PDC[9], activated DMSO[10], MnO_2[11], and hypervalent iodine[12]. In addition, these methods need harsh experimental conditions and the use of toxic organic solvents, causing environmental impact as waste and pollution.

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Alternatively, catalytic aerobic oxidation is one of the most sustainable and environmentally-friendly method driving for a high efficiency and waste reduction process (E factor)[13,14]. Among them, the use of activated nitroxyl radical mediators such TEMPO has proved to be a valuable alternative for this proposal[15–17]. Despite the oxidation of propargylic alcohols using nitroxyl radicals be well known, [18–20] the reported methods mainly involve the use petrochemical solvents. The importance in developing alternative sustainable catalytic methods for the aerobic oxidation of propargylic alcohols, which has been much less studied in the literature, was very recently confirmed by Ma and co-workers, where a $Fe(NO_3)_3 \cdot 9H_2O$/4-OH-TEMPO catalyzed system were developed to prepare a few ynones in gram scale even if still using only organic solvents as reaction medium [21].

To the best of our knowledge there are no attempts to establish a general catalytic chemoenzymatic route for the aerobic oxidation of secondary propargylic alcohols into alkynones in aqueous media reported yet.

The ability of enzymes to effectively catalyze a wide range of oxidation reactions, along with chemo and regioselectivity aspects, upon unnatural substrates were very recently reviewed by Hollmann and co-workers. [22].

The first chemoenzymatic approach based on laccase-TEMPO-system for catalytic aerobic oxidation of alcohols was reported by Macchitella and co-workers in 2001[23]**.** Since then, laccases have been applied as oxidizing agents for, *in situ*, regenerating nitroxyl radicals which are the species that effectively undergo oxidation reactions[24–26].

Hence, due to the permanent demand for improved catalytic and sustainable methods and established chemoenzymatic approaches, we were interested in investigating whether the LMS (Laccase Mediator System) catalytic system could be applied to prepare useful ynone reagents.

2. Experimental

2.1. Materials

Commercially available lyophilized powder Laccase from *Trametes versicolor* (1.2 U mg^{-1}), TEMPO, *n*-butyllithium (1.6 M in *n*-hexane), ethynyl magnesium chloride solution (1.6 M in THF), anhydrous $CeCl_3$ and lithium phenylacetylide solution (0.5 M in THF) were purchased from Sigma-Aldrich company and used without any further purification. The reactions were monitored using the both aluminum TLC plates 20x20 cm on silica gel 60 of Macherey-Nagel® and a SHIMADZU® 2010 Plus GC/FID system coupled with an auto sampler using N_2 as the carrier gas.

2.2. General procedure for the preparation of ynols

2.2.1. Preparation of ynols 1a-h

To a round bottom flask containing a stirred solution of the aromatic aldehyde (10 mmol) in anhydrous THF (20 mL) at -40 °C and under a dry N_2 atmosphere, an ethynyl magnesium chloride solution (10 mmol, 6.25 mL of a 1.6 M solution in THF) was added dropwise. The progress of the reaction was monitored by TLC using *n*-hexane/ethyl acetate (4:1) as eluent. The reaction mixture was quenched with a saturated solution of NH_4Cl (2 mL) and the aqueous phase extracted with EtOAc (2 x 5 mL). The organic layer was washed with brine, dried over magnesium sulphate and the solvents removed in a rotatory evaporator. The crude was purified by silica gel chromatography using n-hexane/ethyl acetate (4:1) as eluent, and then concentrated under vacuum for given yields ranging from 75 to 98%.

2.2.2. Preparations of ynol 1i

A freshly ethynyl lithium solution (10 mmol, 20 mL of a 0.5 M solution in THF) was prepared by bobbling acetylene (welding grade, passed through a sulfuric acid bubbler, followed by a KOH/drierit trap) in a dry 100 ml flask containing 20 mL of THF at -78 °C for 10 minutes. Then *n*-butyllithium (6.25 ml of 1.6 M) in hexane was added dropwise under continuous bubbling of acetylene. The solution was warmed to -40 °C and cannulated to a round bottom flask containing a stirred suspension of hexanal (10 mmol) and anhydrous $CeCl_3$ (1.0 mmol) in THF (10 mL) under a dry N_2 atmosphere. The reaction mixture was slowly warmed to room temperature and the progress of the reaction was monitored by TLC using *n*-hexane/ethyl acetate (3:1) as eluent. The reaction was quenched with a saturated solution of NH_4Cl (2 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 5 mL) washed with brine, dried with magnesium sulphate and the solvents were evaporated under reduced pressure. The crude was purified by silica gel chromatography using *n*-hexane/EtOAc (2:1) as eluent. Yield (65%).

