Highly Efficient Microwave-Assisted CO Aminocarbonylation with a Recyclable Pd(II)/TPP-β-Cyclodextrin Cross-Linked Catalyst

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Highly efficient microwave-assisted CO aminocarbonylation with a recyclable Pd(II)/TPP-β-cyclodextrin cross linked catalyst

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KEYWORDS

Microwaves; Aminocarbonylation; Carbon Monoxide; Heterogeneous catalysis; Palladium

ABSTRACT

Incorporation of the carbonyl moiety into organic molecules using a three-component matrix with carbon monoxide, an organic halide, and a nucleophilic component offers a simple and versatile approach to the formation of carboxylic acids, anhydrides, esters, amides and ketones. The design of a sustainable synthetic protocol for aminocarbonylation can be efficiently accomplished using a multi-faceted strategy that combines solid green catalysts and suitable enabling techniques. The safe and synergistic use of carbon monoxide in a microwave reactor under pressure could create a

technological breakthrough in aminocarbonylation reactions. Moreover a new recyclable catalytic system “CβCAT” based on Pd(II)-triphenylphosphine embedded in cross linked β-cyclodextrin (hexamethylene diisocyanate) was found very efficient in aminocarbonylation reactions of aryl iodides.

1. INTRODUCTION

The term ‘carbonylation’, coined by Reppe in the ‘30s, includes a plethora of reactions[1] such as formylation,[2] hydroformylation, alkoxycarbonylation,[3,4] aminocarbonylation,[5-7] carbonylative Heck,[8] carbonylative Suzuki Miyaura,[9] carbonylative Sonogashira reactions,[10-11] which provide an easy and practical method for the introduction of a carbonyl group into an organic substrate. Since the pioneering work of Heck and co-workers in the 1974[13-14] the palladium-catalyzed carbonylation of aryl halides or pseudohalides with a suitable nucleophile have emerged as the most important tool for the production of substituted arenes, which are the main critical intermediates for various agrochemicals and pharmaceuticals.[15] Noteworthy are the recent advancements in aminocarbonylation reactions[16] that exploit the use of carbon monoxide (CO). Being versatile and cost efficient C_1 building block reagent (in combination with transition metal catalysis),[17-18] CO enables the “amide bond formation avoiding poor atom economy reagent” as voted in 2007 by The American Chemical Society Green Chemistry Institute as the top challenge to be fulfilled by organic chemistry.[19]

Despite the advantages of CO as a high affinity ligand for palladium, (both in 0 and II oxidation states due its dual ability to act as a σ-donor and π-acceptor),[20] and the plentiful of aminocarbonylation protocols described in literature using it as source of carbonyl group,[21] its true potential has not been fully utilized in lab-scale synthesis due to the cumbersome handling of the CO gas.

To overcome the safety problems involved using CO gas, several groups have developed CO-equivalents such as alkyl formats,[22] formic anhydride, and *N*-substituted formamide,[23-27] carbamoylstannanes,[28] carbamoylsilane,[29] silacarboxylic acids,[30] and acid chloride derivatives.[31,32] However, this approach requires harsh reaction conditions to release CO such as the presence of strong base combined with high temperatures involving long reaction time.

Another class of solid *in situ* CO-releasing reagents are the metal carbonyls,[33-39] that currently represents the best alternative to CO-gas in aminocarbonylations.[40-41] These inorganic metal carbonyls and their derivatives, are nevertheless CO releasers and relatively expensive. Moreover they need of a near stoichiometric amounts of an additional transition metal to work, which can encumber the purification of the desired amide products.[42] To avoid this problem and enable the reuse of high-cost catalyst/ligand system, it is necessary to address the sustainability problems of aminocarbonylation reactions. Under the relentless demand to develop ever more efficient methods for the amides production, (in particular in the pharmaceuticals industry), the synthetic routes exploiting the high reactivity of CO gas could offer clear advantages over the aforementioned alternatives CO-source despite involving a certain hazardous potential, which can be avoided using suitable equipment.[43] The use of inexpensive and easily reusable catalytic system combined with the new enabling technologies can make this process cost-effective.

