

# CATALYTIC CYCLOCARBONYLATION IN COMPRESSED CARBON DIOXIDE: PRESSURE INFLUENCE OF CARBON MONOXIDE AND CARBON DIOXIDE

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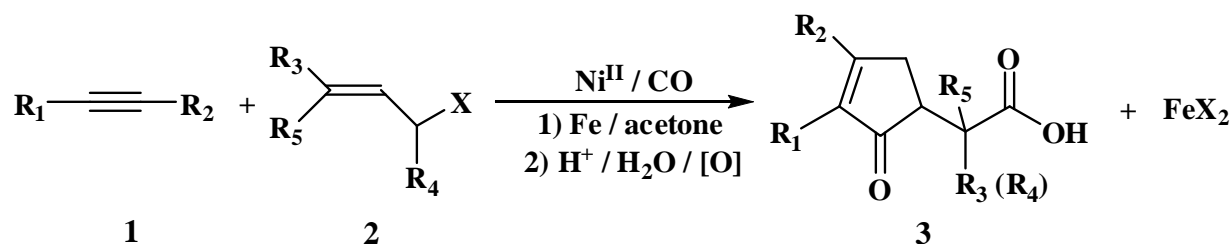
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Among the current interests in organic synthesis are those reactions performing multiple C-C bond formation, in special when they undergo under catalytic conditions<sup>1</sup>. Due to its properties, there is a growing interest on the use of compressed fluids (CF) as solvent media in catalytic processes<sup>2</sup>. In this context, we present herein studies that aim to the development of a cleaner technology for the preparation of cyclopentane derivatives by using the single step catalytic carbonylative cycloaddition, developed in our laboratory, using CO<sub>2</sub>-expanded solvents instead of conventional liquid solvent media. In particular we have studied the effect of total pressure and carbon monoxide partial pressure over the yield of the reaction. This is a very efficient reaction, because at least three C-C bonds are achieved in a single operation in order to generate a cyclopentane derivate. The cyclopentane skeleton is present in numerous natural products, many of them bioactive<sup>3,4</sup>.

## INTRODUCTION

At present there is a growing interest on the use of CF, in liquid or supercritical state, pure or mixed with organic solvents, as sustainable solvents in synthetic processes, in particular, catalytic processes<sup>2</sup>. Supercritical carbon dioxide (scCO<sub>2</sub>) is one of the most attractive alternatives (total or partial substitution) to conventional organic solvents employed in industrial reactions; these organic solvents are often environmentally hazardous. Due to its properties, compressed fluids are especially attractive as solvents for the proposed catalytic processes: high miscibility with gases (*e.g.* CO), high diffusivity, low viscosity and tuneable solvent power allowing facile separation of catalysts and products (selective precipitation) by simple variation of pressure and/or temperature<sup>5</sup>. These properties offer great advantages to catalytic reactions: better solubility, influence on the kinetics, changes on the equilibrium constants, higher selectivities and yields, reduction of mass transfer limitations, etc.

The multiple C-C bond formation reactions (multicomponent reaction) are among the most important reactions in organic synthesis. So far, the application of those reactions has been limited to laboratory scale mainly due to: low yields in organic solvents, and difficult product separation<sup>1</sup>. In this context, our group has been working for a long time on the carbonylative cycloaddition of allyl halides and alkynes mediated by nickel (**Fig. 1**).



**Figure 1:** Catalytic carbonylative cycloaddition of alkynes and allyl halides in conventional solvents

In conventional organic solvents, the reaction gives high yields (70-90 %), takes place at room temperature and atmospheric pressure, is regioselective, and also stereoselective (when starting with an alkyne or allyl derivative that already has a stereocenter)<sup>3</sup>.

By using compressed fluids instead of conventional solvents, we expect to improve the selectivity as well as to diminish the use of organic solvents.

## MATERIALS AND METHODS

The solubility behaviour of the different reactants was studied by a home made high pressure phase analyzer with sapphire windows, which allows visual inspection of the number of phases present. The agitation was accomplished by recirculation, due to the rectangular shape of the variable volume cell.

