Catalysis

One-Pot, Clean Synthesis of Vanillic Acid from Ferulic Acid

Riccardo Delisi,[a] Rosaria Ciriminna,[a] Francesco Parrino,[b] Leonardo Palmisano,[b] Yi-Jun Xu,[c] and Mario Pagliaro*[a]

Ferulic acid dissolved in water is selectively oxidized to vanillic acid in high yield (≈60%) under remarkably mild and green conditions, namely at room temperature with air as primary oxidant, over a catalytic amount of nanostructured Bi_2WO_6. The process is general and opens the route to the selective oxidation of natural substances into derivatives of significant applicative relevance.

The synthesis of valued chemicals from biomass raw materials,[1] likewise to the synthesis of solar hydrogen from water,[2] is one of the main targets of today's chemistry research efforts. One such valued product obtained via photochemical conversion of a bioderived substrate could be vanillin, namely the most important flavor compound in the world,[3] and its oxidised form vanillic acid (VA) (4-hydroxy-3-methoxybenzoic acid).

Less than 2% of the vanillin global output is of natural origin, with most of it being obtained via chemical oxidation of oil-derived isoeugenol carried out in organic solvent.[3] The price of biotechnology vanillin, obtained via the bioconversion of trans-ferulic acid,[4] is high (about $1,000 per kilogram) and prevents large-scale commercialization of the fermentation technology.

Trans-ferulic acid (3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid) is an ubiquitous plant antioxidant present in lignocelluloses, such as pectin and lignin, with a wide variety of biological activities (antioxidant, antiinflammatory, antimicrobial, antiallergic, hepatoprotective, anticarcinogenic, antithrombotic, etc).[5]

One chemical approach alternative to biotechnology makes use of sunlight-driven oxidation of ferulic acid in the presence of titania carried out in water with oxygen as the only oxidant, under ultraviolet radiation.[6] The yield is distinctly low (4.60%), but the highly pure vanillin crystals obtained via membrane separation in a pervaporation photocatalytic reactor (vanillin is recovered as it is formed to prevent its degradation) makes the method potentially relevant from a commercial viewpoint.[7]

Remarkably, the catalytic oxidation of trans-ferulic acid to vanillin with 95% reaction yield in only 1 h over porous coordination polymer HKUST-1 using H_2O_2 as primary oxidant in EtOH/acetonitrile under reflux was recently reported.[8]

A similarly clean, high-yield route to vanillin, or to vanillic acid, starting from ferulic acid would be highly desirable. Vanillic acid, for example, is a valued fragrance and flavoring agent with several further beneficial effects due to its chemopreventive, hepatoprotective and cardioprotective activity,[9] and a global market in various application areas exceeding $200 million.[10]

Now, we report the high yield synthesis of vanillic acid from ferulic acid under remarkably mild and clean conditions. The reaction is carried out in water at room temperature in the presence of a suspension of catalytic amount of flower-like Bi_2WO_6 catalyst in the absence of light (Scheme 1).
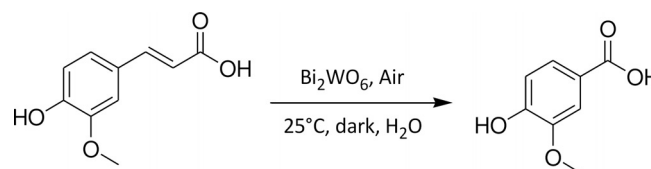
Scheme 1. Catalytic oxidation of ferulic acid to vanillic acid over Bi_2WO_6.

Nanostructured Bi_2WO_6 was synthesized from $Bi(NO_3)_3 \cdot 5H_2O$ and $Na_2WO_4 \cdot 2H_2O$ via a well known hydrothermal route.[11] The crystalline nature of the catalyst was confirmed by powder X-ray diffraction. Figure 1 shows a typical scanning electron microscopy (SEM) image of the Bi_2WO_6 flower-like catalyst microparticles formed after hydrothermal treatment for 8 h, with their diameter ranging from 3 to 4 μm. We remind here that the formation of good quality flower-like structure of nanostructured Bi_2WO_6 needs a careful control of hydrothermal reaction time. The catalyst, furthermore, is mesoporous, with average pore size of 40 nm, surface area of 30 m^2 g^{-1} and 0.16 cm^3 g^{-1} pore volume.