In synthetic organic chemistry, one of the most direct way to pursue Green Chemistry is the use of “enabling technologies” that include traditional techniques such as “solid phase synthesis” and heterogeneous catalysis as well as relatively new ones such as “microwave (MW)-assisted synthesis”, “continuous flow reactors” etc. which were developed to speed up synthetic transformations and ease process workup.[44] The heterogeneous catalysis combined the efficacy of a highly active immobilized catalyst to the simplification the reaction workup being it often readily removed by filtration. Based on our experience, cross-linked chitosan Pd(II) complexes gave successful results in MW catalysed Suzuki reaction.[45] Excellent catalytic activity in Heck, Suzuki and Sonogashira reactions were obtained with Pd(II)-based cross-linked β-cyclodextrin (β-CD) catalyst obtained by an *in situ* polymerization of βCD with diisocyanates under ultrasound irradiation in presence of Pd salts and TPP.[46,47]

Nowadays there is no doubt that MW-assisted chemistry has helped to radically reduce the reaction time , increase product yields, minimizing catalyst loading and reagent excess. Under MW irradiation the reactions are well-targeted and uniformly heated with extraordinary high rate that cannot be reproduced by classical heating.

Nowadays there is no doubt that MW-assisted chemistry has helped to radically reduce the reaction time and increase product yields, minimizing catalyst loading and reagent excessas a consequence of heating rates .[48-50] However, few publications describe this technique with gaseous reagents in closed vessel and in heterogeneous gas-phase reactions. Based on our knowledge very few reports deal with the use of CO gas as aminocarbonylation reagent inside a MW oven.[51,52]

In the course of our quest for aminocarbonylation procedures suitable for MW-accelerated high-speed chemistry,[53] leveraging on our experience in MW promoted reactions with gaseous reagents in a closed pressurized cavity,[54,55] we described herein a fast MW-assisted Pd(II)-catalysed protocol for the synthesis of amides using CO gas. Aim of the work is to maximize the advantages of MW technology in presence of catalytic system immobilized on other polar matrix. This investigation is oriented to the optimization of a heterogeneous phase protocol in presence of supported Pd catalyst (CβCAT). The catalyst was chosen because it combines high performances of the metal, to high efficacy in MW adsobtion, moreover the βCD is able to complex the ligand TPP making the catalyst more effective. The influence on reaction outcome of different substituents on the aryl halides, and different nucleophiles on catalyst performance as well as the catalyst recycling is the object of this investigation.

2. RESULTS AND DISCUSSION

The influence of critical reaction parameters (i.e., temperature, time, CO pressure, base, ligand and solvent) on the MW aminocarbonylation of 4-iodoanisole (1 mmol scale), using tert-butylamine (2 equiv) as a nucleophile, has been investigated as model reaction for optimization. Our initial efforts were directed at performing comparison experiments in presence of triethylamine (Et_3N) and TPP, as base and ligand, by using palladium acetate (0.1 %) instead of the heterogeneous CβCAT as reaction catalyst, carrying out the aminocarbonylations in a multimode MW reactor (Scheme 1, Table 1 and Table 2). This MW device was equipped with a pressure control system and a multiple position rack, which enable multiple gases loading (inert and/or reactive gas) and simultaneous reaction runs.

It was observed that performing the aminocarbonylation of **(1)** in presence of 2 equiv of nucleophile **(2)**, a 82 % yield of amide **(3a)** could be achieved at 125 °C in toluene after 90 min of MW irradiation (average power: 55 W) using 1 bar of CO pressure (diluted up to 10 bar with N_2) in presence of Et_3N (3.5 equiv) and TPP ligand (0.1%) (Table 1, entry 4). No improvements were detected by increasing the MW irradiation time up to 2 h (Table 1, entry 6). In toluene, several nucleophile to aryl iodide molar ratio were explored to maximize conversion and selectivity of **3a** with respect to the ketoamide side product (**3b**) (Table 1, entries 2, 3, 4 and 5). The ratio of 2:1 furnished the best results with 96% conversion and 82% yield. The influence of the CO pressure on the MW aminocarbonylation was also investigated. Raising CO from 1 to 2.5 bar did not enable an improvement of desired product yield **3a** (Table 1, entries 4, and 7), but, as expected, only a slight increase in the ketoamide (**3b**) formation (up to 25%) when the reaction was carried out over 5 bar of CO (Table 1, entry 8). The reaction was repeated under conventional conditions, and on the basis of published results[54], the amount of $Pd(OAc)_2$ was increased to 5%. Complete conversion was obtained after 8 hrs heating at 100 °C and the desired product was collected in 69% yield (Table 1, entry 9).

Scheme 1. MW-assisted aminocarbonylation of 4-iodoanisole.

