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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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3 ABSTRACT
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5 The incorporation of the carbonyl moiety into organic molecules using a three-component
6 matrix, including carbon monoxide, an organic halide and a nucleophilic component offers a
7 simple and versatile approach to the formation of carboxylic acids, anhydrides, esters, amides
8 and ketones. The design of a sustainable synthetic protocol for aminocarbonylation can be
9 efficiently accomplished using a multi-faceted strategy that combines solid green catalysts and
10 suitable enabling techniques. The safe and synergistic use of carbon monoxide in a microwave
11 reactor under pressure may be able to create a technological breakthrough in aminocarbonylation
12 reactions. Moreover, a new recyclable catalytic system “C β CAT” based on Pd(II)-
13 triphenylphosphine embedded in cross linked β -cyclodextrin (hexamethylene diisocyanate) has
14 been found to be very efficient in aryl iodide aminocarbonylation reactions.
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31 KEYWORDS
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34 Microwaves; Aminocarbonylation; Carbon Monoxide; Heterogeneous catalysis; Palladium.
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1. INTRODUCTION

The term ‘carbonylation’, coined by Reppe in the ‘30s, includes a plethora of reactions¹ such as formylation,² hydroformylation, alkoxy carbonylation,^{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 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 The recent advancements in aminocarbonylation reactions,¹⁶ that exploit the use of carbon monoxide (CO), are truly noteworthy. Being a versatile and cost efficient C₁ building block reagent (in combination with transition metal catalysis),¹⁷⁻¹⁸ CO enables “amide bond formation avoiding poor atom economy reagents” as voted by The American Chemical Society Green Chemistry Institute in 2007 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 high number of aminocarbonylation protocols described in the literature which use it as a carbonyl group source,²¹ its true potential has not been fully realised in lab-scale synthesis due to the troublesome handling of CO gas.

To overcome the safety problems involved in using CO gas, several groups have developed CO-equivalents such as alkyl formates,²² formic anhydride and *N*-substituted formamide,²³⁻²⁷ carbamoylstannanes,²⁸ carbamoylsilane,²⁹ silacarboxylic acids,³⁰ and acid chloride

