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# Efficient Aerobic Oxidation of Arylcarbinols and Arylmethylene Compounds Mediated by Nickel (II)/1,2,4-Triazole Ligand Catalyst System

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**Abstract:** The oxidation of benzylic alcohols is a ubiquitous transformation in organic chemistry due to the relevance of aryl ketones, present in natural products and pharmaceutically active compounds and also intermediates in the synthesis of agrochemicals, medicines and other functional materials. Numerous oxidizing agents are available to effect this key reaction. In most instances, these reagents are required in stoichiometric amounts and are usually toxic, or hazardous, or both. In this context, considering environmental and safety issues, oxygen would be the reagent of choice for such organic transformation. Although much effort has been devoted to aerobic oxidation of benzyl alcohols, the amounts of metal catalyst are still relatively high and, sometimes, oxygen pressures above 5 atms.

In this context, we have discovered that systems based upon 1,2,4-triazole ligands and simple Ni (II) salts show extremely high catalytic activity in the aerobic oxidations of alcohols. In fact, primary and secondary benzylic alcohols have provided the corresponding carbonylic derivatives by using molecular oxygen at atmospheric pressure, in the presence of a combination of nickel(II) bromide and 1,2,4-triazole or, alternatively, a 1,2,4-triazole pincer ligand at such a low catalytic loading as $10^{-5}$ mol%. This catalytic system has proven to be efficient also for the benzylic C-H oxidation.

**Keywords:** aerobic oxidation, benzylic alcohols, Nickel, pincer ligand, triazole

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## 1. Introduction

Molecular oxygen is the ideal oxidant for chemical transformations. Therefore, in the last 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, this reaction can be carried out using different transition metals,[1] since the yields and selectivities of chain radical non-catalyzed autoxidation of alcohols and saturated hydrocarbons are often low.[2] Catalyst loadings generally range 0.5-10 mol% of [M], although significantly lower amounts (0.1-0.3 mol%) have been reported in some cases.[3] Regarding reaction media, flammable organic solvents have been mainly employed and just a few examples of oxidations have carried out in more sustainable media.[4]

Removal of metal traces is a serious concern in fine chemicals production. A valuable strategy to achieve this goal is just to decrease the catalyst loading to a point below regulatory requirements, which is particularly difficult for many transition metal catalysts, with very low levels allowed in drug products.[5]

In this paper we wish to present an outstanding catalytic system for the aerobic oxidation of alcohols and arylmethylene compounds based on 1,2,4-triazole type ligands and ($NiBr_2$) that has allowed us to avoid precious metals and fulfill the mentioned regulatory requirements.

## 2. Results and Discussion

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. On the basis of the encouraging results from the initial assays for the nickel-catalyzed oxidation of 1-phenylethanol, we decided to use $O_2$, $NiBr_2$, **1** or **2**, PEG-400, 120ºC and decrease gradually the catalytic amount down to $10^{-5}$ mol% of Ni and **1**/**2**. Blank experiments also showed the need of 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.

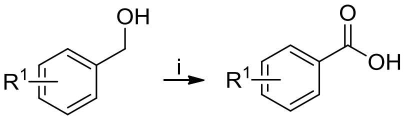
The optimized reaction conditions were accordingly applied to a number of primary and secondary benzyl alcohols, providing good to excellent results regardless the nature of the starting carbinol. As shown in Table 1, oxidation of primary alcohols provided the corresponding carboxylic acids.

Then, we assayed the same conditions in the benzylic C-H bond oxidation of a series of methylene compounds, and to our delight, the carbonyl compounds displayed in Table 1 were obtained in good yields. In both carbinol and methylene oxidation reactions a slightly better catalytic profile was found for the $NiBr_2$/**2** system, as better yields were observed in all cases.

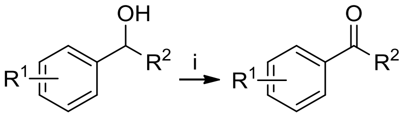
In addition to the fact that oxygen mediates this transformation at atmospheric pressure, it should be also pointed that the reaction is conducted in an environmentally friendly solvent, PEG-400. The role of this solvent in the reported oxidative process might be related to its unusual coordinating properties that remind of crown ethers.[6]

The combination of the above properties and those of 1,2,4-triazoles **1-2** enhance nickel catalytic properties to an exceptional catalytic profile that avoid the need of further purification steps in order to remove metal traces.