Four different amounts of Bi_2WO_6 (0.5 g L^{-1}, 1.5 g L^{-1}, 2.5 g L^{-1}, 4 g L^{-1}) were added to 6 mL of an aqueous solution of ferulic acid (0.6 mM) kept in a tightly closed reaction tube. The resulting mixture was stirred in the dark at room temperature, and the reaction monitored by HPLC. The reaction

[a] Dr. R. Delisi, Dr. R. Ciriminna, Dr. M. Pagliaro
     Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via U. La Malfa 153, 90146 Palermo, Italy
[b] Dr. F. Parrino, Prof. L. Palmisano
     "Schiavello-Grillone" Photocatalysis Group, DEIM, Università degli Studi di Palermo, Palermo, Italy
[c] Prof. Y.-J. Xu
     State Key Laboratory of Photocatalysis on Energy and Environment, College of Chemistry and Chemical Engineering, Fuzhou University, Fuzhou 350002, P.R. China

Figure 1. SEM picture of flower-like nanostructured Bi_2WO_6.

which the concentration of vanillic acid grows at higher rate. We emphasize here that oxygen for the reaction originates from static air (no air bubbling conditions) from the head space of the reaction system, which explains the long induction time of the reaction.

The reaction is extremely selective. The HPLC analysis, indeed, shows only formation of vanillic acid. The sum of remaining ferulic acid and the newly formed vanillic acid is almost the 60% of the starting material. TOC (total organic carbon) analysis, performed before and after reaction, highlights that the difference between the two TOC values is 26.94 ppm, which almost corresponds to the loss of CO_2 from the FA side chain.

This outcome was unequivocally confirmed by the fact that a daily analysis, within 72 h, of the reaction head-space performed via GC shows a progressive and proportional increase of CO_2 concentration along with reaction progress.

Bismuth tungstate is a *n*-type semiconductor with 2.7 eV bandgap, made by a mixed oxide with an orthorhombic structure formed by alternating $Bi_2O_2^{2+}$ and WO_4^{2-} perovskite layers (Figure 3),[12] which is rapidly emerging as a promising visible-

proceeded each time affording high yields of vanillic acid, with best results achieved at 1.5 g L^{-1} catalyst concentration (Table 1).

In slightly less than 90 hours no residual FA could be detected in the reacting solution. The kinetics of vanillic acid formation shows (Figure 2) an induction time of about 15 h, after
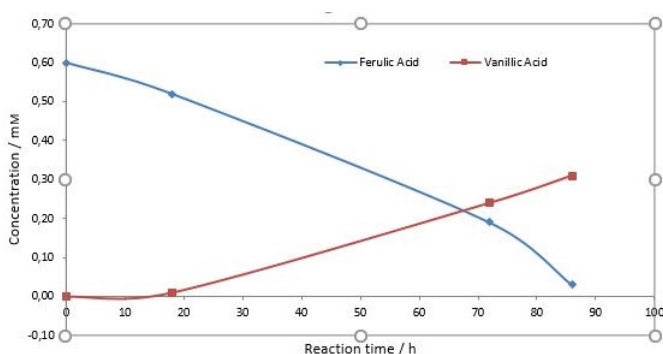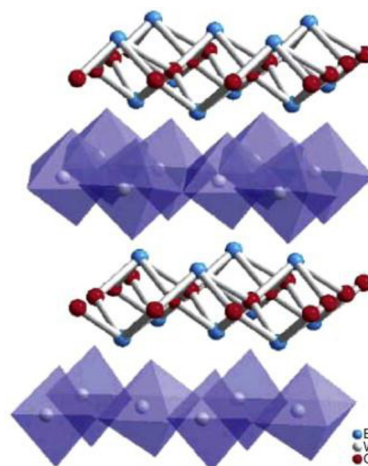

Figure 2. Evolution of VA and FA concentration in the presence of Bi_2WO_6 in the dark.

Figure 3. The alternating WO_4^{2-} and $Bi_2O_2^{2+}$ layers in the structure of Bi_2WO_6.

Table 1. Yield in vanillic acid from ferulic acid conversion over Bi_2WO_6[a]

Reaction time (h)	VA (mM)	VA Yield (%)	FA (mM)	FA left in solution (%)
0	0	0	0.60	100
18	0.01	2.3	0.52	86
72	0.24	40	0.19	31
86	0.31	53	0.03	5.7

[a]Reaction conditions: FA (0.6 mM), Bi_2WO_6 (1.5 g L^{-1}), room temperature, tightly closed tube, under stirring and in the dark.