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3 derivatives.^{31,32} However, this approach requires harsh reaction conditions for CO release, such
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5 as the presence of a strong base combined with high temperatures and long reaction times.
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8 Another class of solid *in situ* CO-releasing reagents are metal carbonyls,³³⁻³⁹ which are
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10 currently the best alternative to CO-gas for aminocarbonylation.⁴⁰⁻⁴¹ These inorganic metal
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12 carbonyls and their derivatives are nevertheless CO releasers and relatively expensive.
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14 Moreover, they require near stoichiometric amounts of an additional transition metal to work,
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16 which can encumber the purification of the desired amide products.⁴² To avoid this problem and
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18 enable the reuse of the high-cost catalyst/ligand system, it is necessary to address the
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20 sustainability problems of aminocarbonylation reactions. Under the relentless demand to develop
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22 ever more efficient methods for amide production, in particular in the pharmaceuticals industry,
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24 the synthetic routes which make use of CO gas' high reactivity may offer clear advantages over
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26 the aforementioned alternative CO-sources despite entailing certain hazards, which can be
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28 avoided using suitable equipment.⁴³ The use of inexpensive and easily reusable catalytic systems
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30 combined with the new enabling technologies can make this process cost-effective.
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36 In synthetic organic chemistry, one of the most direct ways to pursue green chemistry is the
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38 use of “enabling technologies” that include traditional techniques such as “solid phase synthesis”
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40 and heterogeneous catalysis as well as relatively new ones such as “microwave (MW)-assisted
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42 synthesis”, “continuous flow reactors” etc. which were developed to speed up synthetic
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44 transformations and ease process workup.⁴⁴ Heterogeneous catalysts bring the efficacy of a
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46 highly active immobilized catalyst as well as simplifying reaction workup, as they are often
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48 readily removed by filtration. Our experience has helped us to use cross-linked chitosan Pd(II)
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50 complexes to give successful results in MW-catalysed Suzuki reactions.⁴⁵ Excellent catalytic
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52 activity has been obtained in Heck, Suzuki and Sonogashira reactions with Pd(II)-based cross-
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3 linked β -cyclodextrin (β -CD) catalysts which are obtained via the *in situ* polymerization of β CD
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5 with diisocyanates under ultrasound irradiation in the presence of Pd salts and TPP.^{46,47}
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8 Nowadays, there is no doubt that MW-assisted chemistry has helped to radically reduce
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10 reaction times, increase product yields, minimize catalyst loading and reagent excess. Under
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12 MW irradiation, reactions are well-targeted and uniformly heated at extraordinarily high rates
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14 that cannot be reproduced under classical heating.⁴⁸⁻⁵⁰ However, few publications describe this
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16 technique with gaseous reagents in a closed vessel and in heterogeneous gas-phase reactions. To
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18 the best of our knowledge, very few reports deal with the use of CO gas as an
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20 aminocarbonylation reagent inside a MW oven.^{51,52}
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24 In the course of our quest for aminocarbonylation procedures which are suitable for MW-
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26 accelerated high-speed chemistry,⁵³ and using our experience in MW promoted reactions with
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28 gaseous reagents in a closed pressurized cavity,^{54,55} we herein describe a fast MW-assisted
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30 Pd(II)-catalysed protocol for the synthesis of amides using CO gas. The aim of the work is to
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32 maximize the advantages of MW technology in the presence of catalytic systems which are
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34 immobilized on other polar matrices. This investigation carries out the optimization of a
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36 heterogeneous phase protocol in the presence of a supported Pd catalyst (C β CAT). The catalyst
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38 was chosen because it combines high metal performance and high MW adsorption efficacy,
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40 while the β CD is able to complex the TPP ligand making the catalyst more effective. The
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42 influence of different substituents on the aryl halides on reaction outcome, and different
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44 nucleophiles on catalyst performance as well as catalyst recycling are also studied in this
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50 investigation.
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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 *t*-butylamine (2 equiv) as a nucleophile, has been investigated as the model reaction for optimization. Our initial efforts were directed at performing comparison experiments in the presence of triethylamine (Et₃N) and TPP, as a base and ligand, using palladium acetate (0.1 %) instead of the heterogeneous C β CAT 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 enables multiple gas loading (inert and/or reactive gas) and simultaneous reaction runs.

It was observed that performing the aminocarbonylation of **(1)** in the presence of 2 equiv of nucleophile **(2)**, a 82 % amide yield **(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 N₂) in the presence of Et₃N (3.5 equiv) and TPP ligand (0.1%) (Table 1, entry 4). No improvements were detected when the MW irradiation time was increased to 2 h (Table 1, entry 6). Several nucleophile to aryl iodide molar ratios were tested in toluene in order to maximize the conversion and selectivity of **3a** with respect to the ketoamide side product **(3b)** (Table 1, entries 2, 3, 4 and 5). A ratio of 2:1 furnished the best results, giving 96% conversion and 82% yield. The influence of CO pressure on MW aminocarbonylation was also investigated. Raising CO pressure from 1 to 2.5 bar did not give any improvement in **3a** product yield (Table 1, entries 4, and 7), but, as expected, a slight increase in ketoamide **(3b)** formation (up to 25%) was observed 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 results⁵⁴, the amount of Pd(OAc)₂

was increased to 5%. Complete conversion was obtained after 8 h of heating at 100 °C and the desired product was collected in a 69% yield (Table 1, entry 9).

