Versatile chemoselectivity in Ni-catalyzed multiple bond carbonylations and cyclocarbonylations in CO₂-expanded liquids[†]

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Selective mono or double carbonylations could be achieved by using CO₂-expanded liquids in [2 + 2 + 1] carbonylative reactions of alkenes or acetylenes with allyl bromides catalyzed by Ni(1).

Multiple C–C bond formation reactions are among the most important in organic synthesis. In this context, our group has been working for a long time on the carbonylative cycloaddition (Pauson–Khand type reactions)¹ of allyl halides and alkynes, and has finally developed a procedure to carry out these reactions using a catalytic amount of Ni (Scheme 1).²

These types of metal-catalyzed [2 + 2 + 1] carbonylative cycloadditions represent the most straightforward way to synthesize the cyclopentanone skeleton, since at least three C-C bonds are formed in a single experimental operation. This structure is found in many bioactive natural products of interest (perfumes, antibiotics, antitumoral agents, etc.).³ Aside from the synthetic interest, this Ni-catalyzed reaction presents additional advantages: the most promising features being that it gives high yields (70-95%), takes place at room temperature and atmospheric pressure, uses a cheap catalyst, is regio and stereoselective compared with similar processes, and is efficient in the intermolecular version.^{2,4} Also, in early studies, cyclohexenones resulting from a single carbonylative process were also been found as a second product.⁵ However, up until now, by using liquid solvents, it has not been possible to chemoselectively enhance the reaction process towards monocarbonylation.

Recently, this procedure has also been extended to strained olefins (Scheme 2),⁶ always resulting in a mixture of two products, corresponding to single and double carbonylation.



Scheme 1 Catalytic carbonylative cycloaddition of alkynes and allyl halides in acetone.

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Scheme 2 Catalytic carbonylative cycloaddition of strained alkenes and allyl halides in acetone.

At present, there is growing interest in the use of compressed fluids (CF), either in a liquid or supercritical state, as sustainable solvents in synthetic processes, in particular when applied to catalytic processes.⁷ Compressed CO₂ is one of the most attractive alternatives for replacing environmentally-hazardous conventional organic solvents employed in industrial reactions, since it is non-toxic, non-flammable and easy to recover. CO₂-expanded liquids are especially attractive for performing catalytic reactions due to the enhanced solubility of the reactant gases (*e.g.* CO), the enhanced transport rates due to the properties of dense CO₂,^{7,8} the milder operating pressures (tens of bars) compared to $scCO_2$,⁹ the resulting diminished use of organic solvents, and the ability to tune the solvent power by varying the CO₂ composition.^{10,11}

Here, we report the outstanding chemoselectivity reached in this Ni-catalyzed cyclocarbonylation reaction with both alkynes and strained alkenes by tuning the operational parameters, using CO_2 -expanded acetone as the reaction medium instead of liquid acetone.

An *ad hoc* experimental set up (Scheme 3) was designed and built in order to perform the high-pressure catalytic reactions.

The phase behaviour of the reactants was studied on a phase analyzer based on a variable volume cell with sapphire windows, which allows visual inspection of the number of phases present.¹² Preliminary solubility experiments were performed on the different components (reagents and catalyst) involved in the cyclocarbonylation reaction, both in pure CO₂ and CO₂-expanded acetone, at 298 K and pressures up to



Scheme 3 A schematic representation of the equipment used for the cyclocarbonylation reactions at high-pressure. (P1) High-pressure CO_2 pump, (R) chemical reactor, (C) cylinder, (P2) high-pressure liquid pump, (PI) pressure indicator, (MS) mechanical stirrer, (VL) vent line and (V) vacuum line.





Scheme 4 The catalytic carbonylative cycloaddition between 1 and 2 in CO₂-expanded acetone.

100 bar. The results showed that the tested allyl halides, norbornenes and alkynes were highly soluble in both pure CO_2 and CO_2 -expanded acetone. The catalyst, however, was only soluble in CO_2 -expanded acetone under certain conditions. Thus, the reaction was feasible under homogeneous conditions in the new medium.

We used norbornene (1) and allyl bromide (2) as model reagents of the reaction between strained alkenes and allyl halides (Scheme 4).‡ As mentioned before, using acetone as the solvent, this reaction always gave a mixture of the mono- and bicarbonylation products (3 and 4). Under those conditions, we were only slightly able to tune the ratio between 3 and 4 by using water as an additive;⁶ the highest selectivity achieved being a 68% yield of cyclopentanone 3 and a 20% yield of the open product 4 (selectivity ratio 77 : 23) in the complete absence of water.