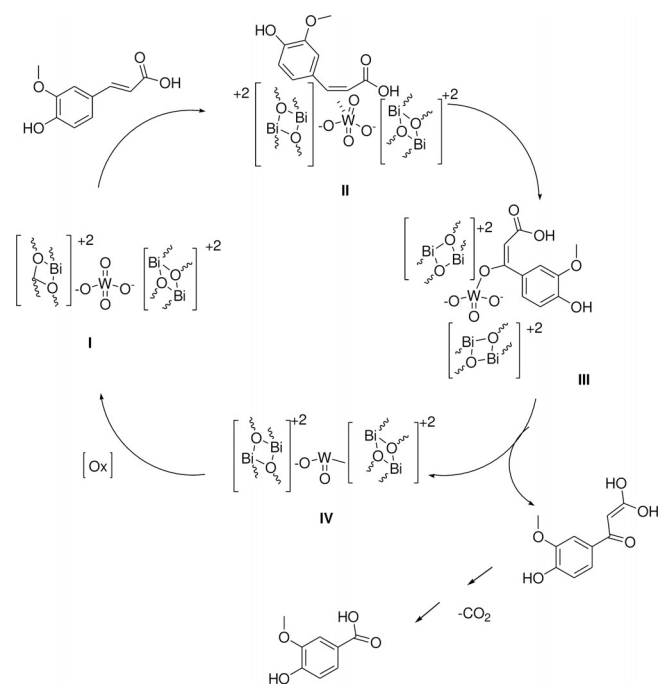light photocatalyst capable to mediate the synthesis of chemicals and fuels.[13]

In the early 1970s, researchers in Italy discovered its remarkable selectivity in the oxidation and ammoxidation of olefins, mostly 1-butene and propylene.[14] Xu and co-workers have shown that an aqueous suspension of flower-like Bi_2WO_6 under visible-light irradiation and in the presence of O_2 selectively oxidizes glycerol to dihydroxyacetone. Notably, it was shown that hydroxyl (•OH) radicals are not involved whereas H_2O_2 molecules are rather formed, with the alcohol substrate reacting with the positive holes at the material's surface leading to exquisite high selectivity in a number of photocatalytic aerobic oxidation reactions.[11]

Remarkably, irradiation with visible light (Solar Box, 1500 W, no UV filter) of the ferulic acid solution results in rapid (30 min) formation of vanillin up to 6% selectivity. However, after about

1 hour, vanillin concentration starts a drastic decrease and after 2 h only vanillin traces are left in solution, pointing to extensive mineralization of the valued aldehyde, which is in agreement with the known photocatalytic activity of flower-like Bi_2WO_6 in the degradation of phenols under visible light.[15]

When light is excluded, however, the adsorbed ferulic acid molecules react with the catalytic centres of Bi_2WO_6, namely the (W=O) active centres whose concentration, among all possible bismuth tungstates, reaches its maximum in Bi_2WO_6 phase. Indeed, the presence of two types of surface sites in Bi_2WO_6, inactive W—O—W and highly active W=O, was established via X-ray diffraction as early as of 1977, when the selective oxidation activity of Bi_2WO_6 towards small olefins was first connected with the presence of corner sharing W—O octahedra in the bulk of the solid giving rise to tetragonal pyramidal W—O sites at the surface.[16]

In the case of ferulic acid in the dark, photocatalysis is excluded. We speculate that the oxidation mechanism is analogous (Scheme 2) to that proposed for the oxidation of olefins

The catalytic nature of the reaction is confirmed by the unmodified crystalline structures of Bi_2WO_6 before and after reaction, as shown by the XRD patterns in Figure 4. Like in photo-
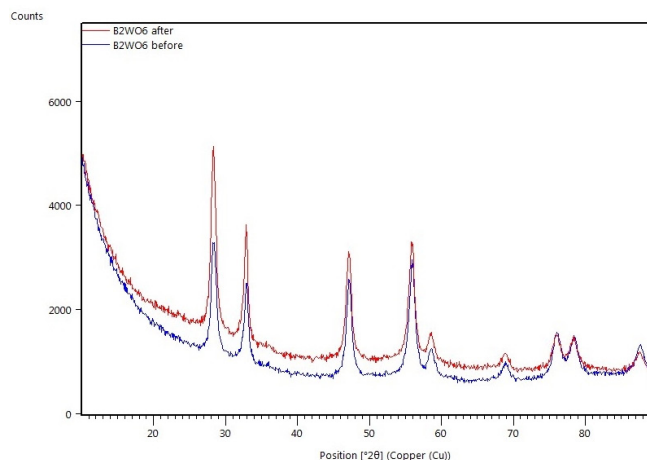

Figure 4. XRD patterns of Bi_2WO_6 before (blu) and after (red) the reaction.

catalytic reactions,[8] the catalyst was truly recyclable, with the same catalyst sample filtered and re-used in all catalytic tests (>10) under the optimal reaction conditions (1.5 g L^{-1}), without any noticeable reduction in activity.

Likewise to any heterogeneously catalysed process, the absorption-desorption equilibrium of the substrate molecules on the catalyst surface plays a critical role. Indeed, results in Figure 5 (and in Table 2 and Table 3) show that when the reaction

Scheme 2. Proposed mechanism for the oxidation of ferulic acid mediated by Bi_2WO_6.

by bismuth molybdate,[17] with double bond adsorption on a tungsten site (II), followed by O insertion into the coordinated intermediate at the tungsten site, and abstraction of a vinyl H (III). Finally the intermediate III collapses releasing the reduced catalyst (IV) and the partially oxidized 3-(4-hydroxy-3-methoxyphenyl)-1,1-dihydroxy-1-propen-3-one which, after spontaneous loss of CO_2, is oxidized to vanillic acid. Rapid re-oxidation of the W sites leads to bismuth tungstate ready for another catalytic cycle.