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

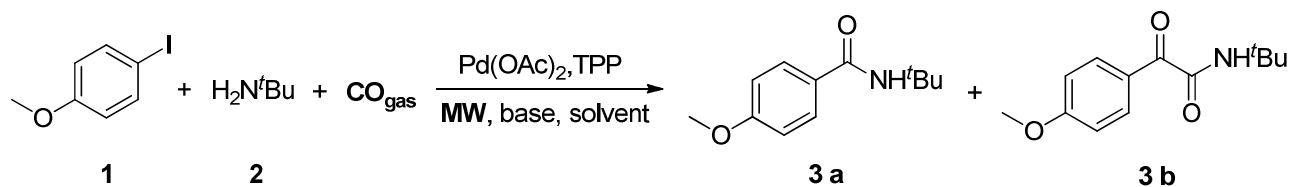


Table 1. Optimisation conditions for the MW-assisted aminocarbonylation of 4-iodoanisole (**1**) with *t*-butylamine (**2**) to **3a** in the presence of Pd(OAc)₂.^a

Entry	Reaction conditions				Conversion (%) ^b	Yield (%)	
	Solvent	H ₂ N ^{<i>t</i>} Bu (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	2 5
10	MeCN	2	1	1.5	89	74	1 1

11	THF	2	1	1.5	80	68	10
12	Dioxane	2	1	1.5	75	59	7
13	Dioxane:H ₂ O (8:2)	2	1	1.5	89	35	<5
14	Dioxane:H ₂ O (2:8)	2	1	1.5	95	21	<5
15	DMF	2	1	1.5	81	70	8

a Reaction conditions: 4-iodoanisole (1, 1 mmol), *t*-butylamine (2), 0.01% of Pd(OAc)₂, 0.1% of TPP and Et₃N (3.5 mmol) in 5 mL of solvent, 125 °C (55 W average MW power) in the presence of a CO and N₂ (9 bar) atmosphere b Determined by GC–MS; c The reaction was performed under conventional conditions. 5% Pd(OAc)₂, TPP (0.1 mmol), Et₃N (3.5 mmol) in 10 mL toluene, 1 bar CO. The solution was heated at 100°C for 8 h.⁵¹

A reduction in reaction yields was noticed (Table 1, entries 10, 11, 12, 15) as we moved from toluene to more polar non-nucleophilic solvents (such as MeCN, THF, dioxane or DMF). As expected, a benzoic acid derivative was detected as the main reaction product when a mixture of dioxane:H₂O (8:2 or 2:8) was used as greener reaction solvent (Table 1, entries 13, 14).

Product yields generally increased slightly (7%) at higher catalyst loading (from 0.01% to 0.1% (Table 2, entry 1-4). Meanwhile, without the TPP ligand, only a poor (**3a**) yield was obtained and no reaction product was detected when Et₃N was omitted 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 Et₃N (Table 2, entries 7-9). Lower reaction temperatures, from 125 °C to 85 °C, were then investigated (Table 2, entries 10-12). The reported results show that yields increase with reaction temperature, while ketoamide selectivity was much higher at lower temperature (Table 2, entries 10-12).

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

Entry	Reaction condition ^a			Conversion(%) ^b	Yield (%)	
	Base (equiv)	Pd(OAc) ₂ (%)	Temp. (°C)		(3a)	(3b)
1	Et ₃ N (3.5)	0.1	125	100	89 (29) ^c (0) ^d	8
2	Et ₃ N (3.5)	0.05	125	99	86	<5
3	Et ₃ N (3.5)	0.02	125	97	84	<5
4	Et ₃ N (3.5)	0.01	125	96	82 (28) ^c (0) ^d	<5
5	Et ₃ N (2.5)	0.01	125	87	71	10
6	Et ₃ N (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 ₃ N (3.5)	0.01	115	89	71	14
11	Et ₃ N (3.5)	0.01	100	83	59	17
12	Et ₃ N (3.5)	0.01	85	75	42	21

^a Reactions performed under MW irradiation (90 min) on a 1 mmol scale of (1), using 2 equiv of amine (2), in presence of CO (1 bar) and N₂ (9 bar) atmosphere ^b Determined by GC-MS. ^c Reaction performed without TPP ligand. ^d Reaction performed without Et₃N.

