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An outstanding catalyst for the oxygen-mediated oxidation of arylcarbinols, arylmethylene and arylacetylene compounds[†]

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A convenient and sustainable protocol for the aerobic oxidation of benzyl alcohols to carbonyl compounds, based on the use of 1,2,4-triazole-type ligands and nickel(II) bromide, is described. This combination leads to the formation of an exceedingly active, enzyme-like system that allows for other oxidative processes, such as benzylic C–H oxidation and oxygen-mediated cleavage of C–C triple bond, a pioneering procedure for transformation of alkynes into carboxylic acids.

Molecular oxygen is an ideal oxidant (readily available, environmentally benign, water as a byproduct, etc.) for most organic and inorganic transformations. Therefore, in recent years, a number of metal catalysts for different oxygen-mediated oxidative processes have been developed. Taking alcohol oxidation to carbonyl compounds as an illustrative example, the yields and selectivities of chain radical non-catalyzed autoxidation of alcohols and saturated hydrocarbons are often low,¹ and therefore several metal catalysts (Ir, Cu, Pd, Zn, Ni, Ru, Rh, Fe, Au, Mn, Co, V, and Pt) have been developed in this context.²⁻⁷ Catalyst loadings are generally in the range of 0.5-10 mol% of [M], although significantly lower amounts (0.1-0.3 mol%) have been reported in some cases.^{3,5} Regarding reaction media, toluene and other flammable organic solvents (dichloroethane, acetonitrile, THF, etc.) have been mainly employed, with just a few examples of oxidations carried out in more sustainable (e.g. aqueous) media.^{3b,7}

Removal of metal traces is a serious concern in the production of fine chemicals. Heterogeneous catalysts or biphasic systems have been employed so far to achieve an effective catalyst separation, since relatively high amounts of the catalysts are required,⁸ and removing residual metals by relatively expensive metal

scavengers is also a common protocol in the food and pharmaceutical industries.⁹ A completely different strategy is to simply decrease the catalyst loading to a point below regulatory requirements, but this is particularly difficult for many transition metal catalysts, with very low levels (<10 ppm) permitted in drug products.⁹

In an attempt to avoid the use of precious metals, in favour of lighter, more convenient elements, and to decrease substantially the amount of the catalyst so that the above regulatory requirements were fulfilled, we proposed and found that a suitable combination of a nickel(II) salt and a 1,2,4-triazoletype ligand could significantly improve the activity profile of the nickel catalyst for the aerobic oxidation of alcohols.

Although 1,2,4-triazole and simple *N*-alkyl-1,2,4-triazole derivatives are relatively common ligands for nickel,¹⁰ their joint exploitation as catalysts for aerobic oxidative processes is limited to azirination of alkenes with azides.¹¹ In this communication we wish to demonstrate that the exploration of the catalytic activity of a combination of 1,2,4-triazole ligands and Ni(π) salts (NiBr₂) led us to find an outstanding catalytic system, not only for the aerobic oxidation of alcohols but also for the oxidative cleavage of alkynes, an unprecedented transformation mediated by molecular oxygen.

In order to analyze the influence of the coordination degree and chelating effects in the reaction outcome, two triazole ligands, simple 1,2,4-triazole 1 and pincer-type bis-triazolyl ligand 2 were assayed. The synthesis of the latter was carried out by treatment of the readily available methyl 3,5-bis(bromomethyl)benzoate¹² with 1, as displayed in Scheme 1.

On the basis of the encouraging results from the initial assays for the nickel-catalyzed oxidation of 1-phenylethanol,¹³ we decided to use O₂, NiBr₂, **1** or **2**, PEG-400, 120 °C and gradually decrease the catalytic amount to 10^{-5} mol% of Ni and **1/2**. Blank experiments also showed the need for both nickel and triazole ligands, since nickel bromide alone provided low yields (20%) at 0.01 mol%, and no product was detected with lower amounts of the nickel halide.¹³

The optimized reaction conditions were accordingly applied to a number of primary and secondary benzyl alcohols, providing good to excellent results regardless of the nature of the starting carbinol.