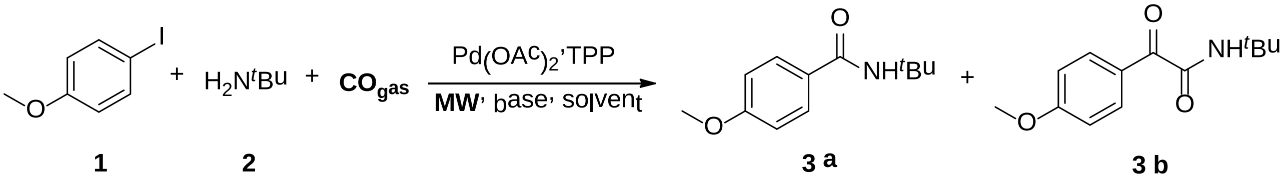


Table 1. Optimisation conditions for MW-assisted aminocarbonylation of 4-iodoanisole **(1)** with *tert*-butylamine **(2)** to **3a** in the presence of $Pd(OAc)_2$.[a]

Entry	**Reaction conditions**				**Conversion (%)[b]**	**Yield (%)**	
	Solvent	***H_2N^tBu (equiv)***	***CO (bar)***	***Time (h)***		**(3a)**	**(3b)**
1	Toluene	5	1	1	71	52	10
2	Toluene	5	1	1.5	89	62	16
3	Toluene	3.5	1	1.5	95	71	12
4	Toluene	2	1	1.5	96	82	8
5	Toluene	1.25	1	1.5	75	61	7
6	Toluene	2	1	2	96	83	11
7	Toluene	2	2.5	1.5	95	71	17
8	Toluene	2	5	1.5	97	64	25

9[c]	Toluene	5	1	8	>99	59	25
10	MeCN	2	1	1.5	89	74	11
11	THF	2	1	1.5	80	68	10
12	Dioxane	2	1	1.5	75	59	7
13	Dioxane:H_2O (8:2)	2	1	1.5	89	35	<5
14	Dioxane:H_2O (2:8)	2	1	1.5	95	21	<5
15	DMF	2	1	1.5	81	70	8

a Reactions condition: 4-iodoanisole (1, 1 mmol), tert-butylamine (2), 0.01% of $Pd(OAc)_2$, 0.1% of TPP and Et_3N (3.5 mmol) in 5 mL of solvent, 125 °C (55 W average MW power) in the presence of CO and N_2 (9 bar) atmosphere b Determined by GC–MS; c The reaction was performed under conventional conditions. 5% $Pd(OAc)_2$, TPP (0.1 mmol), Et_3N (3.5 mmol) in 10 ml toluene, 1 bar CO. The solution was heated at 100°C for 8 hrs.[51]

Moving from toluene to more polar non-nucleophilic solvents (such as MeCN, THF, dioxane or DMF) a reduction in terms of reaction yields was noticed (Table 1, entries 10, 11, 12, 15). As expected benzoic acid derivative was detected as the main reaction product when a mixture of dioxane:H_2O (8:2 or 2:8) have been used as more green reaction solvent (Table 1, entries 13, 14).

Generally, product yields slightly increased (7%) using higher catalyst amount (from 0.01% to 0.1% (Table 2, entry 1-4). Meanwhile, failing the TPP ligand, only poor yield of **(3a)** was obtained and omitting the Et_3N no reaction product was detected even when 0.1% Pd was employed. Various other organic bases, including pyridine, 2,6-lutidine, and 4-dimethylaminopyridine (DMAP), were investigated and were all found to be less effective than Et_3N (Table 2, entries 7-9). Then lower reaction temperatures were investigated from 125 °C to 85 °C (Table 2, entries 10-12). The reported results showed that yields increase with reaction temperature, meanwhile ketoamide selectivity was much higher at lower temperature (Table 2, entries 10-12).

Table 2. Optimisation of conditions for MW-assisted aminocarbonylation reaction.

Entry	Reaction condition[a]			Conversion(%)[b]	Yield (%)	
	Base (equiv)	*$Pd(OAc)_2$ (%)*	*Temp. (°C)*		(3a)	(3b)
1	Et_3N (3.5)	0.1	125	100	89 (29)[c] (0)[d]	8
2	Et_3N (3.5)	0.05	125	99	86	<5
3	Et_3N (3.5)	0.02	125	97	84	<5
4	Et_3N (3.5)	0.01	125	96	82 (28)[c] (0)[d]	<5
5	Et_3N (2.5)	0.01	125	87	71	10
6	Et_3N (1.5)	0.01	125	75	58	11
7	Pyridine (3.5)	0.01	125	87	69	10
8	2,6-lutidine (3.5)	0.01	125	83	64	7
9	DMAP (3.5)	0.01	125	85	66	9
10	Et_3N (3.5)	0.01	115	89	71	14
11	Et_3N (3.5)	0.01	100	83	59	17
12	Et_3N (3.5)	0.01	85	75	42	21