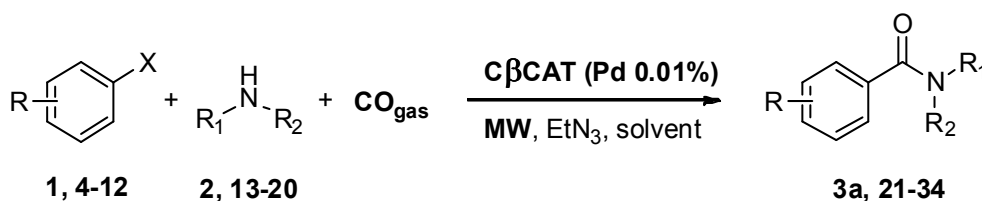
The recovery and recycling of the Pd catalyst from the product mixture is still a big challenge. Heterogeneous catalysts can simplify workup procedures without contaminating desired products with heavy metals and can be reused. Therefore, Pd(AcO)₂ was entrapped in the presence of the TPP ligand on a β-CD cross-linked polymer, thus forming the CβCAT catalyst.

CβCAT was simply obtained via the sonochemical reticulation of (β-CD) with hexamethylene diisocyanate (HDI) in a solution containing Pd(II) salts and triphenylphosphine (TPP). Metal

content was measured by ICP and a 0.65% average was obtained. Moreover, ICP analysis indicated negligible metal leaching, while the absence of TPP or TPPO in the reaction filtrate demonstrated the potential of this catalyst for recycling. Based on our experience, this cross-linked catalyst is particularly efficient owing to the intense MW adsorption.⁵⁹⁻⁶⁰

Having optimised the MW-assisted reaction conditions for the synthesis of *N*-(*t*-butyl)-4-methoxybenzamide (**3a**), the above protocol was subsequently applied to different aminocarbonylations using C β CAT (Scheme 2).

Scheme 2. MW-assisted aminocarbonylations using C β CAT.



As depicted in Table 3, numerous solvents were preliminarily tested for the aminocarbonylation of **(1)** with **(2)** in the presence of C β CAT to achieve the best catalytic performance. The great results obtained previously lead us to performing the reaction under MW irradiation. Compared to Pd(OAc)₂, better results were obtained with polar solvents and acetonitrile was selected as the optimal choice (Table 3, entry 2). The reaction in acetonitrile was repeated in a Parr reactor (80 mL), with the aim of verifying method feasibility under conventional heating, but worse results were obtained (Table 3, entry 3).

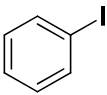
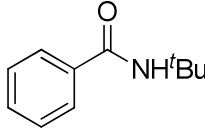
Table 3. MW-assisted aminocarbonylation of (1) with (2) in the presence of C β CAT.

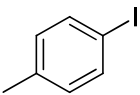
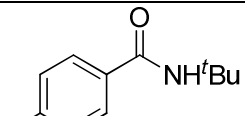
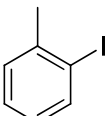
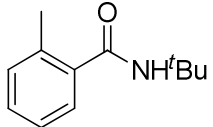
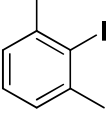
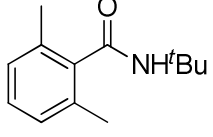
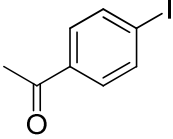
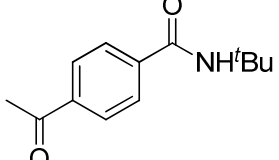
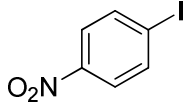
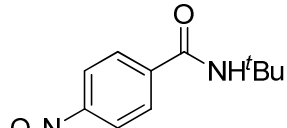
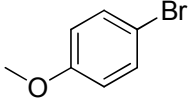
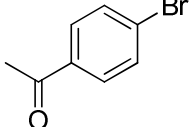
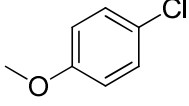
Entry ^a	Solvent	Conversion (%) ^b	Yield (%) ^c (3a)
1	Toluene	98	73
2	MeCN	100	94
3 ^d	MeCN	30	28
4	THF	98	82
5	Dioxane	98	85
6	Dioxane:H ₂ O (8:2)	100	75
7	Dioxane:H ₂ O (2:8)	100	23
8	DMF	98	81

^a Reactions were performed under MW irradiation (125 °C, 90 min) on a 1 mmol scale of (1), using 2 equiv of amine (2), 0.01 % of C β CAT and 3.5 equiv of Et₃N, CO (1 bar) and N₂ (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 as simultaneous MW reactions were performed under CO pressure and interesting results were achieved (Tables 4 and 5). All the products were synthesized and the efficiency of homogeneous and heterogeneous conditions compared.