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[†] Electronic supplementary information (ESI) available: Full experimental details, including a summary of the assays performed for the oxidation of 1-phenylethanol, the preparation of the bis-triazolyl ligand 2, the conversion rate of phenylacetylene *vs.* time kinetic plot, a summary of poisoning experiments, spectroscopic data and copies of NMR spectra. See DOI: 10.1039/c5cc00750j



Scheme 1 Synthesis of bis(triazolylmethyl) derivative 2.

As shown in Table 1, oxidation of primary alcohols provided the corresponding carboxylic acids, with the exception of 3,4,5trimethoxybenzyl alcohol, which rendered the aldehyde. However, aside from cyclohexanol, other aliphatic, allylic and propargylic alcohols such as octan-2-ol, (–)-menthol, 2-cyclohex-2-en-1-ol and hex-2-yn-1-ol did not undergo the desired oxidation and only dehydration by-products were detected along with the unreacted material.

Subsequently, we assayed the same conditions in the benzylic C-H bond oxidation of a series of methylene compounds, and carbonyl compounds were obtained in good yields (Table 2). However, the fact that three tetrahydroisoquinoline derivatives (NH-, N-methyl- and N-Boc-1,2,3,4-tetrahydroisoquinoline) failed to provide any oxidation product suggests that the presence of benzylamine or benzylcarbamate moieties is not compatible with our oxidation procedure. Nevertheless, it should be pointed out that pyridine derivatives did not interfere with the outcome of the reaction (e.g. oxidation of phenyl(pyridin-4-yl)methanol to phenyl(pyridin-4-yl)methanone, as displayed in Table 2). It is somewhat surprising that a competing ligand for nickel and therefore potentially catalyst deactivating molecule such as pyridine has little effect in the reaction outcome. In fact, when we performed the oxidation of 1-phenylethanol to acetophenone in the presence of 5 \times 10⁻³ mol% of pyridine a similar yield (96%) was obtained.

Interestingly, high-yielding C–C oxidative cleavage was observed from some benzyl alcohols such as mandelic acid and 1,2-diarylethane derivatives (benzoin, hydrobenzoin, and diphenylethanol), as displayed in Table 3. Oxidative cleavage to benzoic acid was also observed from deoxybenzoin and phenylacetic acid (Table 3). In both carbinol and methylene oxidation reactions a slightly better catalytic profile was found for the NiBr₂–2 system, as better yields were observed in all cases and 1,2-diphenylethanol did not react with ligand **1**.

We became interested in such uncommon cleavages undergone by some alcohols and the latter methylene compounds (Table 3), and especially by 3-phenylprop-2-yn-1-ol (Table 4), since it, unlike the other cases, implied the splitting of a C–C triple bond.

Traditionally, this latter transformation has been carried out by ozonolysis,¹⁴ and due to the risk associated with this procedure, new alternatives have been developed. In this context, photooxidative cleavage $(O_2/CBr_4/h\nu)$,¹⁵ and the use of other oxidants (oxone, H₂O₂, *tert*-butyl hydroperoxide, I(III) reagents)¹⁶ alone or in the presence of W, Ru, Os, Fe and In catalysts^{16,17} provide carboxylic acids from alkynes.

Therefore, the development of a protocol based on the use of simple dioxygen as the most convenient oxidant without the

 Table 1 Oxidation of alcohols to carbonyl and carboxy compounds.
 General substrate scope^a



^{*a*} Isolated yields. Reaction conditions: O_2 (1 atm), NiBr₂ (10⁻⁵ mol%), 1 or 2 (10⁻⁵ mol%), NaOAc, PEG-400, 120 °C, 48 h. ^{*b*} Reaction time: 72 h. ^{*c*} Reaction time: 96 h.

need for further harmful chemicals or photochemical activation is highly desirable.

To check if other alkynes could be oxidatively cleaved into carboxylic acids, a set of structurally diverse terminal and internal alkynes were subjected to the same conditions. The results shown in Table 4 define the scope of this novel protocol, which has been successfully applied to substrates bearing halogen (F, Br, Cl), alkyl, carboxy, keto and ester moieties. The reaction outcome was conditioned more by the ligand than in previous oxidative processes (alcohols and methylene compounds), as in several cases ChemComm



 a Isolated yields. Reaction conditions: O₂ (1 atm), NiBr₂ (10⁻⁵ mol%), 1 or 2 (10⁻⁵ mol%), NaOAc, PEG-400, 120 °C, 48 h. b Reaction time: 72 h.