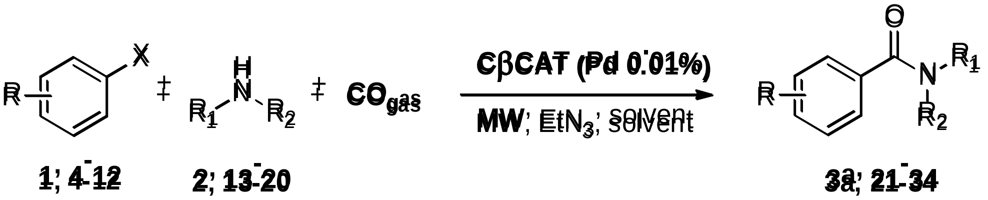
[a] Reactions performed under MW irradiation (90 min) in a 1 mmol scale of (1), using 2 equiv of amine (2), in presence of CO (1 bar) and N_2 (9 bar) atmosphere [b] Determined by GC–MS. [c] Reaction performed without TPP ligand. [d] Reaction performed without Et_3N.

The recovery and recycling of the Pd catalyst from the product mixture remains a big challenge. Heterogeneous catalysis is a mean to simplify workup procedure avoiding the contamination of desired products from heavy metals and to reuse it. Therefore $Pd(AcO)_2$ was entrapped in presence of TPP ligand on a β-CD cross-linked polymer forming the CβCAT catalyst.

CβCAT was simply obtained by sonochemical reticulation of (β-CD) with hexamethylene diisocyanate (HDI) in solution containing Pd(II) salts and triphenylphosphine (TPP). The metal content was measured by ICP and 0.65% average was obtained. Moreover, by ICP analysis we could observe its negligible metal leaching, while the absence of TPP of TPPO in the reaction filtrate demonstrate the potential of this catalyst for recycling. Based on our experience, this cross-linked catalyst is particularly efficient for MW irradiation adsorption. [59-60]

Having optimised MW-assisted reaction condition for the synthesis of *N*-(*tert*-butyl)-4-methoxybenzamide **(3a)**, the above protocol have been subsequently applied to different aminocarbonylations using CβCAT (Scheme 2).

Scheme 2. MW-assisted aminocarbonylations using CβCAT.



As depicted in Table 3, different solvents were preliminarily tested for the aminocarbonylation of **(1)** with **(2)** in the presence of CβCAT to achieve the best catalytic performances. On the basis great results obtained before the reaction was performed under MW irradiation.Compared to $Pd(OAc)_2$, better results were obtained with polar solvents and acetonitrile was selected as the optimal one (Table 3, entry 2). With the aim to verify the method feasibility under conventional heating, the reaction in acetonitrile was repeated in a Parr reactor (80 mL) but worse results were obtained (Table 3, entry 3.

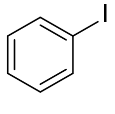
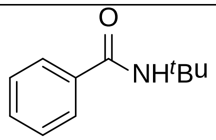
Table 3. MW-assisted aminocarbonylation of **(1)** with (**2)** in the presence of CβCAT.

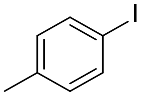
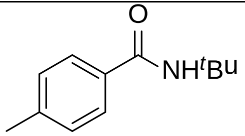
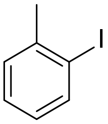
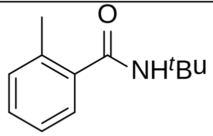
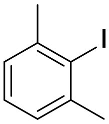
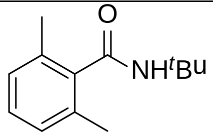
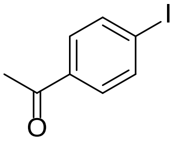
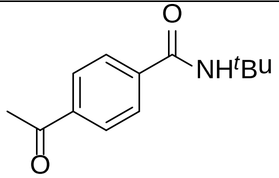
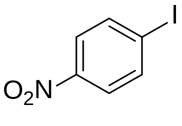
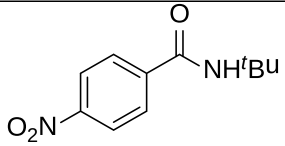
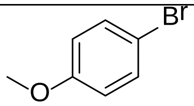
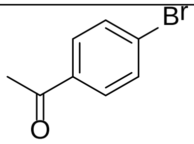
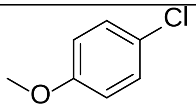
Entry[a]	**Solvent**	**Conversion (%)**[b]	**Yield (%)**[c] **(3a)**
1	Toluene	98	73
2	MeCN	100	94
3[d]	MeCN	30	28
4	THF	98	82
5	Dioxane	98	85
6	Dioxane:H_2O (8:2)	100	75
7	Dioxane:H_2O (2:8)	100	23
8	DMF	98	81