2.2.3 Preparation of ynols 1j-l

To a round bottom flask containing a stirred solution of the aromatic aldehyde (10 mmol) in anhydrous THF (10 mL) at -40 °C and under a dry N_2 atmosphere, a commercially available lithium phenylacetylide solution (10 mmol, 10 mL of a 1.0M solution in THF) was added dropwise. After monitoring the progress of the reaction by eluting a TLC plate with *n*-hexane/ethyl acetate (4:1) it was quenched with a saturated solution of NH_4Cl (2 mL). The aqueous phase was extracted with ethyl acetate (2 x 5 mL), washed with brine, dried over magnesium sulphate. After removing the solvents under reduced pressure, the crude was purified by silica gel chromatography using *n*-hexane/ethyl acetate (4:1) as eluent, and then concentrated under vacuum for given yields ranging from 85 to 99%.

2.3. General procedure for the chemoenzymatic preparation of ynones

2.3.1. Oxidations to obtain ynones 2a-b, 2d, 2j and 2l

To a magnetically stirred solution containing 1-phenylprop-2-yn-1-ol (**1a)** (2 mmol, 264 mg, [250 mM]) and TEMPO (0.1 mmol, 15.6 mg [12.5 mM], 5 mol%) in aqueous HCl (0.1 M, pH 6.0, 8 mL), laccase from *Trametes versicolor* (8 mg, 1.2 U mg^{-1}) was then added. The solution

was magnetically stirred at 30 °C under atmospheric air in an opened flask for 1.5 hours. The total conversion of **1a** was monitored by GC/FID. Then, the crude mixture was transferred to a funnel and extracted with EtOAc (3 × 4 mL). The organic phase was dried over $MgSO_4$ and the solvents removed under reduced pressure. The crude was purified by filtration in silica gel using a minimal amount of ethyl acetate furnishing 241.8 mg of the pure 1-phenylprop-2-yn-1-one (**2a**) in 93% yield. The reaction time, conversion, and the values of TON/TOF are given in the table 3.

2.3.2. Oxidations to obtain ynones 2c, 2e-I and 2k

To a magnetically stirred solution containing 1-(furan-2-yl) prop-2-yn-1-ol (**1h**) (1 mmol, 122 mg, [250 mM]), TEMPO (0.1 mmol, 7.8 mg, [12.5 mM]) in aqueous HCl (0.1 M, pH 6.0, 4 mL), was sequentially added Ethyl Acetate (0.2 mL, 5% v/v) and laccase from *Trametes versicolor* (4 mg, 1.2 U mg^{-1}). The progress of the reaction was monitored by GC/FID and the crude mixture was transferred to a funnel and extracted with EtOAc (3 × 2 mL). The organic phase was dried over $MgSO_4$ and the solvents removed using a rotary evaporator under vacuum. The crude was purified by filtration in silica gel using a minimal amount of ethyl acetate furnishing 110 mg of the pure 1-(furan-2-yl) prop-2-yn-1-one (**2h**) in 92% yield. The reaction time, conversion, and the values of TON/TOF are given in the table 3.

2.4. Structure verification

Verification of the ynones structures was achieved by means of recording ^1H NMR (300 MHz, 400MHz and 500MHz), and ^{13}C (75 MHz, 100 MHz and 125 MHz) spectra, using deuterated chloroform ($CDCl_3$) as solvent and Me_4Si as internal standard. The chemical shifts are expressed in ppm and coupling constants (*J*) are in Hz.