 Table 3
 Oxidative cleavage of alcohols and methylene compounds^a

$Ph \xrightarrow{OH} R \xrightarrow{O} Ph \xrightarrow{OH} OH$	$Ph \land R \rightarrow Ph \land OH$
1 (%) 2 (%)	1 (%) 2 (%)
R= COOH 70 ^[b] 98 ^[b]	R= COOH 45 50
R= CHOHPh 70 80	R= Bz 68 90
R= Bn - 97	
R= Bz 75 94	

 a Isolated yields. Reaction conditions: O₂ (1 atm), NiBr₂ (10⁻⁵ mol%), 1 or 2 (10⁻⁵ mol%), NaOAc, PEG-400, 120 °C, 48 h. b Reaction time: 72 h.

(*p*-bromophenylacetylene, diphenylacetylene, and 1-phenyl-1propyne) simple triazole **1** resulted in being ineffective to aid the target metal-catalyzed cleavage.

The newly developed method proved to be suitable for largescale processes, since benzoic acid was obtained in an excellent yield by reacting 1.5 grams of phenylacetylene, although at the cost of longer reaction times (67% yield after 48 h, 96% after 120 h). A similar assay was performed with phenylethanol (1.5 g) providing acetophenone with a 96% yield after 120 h.¹³

In addition to the fact that oxygen mediates this transformation at atmospheric pressure, it should be also pointed that the reaction is conducted in an environmentally friendly solvent, PEG-400, widely used as a very convenient media for chemical

Table 4 Oxidative cleavage of alkynes^a



^{*a*} Isolated yields. Reaction conditions: O_2 (1 atm), NiBr₂ (10⁻⁵ mol%), **1** or **2** (10⁻⁵ mol%), NaOAc, PEG-400, 120 °C, 48 h. ^{*b*} Benzoic acid was also obtained (35% from **1** and 47% from **2**). ^{*c*} Benzophenone was also isolated (30% from **1** and 20% from **2**).

and medicinal purposes.¹⁸ The role of this solvent in the reported oxidative process might be related to its unusual coordinating properties, similar to those of crown ethers.¹⁹

The combination of the above properties, and those of 1,2,4triazoles 1–2, enhance nickel catalytic properties to an exceptional catalytic profile (turnover number and frequency – TON and TOF – values were found to be in the range of 9 700 000–4 700 000 and 202 083–97 916 respectively)²⁰ that avoid the need for further purification steps in order to remove metal traces. In fact, ICP-MS analysis of *p*-bromobenzoic acid (obtained from *p*-bromophenylacetylene) revealed a Ni content of 1.2 ppm, which is below the concentration limit for oral and parenteral drugs with a maximum daily dose of 10 g per day.^{9c}

Although the exact mechanism of nickel catalyzed oxidative cleavage of alkynes is still being studied, the participation of nickel nanoparticles or other heterogeneous catalysts can be dismissed.²¹ No poisoning effect was observed when adding sub- and overstoichiometric (up to 300 equiv.) quantities of several poisons used in this context (Hg drop test, CS₂, PPh₃, pyridine, polyvinylpyridine).¹³ Moreover, a pseudolinear kinetic curve (conversion rate *vs.* time) was plotted for the oxidative cleavage of phenylacetylene.¹³ Besides, the addition of radical initiators as AIBN neither affected the reaction outcome nor enabled the process with lower NiBr₂/1 amounts, and no difference was detected in the presence of radical inhibitors or radical trapping agents (*e.g.* 3,5-dihydroxybenzoic acid), so that a chain radical autoxidation-like process could also be discarded.

In summary, in addition to the advantages in terms of safety and sustainability associated with the use of molecular oxygen at atmospheric pressure and PEG-400, the infinitesimal amounts of the metal-ligand system allow isolation of "*metal-free*" compounds for pharmaceutical uses. These features, close to those exhibited by oxidase enzymes, apply not only to the alcohol and benzylic C–H bond oxidations, but also to the unexampled cleavage of alkynes mediated solely by molecular oxygen.

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