In Table 1 are summarized the results achieved when performing the reaction in CO₂-expanded acetone at different operational conditions and in presence or absence of water.

The result in Table 1 entry 2 shows that the cyclocarbonylation reaction between 1 and the allyl halide gives better yields (both total yield and yield of the cyclopentanone 3) in CO_2 -expanded acetone than in the previously described work (in acetone at atmospheric pressure (Table 1 entry 1)). Furthermore, contrary to the results obtained at atmospheric pressure, the use of a certain amount of H₂O did not inhibit the two carbonylation reactions, but even increased the selectivity in favour of cyclopentanone 3, as seen in Table 1 entry 3. A possible explanation may arise from the presence of the large amounts of CO₂ reacting with H₂O, resulting in acidification of the medium. The decrease of the OH⁻ concentration would then prevent, to a certain extent, hydroxyl attack at the acyl metal intermediate, which would interrupt the cyclisation. This hypothesis is currently being studied. In Table 1 entries 3-6, we can see that increasing the CO content in the liquid phase increases the ratio of open product to cyclopentanone, with open product 4 being the main product at $x_{CO} = 0.0066$ (Table 1 entry 5) and the sole product at $x_{CO} = 0.0093$ (Table 1 entry 6), despite the presence of water.

We can conclude that by using CO_2 -expanded acetone in the catalytic carbonylative cycloaddition between 1 and 2, we can

significantly tune the ratio of the two products by changing the CO content of the reaction medium in the presence of water. At low CO content, cyclopentanone **3** is obtained with almost complete selectivity, and the open product is exclusively produced at higher CO concentrations. Indeed, at high concentrations, CO efficiently competes with the distal double bond for the Ni coordination site, precluding its insertion onto the acyl carbon center, favouring the formation of open product **4**, corresponding to a single carbonylation (Scheme 5).

In view of the good results obtained in the reaction between norbornenes and allyl halides, we decided to try reactions between alkynes and allyl halides in CO₂-expanded acetone using the same equipment to see the effect of the CO content on these reactions. We chose phenylacetylene (5) and 2 as the model reagents (Scheme 6). To start with, we studied the effect of the CO content in the absence of CO₂ when the reaction was performed in acetone. In all cases, cyclopentanone 6 was produced, but we did not detect cyclohexenone 7, corresponding to the single carbonylation, and a mixture of polyinsertion products were produced as by-products. The best result with regard to cyclopentenone formation and reaction rate was at $x_{CO} = 0.0007$ (82% yield of cyclopentenone 6). The higher the CO content, the lower the yield and the slower the rate of the reaction. As we expected, considering the results obtained with norbornenes, at $x_{CO} = 0.019$, the yield of the bicarbonylation product decreased to 37%, and at $x_{CO} = 0.033$, a mixture of unidentified products was obtained.

In agreement with the results achieved in acetone, when we attempted the reaction in CO₂-expanded acetone (see Table 2), the yield of cyclopentenone **6** decreased as the CO content increased. However, in this solvent medium, we were surprised to find increasing amounts of cyclohexenone **7**, resulting from a 6-*exo-trig* cyclization, as x_{CO} augments. When the CO content in the reaction medium was 0.0043 (Table 2 entry 5), this product was obtained preferentially as the main product

Scheme 5 The selective formation of products 3 and 4, controlled by the content of CO in the liquid phase.

Scheme 6 Catalytic carbonylative cycloaddition between 5 and 2, yielding cyclopentenone 6 and cyclohexenone 7.

Table 1 The effect of the CO and H_2O content on the cyclocarbonylation reaction of 1 and 2 performed in CO_2 -expanded acetone^{*a*}

Entry	P _{total} /bar	$z_{\rm CO_2}^{d}$	$z_{\rm CO}^{d}$	$x_{\rm CO_2}^{e}$	$x_{\rm CO}^{e}$	Yield (%)	Product ratio 3 : 4
1^b	1.0		0.34		0.0005	88	77:23
2^b	48.5	0.92	0.029	0.79	0.0027	90	80:20
3 ^c	48.5	0.92	0.029	0.79	0.0027	92	98:2
4 ^{<i>c</i>}	49.0	0.91	0.039	0.78	0.0035	82	93:7
5^c	51.0	0.88	0.075	0.76	0.0066	88	9:91
6 ^{<i>c</i>}	53.0	0.85	0.108	0.74	0.0093	71	0:100

^{*a*} All reactions were carried out at 25 °C, and the reaction mixture was stirred for 15 h in order to ensure a complete process. ^{*b*} In the absence of H₂O. ^{*c*} With 1 equivalent of H₂O. ^{*d*} z_i = overall mole fraction of component i. ^{*e*} x_i = mole fraction of component i in the liquid phase, where the reaction takes place.