### Materials

The catalyst employed for the reaction was prepared in-situ using: nickel bromide (98%, Aldrich), sodium iodide (98%, Panreac), and iron (powder, particle size 10  $\mu\text{m}$ , Merck) as the reducing agent. The substrates employed were allyl bromide (Aldrich, 99%) and phenylacetylene (Panreac, 97%). Carbon monoxide with a stated purity of 99.3% and carbon dioxide (ultra pure) were supplied by Carbueros Metálicos. Acetone was previously distilled (under Ar) before each reaction.

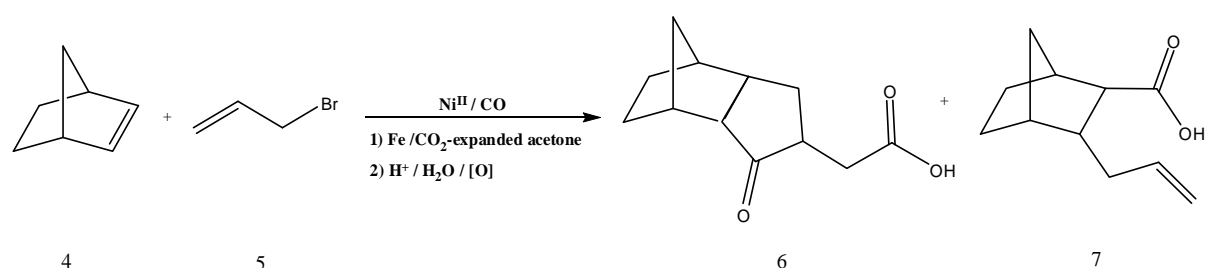
### Procedure

A new apparatus was designed and built in order to run the high pressure reactions. Reaction experiments were carried out batch wise at room temperature, and the kinetics were controlled by the decrease in total pressure.

In a typical experiment the reactor is manually charged with  $\text{NiBr}_2$ ,  $\text{NaI}$  and  $\text{Fe}$ , and then sealed. The vacuum line is connected to the reactor in order to get rid of all the air. After that, acetone is introduced in the reactor. Carbon monoxide and carbon dioxide are introduced under different conditions (different partial pressures) for each reaction.  $\text{CO}_2$  is introduced from the cylinder via a high pressure pump and  $\text{CO}$  directly from the cylinder (connected to a pressure regulator). At this point, we start with the mechanical stirring and wait so that the catalyst precursor could be formed in-situ (prepared by a single electron reduction of a  $\text{Ni(II)}$  salt). Then, the substrates are slowly added by means of a high pressure pump. After that, the reaction is left running overnight. The following day the stirring is stopped, and gases inside the reactor are vented to atmosphere (in a fume hood). The product is collected with acetone and evaporated. After the work up, the reaction products are separated by flash chromatography, and identified and quantified by  $^1\text{H}$  and  $^{13}\text{C}$  NMR.



when using 2-norbornene (**Fig. 3**) instead of phenylacetylene, the reaction yield was highly improved in CO<sub>2</sub>-expanded acetone, compared to the conventional reaction in acetone<sup>7</sup>, as well as the selectivity (~100%) towards the desired product **6**, in relation to 77% when using liquid acetone<sup>8</sup>. In all cases, the conventional organic solvent has been mostly replaced by dense CO<sub>2</sub>.



**Figure 3:** Catalytic cyclocarbonylation of 2-norbornene in CO<sub>2</sub>-expanded acetone

## CONCLUSION

In conclusion, we report here some studies of a highly efficient catalytic method to synthesize *intermolecularly* the cyclopentane skeleton starting from products as simple as allyl halides, alkynes, alkenes and carbon monoxide under very mild reaction conditions by means of a stoichiometric amount of iron, a catalytic amount of Ni halide and CO<sub>2</sub>-expanded acetone as the solvent.

The effect of carbon dioxide solvent content and total pressure over the reaction yield are currently under further study.

## ACKNOWLEDGMENTS

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