[a] Reactions were performed under MW irradiation (125 °C, 90 min) in a 1 mmol scale of (1), using 2 equiv of amine (2), 0.01 % of CβCAT and 3.5 equiv of Et_3N, CO (1 bar) and N_2 (9 bar) atmosphere. [b] Determined by GC–MS. [c] Ketoamide (**3b**) yield: always lower than 2%. d) the reaction was performed in a Parr reactor

A wide range of substrates were tested performing simultaneous MW reactions under CO pressure and achieving interesting results (Tables 4 and 5). All the products were synthesized comparing the efficiency of homogeneous *vs* heterogeneous conditions.

Table 4. CO aminocarbonylations of different aryl halides with *tert*-butylamine using CβCAT.

Entry[a]	**Aryl-X**	**Product**	**Yield (%)** **CβCAT**	**Yield (%)** **Pd(OAc)₂**
1	1	3a	94	74
2	 4	 21	100	79

3	 5	 22	95	75
4	 6	 23	74	61
5	 7	 24	41	25
6	 8	 25	83	60
7	 9	 26	78	58
8	 10	3	29 (35)[b]	2
9	 11	25	13 (21)[b]	0
10	 12	3	0 (0)[b]	0

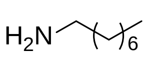
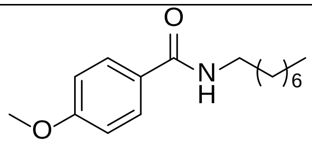
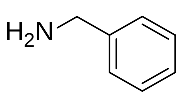
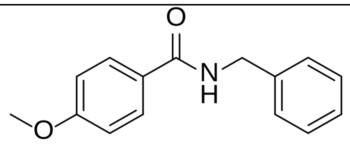
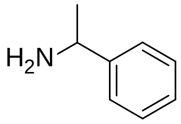
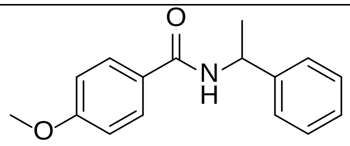
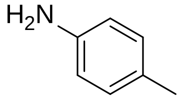
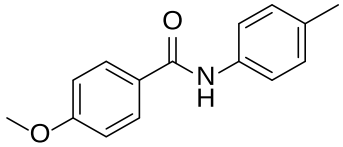
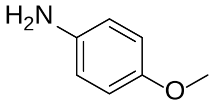
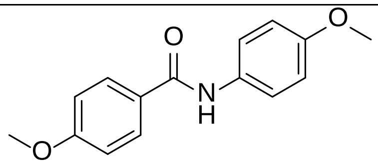
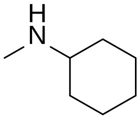
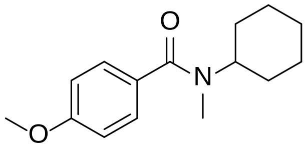
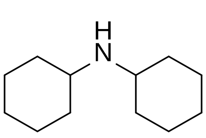
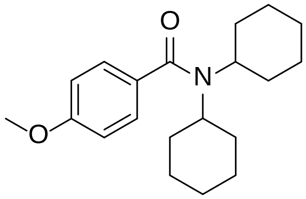
[a] Twenty reactions were performed simultaneously in the SynthWAVE reactor multi-rack position in a 2 mmol scale of aryl halides (1-12), using 2 equiv of (2), 0.01 % of CβCAT and 3.5 equiv of Et_3N in presence of CO (1 bar) and N_2 (9 bar) atmosphere (125 °C, 90 min).[b] Reactions performed at 150 °C (3 h).

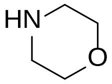
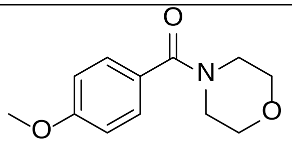
In the MW reactor (SynthWAVE, Milestone Srl - MLS Gmbh) equipped with a multi-position rack and a fine pressure control, it was possible to perform twenty simultaneous reactions (2 mmol scale x 20 tubes) at very low CO pressure (1 bar). Moreover, thanks to a multiple-gas loading system, 1 bar CO was loaded and inert and cheaper N_2 was added to reach 10 bar total pressure.