Entry	$P_{\rm total}/{\rm bar}$	$z_{\rm CO_2}^{\ \ b}$	$z_{\rm CO}^{b}$	$x_{\rm CO_2}^{c}$	$x_{\rm CO}^{c}$	Yield (%)	Product ratio 6:7
1	14.0	0.79	0.060	0.24	0.0008	80	100:0
2	31.0	0.89	0.030	0.53	0.0011	74	100:0
3	48.0	0.93	0.020	0.79	0.0019	74	81:19
4	51.0	0.93	0.019	0.83	0.0022	73	73:27
5	59.0	0.94	0.016	0.92	0.0043	60	32:68

Table 2 Influence of the CO₂ pressure on the carbonylative cycloaddition between 5 and 2, performed in CO₂-expanded acetone^a

^{*a*} All reactions were carried out at 25 °C, and the reaction mixture was stirred for 15 h in order to ensure a complete process. ^{*b*} z_i = overall mole fraction of component i. ^{*c*} x_i = mole fraction of component i in the liquid phase, where the reaction takes place.

of the reaction over the cyclopentenone. Although this type of ring closure has been seen previously, these products were always synthesized from internally-substituted allyl halides, and were obtained as aromatic adducts.⁵

Therefore, we can conclude that in the case of acetylenes, in agreement with the results obtained for strained alkenes, the formation of cyclohexenone 7 (monocarbonylated adduct) is favored with increasing CO molar fraction in the liquid phase.

In conclusion, we have reported studies of a highly efficient catalytic method to selectively synthesize cyclopentanes, cyclohexanes or plainly-carbonylated adducts by tuning the reaction conditions, namely the water and CO content. The reaction is intermolecular, starting from products as simple as allyl halides, alkynes, strained alkenes and CO under mild reaction conditions by means of a stoichiometric amount of iron, a catalytic amount of Ni halide and CO2-expanded acetone as the solvent. This method allows, by changing the CO content of the reaction medium, the ratio of the products obtained to be tuned, especially in the case of 1, where we obtained two different products with almost complete chemoselectivity. Moreover, the use of CO2-expanded acetone allowed a reduction of the acetone consumption by more than 70%. The reported results open up a wide range of possibilities for synthesizing more complex cyclopentanones in high yields and with total chemoselectivity, work that is now in progress.

Notes and references

‡ In a typical experiment, the reactor was manually charged with NiBr₂ (0.43 mmol), NaI (2.55 mmol), Fe powder (8.5 mmol, reducing agent) and granulated Fe (10.8 mmol, for efficient mixing), and then sealed. The air inside the reactor and the cylinder was vented through a vacuum line, and afterwards acetone (1.5 ml) was introduced into the reactor. CO and CO₂ were mixed in a gas cylinder under different conditions (different partial pressures) for each reaction, and then a valve connecting the cylinder and the reactor was opened to allow equilibrium. This valve was kept open during all reactions, as well as mechanical stirring taking place. After 30 min of reduction, 8.5 mmol of each substrate pair (1 + 2 or 5 + 2) was slowly added by means of a high-pressure pump for 3 h. After this, the reaction was left overnight (approx. 15 h). The following day, the stirring was stopped, the gases inside the reactor vented into atmosphere and the products collected with acetone. The solvent was removed and the contents of the flask transferred to a separation funnel by washing the flask (with the remaining iron) with dichloromethane. The dark reaction mixture was treated with portions of 5N HCl solution until no further discoloration was observed. After washing the organic phase with water to neutralize it, the organic layer was treated with a solution of $Na_2S_2O_3$ (to remove any I_2 produced by the oxidation), washed again with water and dried over MgSO4. The solvent was then removed in a rotatory evaporator. After this work up, the reaction products were separated by flash chromatography, and identified and quantified by ¹H and ¹C NMR spectroscopy. Characterization data for the isolated products are provided in the ESI.†

The CO₂ and CO contents in the liquid phase, where the reaction takes place, were estimated by flash separation calculations using the Peng Robinson EoS (PR EoS), assuming a ternary CO–CO₂–acetone system and neglecting the effect of the reactants and water. The values of the binary interaction parameters employed were reported by López-Castillo *et al.*,¹³ who previously reliably used the PR EoS to model CO–CO₂–expanded solvent systems. The software used for the calculations was Hysys Plant.

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