3. Results and discussion

To synthesize some of the propargylic alcohols, which were used as substrates in the chemoenzymatic assays and are not commercially available, we adopted two reported procedures[27,28].

Initial investigations for the laccase/TEMPO-catalyzed oxidations were carried out using compound **1a** (1-phenylprop-2-yn-1-ol) as model substrate in the presence of fixed amounts of *Trametes versicolor* laccase and TEMPO.

According to literature, [23] optimal operating conditions for the use of LMS consist of buffered solutions (0.1 mol/L citrate) with pH values ranging from 4 to 5. Furthermore, this could relate with the possibility of the propargylic moiety being converted into other functional groups under acidic pH (e.g. hydration to keto-enol form or Meyer−Schuster rearrangement to enones[29]).

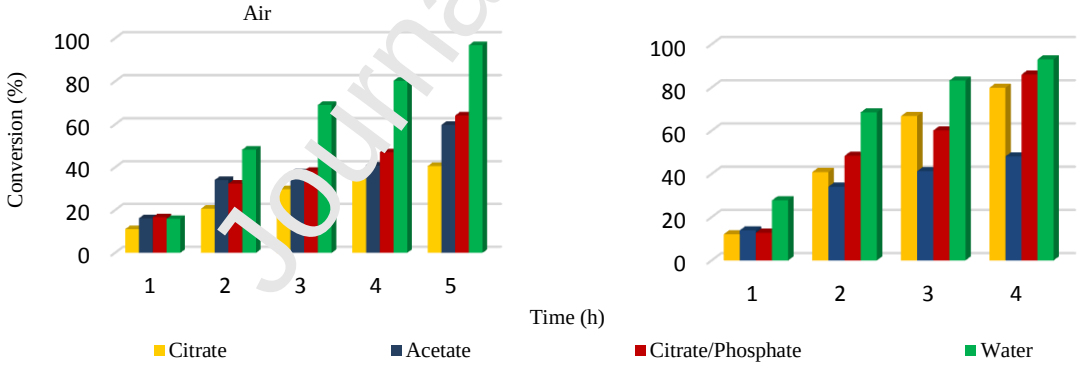


Fig 1. Conversions of 1a on the Laccase/TEMPO-catalyzed oxidation in aqueous media at pH 5. Conversion determined by GC-FID.

As a result, the use of **1a** as a model offers utility to monitoring the reaction and stablish the initial screening conditions for the conversion of **1a** into ynone **2a.** Reactions were carried out either in buffered solutions at pH 5 (citrate, acetate and citrate/phosphate), at room temperature (28 °C); or to further simplify the reaction condition, in aqueous HCl (pH 5) solutions.

Initially, the oxidation of alcohol **1a** [1 mmol, 250 mM] was carried out in an open flask, in a reaction system composed by TEMPO [25 mM, 10 mol%] and Laccase [0.1 U mg^{-1}]. These reactions were carried out comparing the use of two different sources of oxygen: under atmospheric air pressure and bubbling O_2 into the solutions (Fig 1).

Surprisingly, as showed in fig.1, the most effective reaction conditions, leading to the higher conversion of **1a** into **2a**, were those composed by the buffered-free aqueous hydrochloric solution at pH 5. This result was independent on the oxygen source (atmospheric or bubbled).

In these reactions, while the conversion of **1a** (93%) under atmospheric air, required 5 h to be completed, 4 h were necessary for the total conversion of **1a,** under direct O_2 bubbling. In both experiments, it was possible to isolate **2a** in very good yields (93%). It is worth to point out that in the literature the same oxidation under aerobic conditions furnished the ynone **2a** in very low and not isolated yield (~38%)[30].

In addition, as depicted in Fig. 1, Bubbling O_2 directly over using atmospheric air makes a significant difference only for the reactions performed in buffered solutions. This suggests that the ability of oxygen to be transported in buffers is crucial for the progress of the reaction and may be the rate determining step for the reoxidation of TEMPO.