As shown in Table 4 different aryl iodides were converted to the corresponding *tert*-butylamides using our optimal MW condition in MeCN, including *ortho*-substituted compounds, even if in moderate yields (Table 4, entries 4, 5). Aryl bromides allow less product yields, meanwhile aryl chloride proved to be completely inactive even with increasing temperature up to 150 °C and MW irradiation up to 3 h (Table 4, entries 8-10).

As the 4-iodoanisole was found to produce one of the best amide yields, it was chosen as the standard electrophile for the screening of various commercially available amines such as benzylamine, *p*-toluidine, *p*-anisidine, dicyclohexylamine, morpholine, etc. The primary amines were found to be the more reactive (Table 5, entries 1-3), affording good results. The more demanding substrates, including the sterically disfavoured secondary amine **(19)** were then investigated, giving only incomplete conversion and consequently lower yields of isolated products (Table 5, entry 6-7). As already reported in the literature,[56-59] we confirmed that solid supported Pd showed better results when compared to the homogeneous phase conditions for the same amount of catalyst. The biggest advantage of the β-CD system was the very low leaching of the metals and the total capture of TPP and the TPP-oxide formed during the reaction. This greatly simplified the purification step and resulted in quantitative yields, without TPP and Pd impurities in the products.

Table 5. MW-assisted CO aminocarbonylations of 4-iodoanisole **(1)** with different amines using CβCAT.

Entry[a]	**Amine**	**Product**	**Yield (%)** **CβCAT**	**Yield (%)** **Pd(OAc)$_2$**
1	 13	 27	93	70
2	 14	 28	89	65
3	 15	 29	72	51
4	 16	 30	76	50
5	 17	 31	82	64
6	 18	 32	65	46
7	 19	 33	59	31

8	 20	 34	73	49

[a] Sixteen reactions were performed simultaneously in the SynthWAVE reactor with a multi-position rack in a 2 mmol scale of (**1**), using 2 equiv of amine (**13-20**), 0.01 % of CβCAT and 3.5 equiv of Et_3N in the presence of CO (1 bar) and N_2 (9 bar) atmosphere (125 °C, 90 min).

The optimized protocol was tested performing 10 simultaneous reactions ranging from 1 to 10 mmol level of aryl iodide (**1)** (1, 2.5, 5, 7.5 and 10 mmol, respectively) in presence of amine (**2)** or (**14)** using 0.01% of CβCAT. We flushed first the MW reactor chamber with the CO amount needed for the five reactions run simultaneously (56 mmol scale) (2 bar) and added up to 10 bar with N_2. During the course of the reaction, a drop pressure to 2 bar was observed, this clearly indicating the CO consumption. Upon reaction completion, the reactor cavity was cooled down to 40° C before releasing the residual pressure into a well-ventilated hood. Amide products (**3)** were obtained in a yield range of 75-94% and 68-89% ,respectively, in accordance with that obtained in our previous smaller–scale trials.

Table 6. Scaling up of the MW-assisted CO aminocarbonylation reaction in the presence of CβCAT.

Entry[a]	**Amine**	**mmol**	**Yield (%)**
1	(2)	1	94
2	(2)	2.5	90
3	(2)	5	89
4	(2)	7.5	83

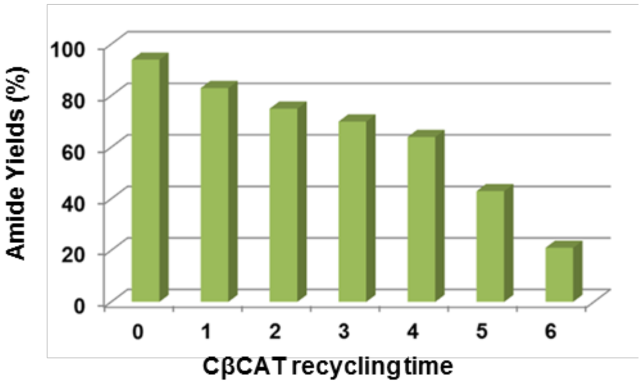
5	(2)	10	78
6	(14)	1	89
7	(14)	2.5	86
8	(14)	5	85
9	(14)	7.5	78
10	(14)	10	68

[a] Ten reactions were run simultaneously in the SynthWAVE reactor with a multi-position rack, using the noted quantity of aryl iodide (1), 2 equiv of amine (2) or (14), 0.01% of CβCAT, and 3.5 equiv of EtN_3 in the presence of MeCN. (Reaction condition: 125 °C, 90 min, CO (1.5 bar) and N_2 (8.5 bar).