Table 2. Yield in vanillic acid from ferulic acid conversion over Bi_2WO_6 at 4°C

Reaction time (h)	VA (mM)	VA Yield (%)	FA (mM)	FA left in solution (%)
0	0	0	0.6	100
24	0	0	0.15	24
48	0	0	0.14	23
72	0.00084	0.14	0.058	9.5
120	0.0019	0.32	0.09	15

Table 3. Yield in vanillic acid from ferulic acid conversion over Bi_2WO_6 at 80°C

Reaction time (h)	VA (mM)	VA Yield (%)	FA (mM)	FA left in solution (%)
0	0	0	0.6	100
24	0	0	0.58	96
48	0	0	0.58	96
72	0.0019	0.32	0.58	96
120	0.013	2.2	0.40	66.6

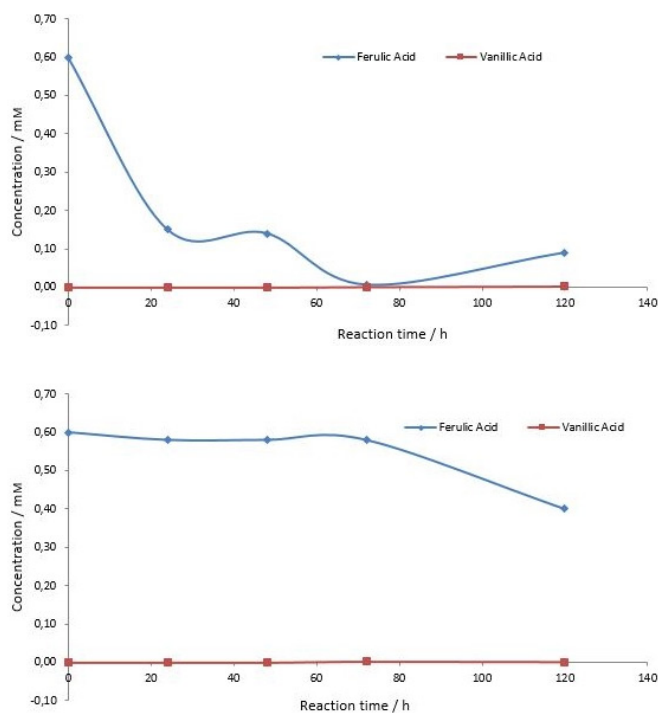[a]Reaction conditions: FA (0.6 mM), Bi_2WO_6 (1.5 g L^{-1}), tightly closed tube, under stirring and in the dark.

Figure 5. FA and VA concentration (mM) in the presence of Bi_2WO_6 at 4 °C (top) and at 80 °C (bottom).

We did not test other catalyst morphologies such as nanospheres or nanoplates, though morphology, which greatly affects the material's textural properties, and surface oxygen defects, is expected to play a significant role as it happens with photocatalytic reactions mediated by Bi_2WO_6.[18]

In conclusion, we have discovered that *trans*-ferulic acid dissolved in water is selectively oxidized to vanillic acid in high yield ($\approx 60\%$) under remarkably mild and green conditions, namely at room temperature with air as primary oxidant, over a catalytic amount of flower-like, nanostructured Bi_2WO_6. The process is general and may be applied to a wide variety of phenols, as will be shown in further reports.

Acknowledgements

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is carried out at 4 °C no significant formation of vanillic acid takes place even after 72 h, but rather the substrate concentration decreases up to 0.058 mM due to precipitation of ferulic acid dissolved at room temperature.

Similarly, the reaction carried out at 80 °C shows no significant formation of vanillic acid and no decrease of ferulic acid concentration even after 72 h, likely due to high temperature preventing stable adsorption of ferulic acid molecules at the outer surface of Bi_2WO_6.

Adding arguments supporting this insight, it is relevant to notice that when the above reaction mixtures kept at 4 °C and 80 °C after 72 h are, respectively, warmed and cooled to room temperature, the substrate in solution is then smoothly converted into vanillic acid.

It is also remarkable that carrying out the reaction under oxygen, rather than under air, results in reaction inhibition, probably due to competitive adsorption of oxygen on W active sites.

To check possible leaching of active Bi_2WO_6 reaction centers in solution, the solid catalyst was removed after 48 h (50 % of total conversion) by filtration through a 0.20 μm nylon filter. The filtrate was monitored for activity within subsequent 72 h showing no further reaction, indicating that no catalytically active species are present in the filtrate.