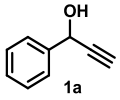
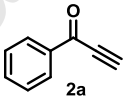
Another feature is associated to the robustness of the laccase from *Trametes versicolor* to the acidic conditions, being not necessary to employ a buffer to maintain the enzymatic performance and stability. Aiming to explore these observations, a wider pH spectrum for the reactions conducted in buffered-free solutions was evaluated. Thus, after ranging the pH from 3 to 9 we found the pH=6 as the optimal value for the oxidation of **1a.**

Under these conditions, was possible to observe, after approximately 6h, a total conversion of **1a** into **2a** (Fig 2).

Bubbled oxygen

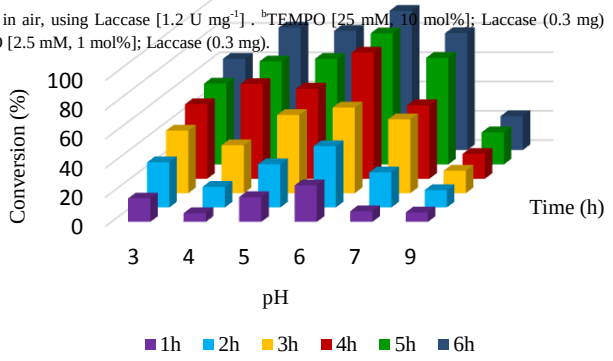
Fig 2. Effect of the aqueous HCl pH on the Laccase/TEMPO-catalyzed oxidation.

The optimization process was also directed to the determine enzyme and TEMPO amounts. Thus, based on initial parameters (Table 1, Entry 1), when TEMPO concentration was reduced from 10 to 5% in the presence of higher amounts of laccase (1.2 U mg^{-1}), the ynone **2a** was obtained with the same yield but only a quarter of the reaction time was needed (Table 1, Entry 2).

Entry	Substrate	Ynone	Yield (%)[a]	Time (h)
1			93	6[b]
2			93	1.5[c]
3			48	24[d]
4			32	48[e]

[a]Isolated yield after reacting 1mmol of **1a** [250 mM] in 4 ml of aqueous HCl (pH = 6.0) at 30°C in air, using Laccase [1.2 U mg^{-1}] . [b]TEMPO [25 mM, 10 mol%]; Laccase (0.3 mg) [c]TEMPO [12.5 mM, 5%]; Laccase, (4 mg); [d]TEMPO [7.5 mM, 3 mol%]; Laccase (0.3 mg); [e]TEMPO [2.5 mM, 1 mol%]; Laccase (0.3 mg).

Table 1. Laccase/TEMPO concentration effect for the oxidation of **1a**



Nonetheless, when laccase amount was diminished to ca. 1 U mg^{-1}, and TEMPO was ranged from 3-5 mol% the reaction turned out to be very slow leading to the very unsatisfactory results (Table 1, Entry 3 and 4). Summarizing, the usage of 1.2 U mg^{-1} of laccase from *T. versicolor* and 5 mol% of TEMPO was found to be a best reaction condition for the conversion of **1a** into **2a**.

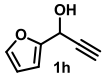
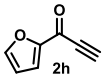
Comparing the improved conditions to chemical, classical oxidation methodologies described in the literature, the advantages in favor of our system are quite evident. For example, the oxidation of **1a** using MnO_2 (15 equiv.) in DCM, as described by Yin and co-workers[31] the compound **2a** was obtained in lower yield (80%) in both cases.

Without exception, this protocol presents excellent results and, when compared to many other classical reported procedures, proves to be superior if considering product yields and environmental aspects. As examples, we can mention the preparation of **2b** in 97% yield by using the methodology described in the present work (Table3, Entry 2). The latter was achieved within 4h at 30°C in contrast with using 7 equiv. of MnO_2 that renders **2b** in only 44% yield[32].

Albeit propargyl/benzylic substrates furnish the correspond-ding ynones in reasonable to excellent yields, when a furan-containing derivative as well as an alkyl-substrate were used, under similar reaction conditions, the desired products were obtained in lower

average yields. Yields were largely improved by using ethyl acetate as co-solvent, assuming that it should enhance the solubility of the compound, diminishing the residence time of the less polar ynone in aqueous system.

Table 2. Effect of the co-solvent EtOAc in the *T. versicolor* laccase/TEMPO catalyzed oxidation of 1h and 1i.