2.1. CβCAT recycling

Key feature of heterogeneous catalysts are recovery and reuse, an essential perspective for green chemistry involving both ecologic and economic consideration. We also evaluated the activity and recycling of CβCAT in MW-assisted aminocarbonylation of (**1**) with (**2**) in presence of CO gas (reactions performed in MeCN at 125 °C for 90 min in the presence of CO (1.5 bar) and N_2 (8.5 bar). It should be pointed out that after the completion of the reaction the used CβCAT could be easily recovered by filtration, washed with a Petroleum Ether 40-60/EtOAc (1:1) mixture, dry under vacuum and reused under the same reaction conditions. The recovered catalyst could be reused at last five time giving consistent isolated yields of amide (**3a)** (83%, 75%, 70% and 64%, respectively) (Figure 1). The slight change may be due to the loss of catalyst during handling and transferring of β-CD catalytic system.

Figure 1. CβCAT recycling.



In this context, it is noteworthy that the β-CD network serves as an efficient metal chelator which encapsulates the organic ligand as well.

3. CONCLUSION

A highly efficient and reusable catalyst (CβCAT) has been applied for the first time to perform MW-assisted aminocarbonylation reactions under mild CO pressure. Several amide derivatives were synthesized in good yields starting from an aryl iodide/nucleophilic amine 1:2 ratio, applying a mixture of CO/N_2. This novel catalyst is well suited for MW-assisted reaction, an alternative to common palladium complexes based homogeneous catalytic systems, has competitive advantages, including easy recyclability with no significant loss in activity and selectivity and negligible leaching of the entrapped metal catalyst. This inexpensive and effective catalyst should have a bright future in industrial applications enabling the MW production of multi-kg quantities of amides starting from CO gas in a safety manner.

4. EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich (solvents from Carlo Erba SpA) and used without further purification. β-CD was kindly provided by Wacker Chemie (Munich, Germany).

CβCAT was prepared following a previously reported procedure.[59]

Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized by UV inspection and/or by heating after a spraying with 5% H_2SO_4 in ethanol or phosphomolybdic acid. MW-promoted reactions were carried out in the multimode MW reactor SynthWAVE (Milestone Srl, Italy; MLS Gmbh, Germany).

This instrument equipped with a high-pressure stainless steel reaction chamber which can work up to a maximum of 300 °C temperature and 199 bar, enables microwave reactions both in simultaneous small-scale (mL) and large scale (L) manner. Moreover, integrated reactor sensors continuously monitored the internal pressure, temperature and power applied inside the reactor cavity during all reactions run, adjusting the applied microwave power in real time to follow a predefined temperature profile.

Product purification was performed by flash-chromatography (CombiFlash RfsTeledyne ISCO) on appropriate silica cartridges. NMR spectra were recorded on a Bruker Avance 300 (operating at a magnetic field strength of 7T) at 25 °C; chemical shifts were calibrated to the residual proton and carbon resonance of deuterated solvents: $CDCl_3$ (δ H=7.26, δ C=77.16). GC-MS analyses were performed in a GC Agilent 6890 (Agilent Technologies - USA) that was fitted with a mass detector Agilent Network 5973, using a 30 m long capillary column, i.d of 0.25 mm and film thickness 0.25 µm. GC conditions were: injection split 1:20, injector temperature 250 °C, detector temperature 280 °C. Gas carrier: helium (1.2 mL/min), temperature program: from 70 °C (2 min) to 300 °C at 5 °C/min. HRMS was determined using MALDI-TOF mass spectra (Bruker Ultraflex TOF mass spectrometer). The metal content in solution was determined by ICP-MS on a Quadrupole-ICP-MS X Series II (Thermo Fisher Scientific) after the samples digestion in HNO_3 and *aqua regia*. The oxidation state of the adsorbed palladium or copper was measured by X-ray photoelectron spectroscopy (XPS) with a Quantum 2000 (PHI Co., Chanhassen, MN, USA) with a focused monochromatic Al K source (1486.7 eV) for excitation.