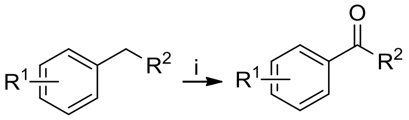
**Table 1.** Oxidation of alcohols and methylene compounds. General substrate scope.[a



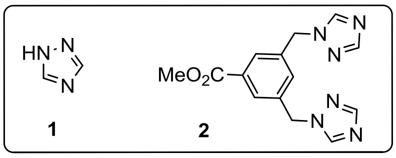
| | **1** (%) | **2** (%) |
|---|---|---|
| $R^1$= H | 98 | 98 |
| $R^1$= *p*-$^i$Pr | 70[b] | 94[b] |
| $R^1$= *p*-Et | 67[b] | 94[b] |
| $R^1$= *p*-Me | 70[b] | 90[b] |
| $R^1$= *p*-$CF_3$ | 90[b] | 97[b] |
| $R^1$= *m*-OMe | 75[c] | 90[c] |
| $R^1$= *p*-OMe | 67[c] | 80[c] |
| $R^1$= *m*-OPh | 60[b] | 88[b] |



| | **1** (%) | **2** (%) |
|---|---|---|
| $R^1$= H; $R^2$= Me | 80 | 97 |
| $R^1$= H; $R^2$= CN | 96 | 97 |
| $R^1$= H; $R^2$= Ph | 74 | 93 |
| $R^1$= *p*-Me; $R^2$= Me | 90 | 98 |
| $R^1$= H; $R^2$= Et | 86 | 94 |
| $R^1$= *o*-OMe; $R^2$= Me | 75[b] | 98[b] |
| $R^1$= H; $R^2$= $^t$Bu | 70[b] | 90[b] |
| $R^1$= *p*-Cl; $R^2$= Me | 82 | 87 |
| $R^1$= *H*; $R^2$= *o*-tol | 89 | 88 |



| | **1** (%) | **2** (%) |
|---|---|---|
| $R^1$= H; $R^2$= Me | 90 | 97 |
| $R^1$= H; $R^2$= Ph | 84 | 97 |
| $R^1$= H; $R^2$= 4-Py | 50[b] | 70[b] |
| $R^1$= *p*-Me; $R^2$= CN | 79[b] | 82[b] |



**1** **2**

[a] Isolated yields. i: $O_2$ (1 atm), $NiBr_2$ ($10^{-5}$ mol%), **1** or **2** ($10^{-5}$ mol%), NaOAc, PEG-400, 120ºC, 8h. [b] 72h. [c] 96h.

## 3. Materials and Methods

A round bottom flask equipped with a magnetic stirrer bar was charged with the alcohol (1 mmol), NaOAc (8.0 mg, 0.1 mmol), $NiBr_2$ (2.7 $10^{-5}$ mg, $10^{-7}$ mmol), **1** (8.6 $10^{-6}$ mg, $10^{-7}$ mmol,) and PEG 400 (1 mL) at room temperature. The system was purged with molecular oxygen, and an oxygen-filled balloon (1-1.2 atm) was connected. The mixture was heated at 120 ºC under stirring for 24 h. The reaction outcome was monitored by $^1$H-NMR. Upon completion, the mixture was cooled to room temperature and water was added (50 mL aprox.). The resulting solution was acidified with HCl 1M (pH≈1-2) and extracted with $Et_2O$ (4 x 6 mL) and the combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexane:ethyl acetate as eluent.

## 4. Conclusions

In summary, the combination of nickel(II) bromide and the 1,2,4-triazole pincer ligand **2** constitutes a highly active catalytic system for the aerobic oxidation of arylcarbinols and arylmethylene compounds. In addition to the advantages in terms of safety and sustainability associated to 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.

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## Conflicts of Interest

The authors declare no conflict of interest.

## References and Notes

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