Entry	Substrate	Ynone	Yield (%)[a]	Time (h)
1	 1h	 2h	32	8[b]
2			92	6[c]
3	 1i	 2i	45	5[b]
4			78	8[c]

[a]Isolated yield. Typical conditions: 1mmol of **1** [250 mM] in 4 ml of aqueous HCl (pH = 6.0) at 30°C in air. [b]TEMPO [12.5 mM, 5 mol%]; Laccase [4 mg, 1.2 U mg^{-1}]; [c]TEMPO [12.5 mM, 5%], Laccase [4mg, 1.2 U mg^{-1}], EtOAc [0.2 mL (5% v/v)]

In case of alcohol **1h**, a significant increment in yield (32 to 92%, in 6 hours) was achieved by using only 5% v/v of EtOAc as auxiliary co-solvent (Table 2, entries 1 and 2). In the case of **2i,** the yield was increased from 45% (5h) to 78% after 8 h of reaction (Table 2, entries 3 and 4).

The results obtained for the synthesis of **2h** and **2i** using the conditions depicted in Table 2, represent a substantial upgrading from the synthetic point of view, since some of these oxidations are hard to perform requiring environmentally deleterious heavy metal-based reagents and harsh reaction conditions.

Thus, after this virtually perfect improvement, we decided to subjected other secondary propargylic alcohols to the oxidation in the presence or absence of EtOAc (5% v/v) in order to find the best condition for each substrate and in order to demonstrate its robustness, scopes and limitations (Table 3).

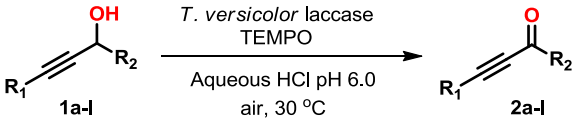
As can be seen in Table 3, the procedure is quite general, admitting propargyl benzylic alcohols as substrates, as well as alkylic ones, and leading to the corresponding ynones differing basically in reaction time. Comparing substrates such as **1c** and **1j** (Table 3, entries 3 and 10), under our conditions, we succeeded to obtain ynones **2c** and **2j** in 91% and 94% of yield, respectively, in contrast to 41% and 24% using a vanadate-based aerobic oxidation[33].

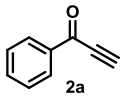
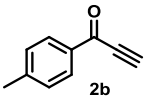
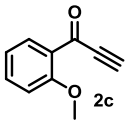
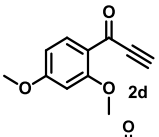
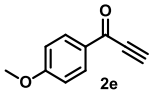
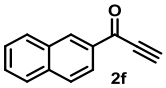
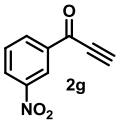
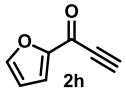
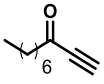
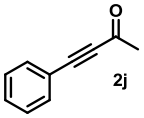
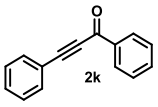
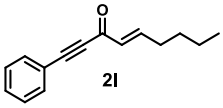
The outcome and efficiency of the current approach, which gave ynones in good yields, can be attributed to the rate of the propargylic carbinol α-C-H deprotonation onto the alkynyl-oxoammonium adduct formed *in situ*. This observation corroborates for the faster reaction of the alkynyl substrates when compared with alkylic, allylic or benzylic analogues.

The anionic mechanism that takes into account the abstraction of the α-C H of the propargylic intermediate is in agreement with a study reported by Gentili *et al*[34], who describes that the increase in reactivity is due to the easy hydrogen abstraction than steric effects.

In addition, the success in performing the reactions under the improved conditions (aqueous HCl at pH = 6.0) is probably due to the both a smoother salting-out effect regarded for the alkynyl substrate and enhanced TEMPO stability in the more neutral conditions, which probably prevent the loss of its oxidizing ability in longer reaction times. This explains the observed shorter reaction times when compared to literature. For example, 1-phenylpropanol is oxidized to acetophenone after seven days using the laccase/TEMPO system[23,35] while in the present work the chemoenzymatic oxidation of **1a** takes only 1.5 hours to be completed.