4.1. GENERAL PROCEDURES

Single MW-assisted aminocarbonylation procedures using Pd(OAc)$_2$

In a typical experiment 4-iodoanisole (**1**) (1 mmol) was reacted in the SynthWAVE reactor with *tert*-butylamine (**2**) (2 mmol), 0.01% of Pd(OAc)$_2$, 0.1% of TPP and Et$_3$N (3.5 mmol) in toluene or MeCN (5 mL), at 125 °C for 90 min (55 W average MW power) in the presence of CO (1 bar) and N$_2$ (9 bar) atmosphere. The reaction mixture was magnetically stirred throughout the run. Upon completion of the heating stage, before the slowly release of the internal residual pressure, the reaction chamber was cooled to 35 °C and then slowly vented and opened. Reaction solvent was removed under vacuum; the residue was dissolved in EtOAc (20 mL) and washed with HCl (2 x 20 mL, 1N), saturated NaHCO$_3$ (2 x 20 mL) and brine (2 x 20 mL). The organic phase was finally dried over Na$_2$SO$_4$ and the solvent removed by distillation. Product purification was performed by flash-chromatography (CombiFlash RfsTeledyne ISCO) on appropriate silica cartridges (petroleum ether 40-60/EtOAc = 8:2 v/v) yielded amide (**3a)** and ketoamide (**3b)**.

4.1.1. Single MW-assisted aminocarbonylation procedure using CβCAT.

In a typical experiment 4-iodoanisole (**1**) (1 mmol) was reacted in the SynthWAVE reactor with *tert*-butyl amine (**2**) (2 mmol), 0.01% of CβCAT and Et$_3$N (3.5 mmol) in toluene or MeCN (7.5 mL) at 125 °C for 90 min in the presence of CO (1 bar) and N$_2$ (9 bar) atmosphere. The reaction mixture was magnetically stirred throughout the run. Upon completion of the heating stage, before the slowly release of the internal residual pressure, the reaction chamber was cooled to 35 °C and then slowly vented and opened. The CβCAT was filtered off on a sintered-glass Buchner funnel and washed twice with EtOAc. Organic solvents were removed under vacuum and the residue was dissolved in EtOAc (20 mL) and washed with HCl (2 x 20 mL, 1N), saturated $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL). The organic phase was dried over Na_2SO_4 and the solvent removed by distillation. Product purification was performed by flash-chromatography (CombiFlash RfsTeledyne ISCO) on appropriate silica cartridges (petroleum ether 40-60/EtOAc = 8:2 v/v) yielded amide (**3a)** and ketoamide (**3b)**. The crude products do not require further purification for metal contamination showed by ICP-MS analysis (Pd content < 6-8 ppm in all cases).

4.1.2. Simultaneous MW-assisted aminocarbonylation of aryl iodides with different amines with CβCAT.

To each of twenty reaction vessels (15 mL capacity) equipped with magnetic stir bar and placed into a multiple-position rack all, reagents and catalyst were added: aryl halide (**1** or **4-12**) (2 mmol), CβCAT (0.01%), 0.1 % of TPP, Et_3N (3.5 mmol) and the corresponding amine (**2** or **13-20**) (2 mmol) in MeCN (7.5 mL). The multiple-position rack was immersed few cm in ethylene glycol (250 mL) present in the reactor cavity (1L Teflon® vessel) as a moderating fluid. The vessel was loaded and purged three times with N_2 then loaded with 1 bar CO (a near-stoichiometric amount based on the twenty reactions tubes) and further pressurized by N_2 (9 bar), giving a total pressure of 10 bar. An identical heating program was used as in previous single experiments (MW heating at 125 °C for 90 min). After reaction completion, each product mixture was worked up individually using the same protocol as previously described for the single reaction procedure, thus obtaining amides (**21-34)** in good to excellent yields. The crude products do not require further purification for metal contamination showed by ICP-MS analysis (Pd content < 6-8 ppm in all cases).

4.2. *CβCAT recycling*

In a typical experiment 4-iodoanisole (**1**) (1 mmol) was reacted in the SynthWAVE reactor with *tert*-butyl amine (**2**) (2 mmol), 0.01% of CβCAT and Et_3N (3.5 mmol) in MeCN (7.5 mL) at 125 °C for 90 min in the presence of CO (1.5 bar) and N_2 (8.5 bar) atmosphere.

The previous reaction procedure was followed and the CβCAT was filtered off on a sintered-glass Buchner funnel and washed with a petroleum ether 40-60/EtOAc (1:1) mixture (3 x 20 mL), dry under vacuum and reused in the next run under the same reaction conditions. Using the same work up protocol, the amide (**3a)** was obtained in 83%, 75%, 70%, 64%, 43% and 21% yields, respectively, after each recycle.

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ASSOCIATED CONTENT

The characterization of products are reported in supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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