Table 3. Chemoenzymatic oxidation of ynols with Laccase/TEMPO system[a]



Entry	Ynone	Yield (%)[b]	Time (h)	TON[d]	TOF[e] (h^{-1})	E-factor (kg/kg^{-1})
1	 2a	93	1.5	15346	10231	0.39
2	 2b	97	4	16006	4001.7	0.31
3	 2c	91	7[c]	150[illegible]	2145.2	0.35
4	 2d	96	7	15841	2263.1	0.09
5	 2e	89	6[c]	14686	2447.7	0.39
6	 2f	88	11[c]	14521	1320.1	0.38
7	 2g	69	7[c]	11386	1626.6	0.77
8	 2h	92	6[c]	15181	2530.3	0.53
9	 2i	78	8[c]	12871	1608.9	1.04
10	 2j	94	8	15511	1938.9	0.35
11	 2k	87	7[c]	14356	2050.9	0.36
12	 2l	100	8	16501	2062.7	0.18

[a]Conditions: air; r.t.; subst. 2 mmol [250 mM], TEMPO (0.1 mmol, 15.6 mg [12.5 mM], 5 mol%) in aqueous HCl (0.1 M, pH 6.0, 8 mL), Laccase from *Trametes versicolor* (8 mg, [1.2 U mg^{-1}]). [b]Isolated Yield. [c] 1mmol of 1 [250 mM], TEMPO (0.05 mmol, 7.8 mg [12.5 mM], 5 mol%) in aqueous HCl (0.1 M, pH 6.0, 4 mL), Laccase from Trametes versicolor (4 mg, [1.2 U mg^{-1}]), EtOAc (0.2 mL, 5% v/v). [d]Turnover number = number of moles of product per mol of catalyst precursor; [e]TOF = TON per hour.

Thus, compared to the literature, the current method demonstrates some advantages. For example, it does not use stoichiometric amounts of oxidant or toxic solvents, the reactions show very high atom efficiency, and the use of aqueous HCl as a solvent. Additionally, no tedious preparation/recovery of complex catalyst is needed.

It is also important to compare the present approach, which furnished ynones with E factor from 0.09 to 1.04 $Kg.Kg^{-1}$, with other aerobic oxidations that also use activated nitroxyl radical mediators. For example, whereas in the present protocol the oxidation of **1a** furnishes E = 0.39 $Kg.Kg^{-1}$ (Table 3, Entry 1) an E value of 43.58 $Kg.Kg^{-1}$ is obtained by using $Fe(NO_3)_3$•$9H_2O$/4-OH-TEMPO system[21]. Other relevant comparison is the oxidation of **1k** E = 0.36 (Table 3, Entry 11) with CuI/TEMPO system, which furnishes an E value of 20.29 $Kg.Kg^{-1}$ [18].

Normally, higher E values are expected for fine chemicals when equimolar oxidants are employed [13]. E.g. when **1a** is oxidized with 15 eq. of MnO_2 in 10 mL of DCM [31] the E value is 76.61$Kg.Kg^{-1}$.

Besides being operationally simple, the developed protocol is also environmentally benign, robust and synthetically useful since it did not require any special training as could be assumed by a chemist when confronted with the usage of an enzyme as a chemical reagent.

The smoothness of the reaction conditions, the generality, selectivity and high yields achieved, certainly makes the procedure a very promissory tool for the synthetic arsenal in the construction of complex molecules. In this respect, we are currently applying the developed chemoenzymatic protocol to the oxidation of more structurally complex alkynols with biochemical relevance.

4. Conclusion

The conditions described here can be widely used for the efficient synthesis of ynones in more environment-friendly reaction condition. It is important to remark that neither alkyl or furyl derivatives containing alkynols were reported to successfully undergo chemoenzymatic oxidation yet. This clearly indicates the potentiality of the current approach in the preparation of more complex ynones containing sensitive functional groups particularly in industrial applications where sustainability issues are crucial.

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Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- High yield of the products.
- O_2 as source of oxidant
- Efficient approach for the synthesis of ynones.
- The current strategy is based on a chemoenzymatic approach.