Table 4. CO aminocarbonylations of different aryl halides with *t*-butylamine using C β CAT.

Entry ^a	Aryl-X	Product	Yield (%)	
			C β CAT	Pd(OAc) ₂
1	1	3a	94	74
2			100	79
	4	21		

3			95	75
4			74	61
5			41	25
6			83	60
7			78	58
8		3	29 (35) ^b	2
9		25	13 (21) ^b	0
10		3	0 (0) ^b	0

^a Twenty reactions were performed simultaneously in the SynthWAVE reactor multi-rack position on a 2 mmol aryl halide scale (1-12), using 2 equiv of (2), 0.01 % of C β CAT and 3.5 equiv of Et₃N in presence of CO (1 bar) and N₂ (9 bar) atmosphere (125 °C, 90 min).^b Reactions performed at 150 °C (3 h).

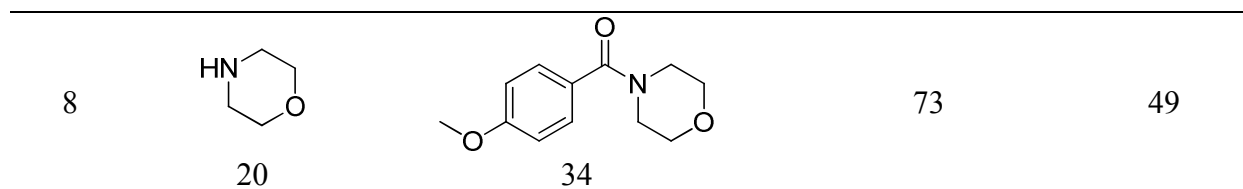
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3 It was possible to perform twenty simultaneous reactions (2 mmol scale x 20 tubes) at very low
4 CO pressures (1 bar) in the MW reactor (SynthWAVE, Milestone Srl - MLS GmbH) which was
5 equipped with a multi-position rack and a fine pressure control. Moreover, 1 bar CO was loaded
6 and the inert and cheaper N₂ was added to achieve 10 bar of total pressure, thanks to a multiple-
7 gas loading system.
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10 As shown in Table 4, different aryl iodides were converted to the corresponding *t*-butylamides
11 using our optimal MW condition in MeCN, including *ortho*-substituted compounds, even if in
12 moderate yields (Table 4, entries 4, 5). Aryl bromides give lower product yields, while aryl
13 chloride proved to be completely inactive even when the temperature was increased to 150 °C
14 and MW irradiation up to 3 h (Table 4, entries 8-10).
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17 As 4-iodoanisole was found to produce one of the best amide yields, it was chosen as the
18 standard electrophile for the screening of various commercially available amines such as
19 benzylamine, *p*-toluidine, *p*-anisidine, dicyclohexylamine and morpholine, etc. The primary
20 amines were found to be more reactive (Table 5, entries 1-3), and gave good results. The more
21 demanding substrates, including the sterically disfavoured secondary amine (**19**), were then
22 investigated. They only gave incomplete conversion and consequently lower isolated product
23 yields (Table 5, entry 6-7). As already reported in the literature,⁵⁶⁻⁵⁹ we confirmed that solid
24 supported Pd showed better results than homogeneous phase conditions for the same amount of
25 catalyst. The biggest advantage of the β-CD system is the very low metal leaching and the total
26 capture of TPP and the TPP-oxide formed during the reaction. This greatly simplifies the
27 purification step and resulted in quantitative yields, without TPP and Pd impurities in the
28 products.
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Table 5. MW-assisted CO aminocarbonylations of 4-iodoanisole (**1**) with different amines using C β CAT.

Entry ^a	Amine	Product	Yield (%) C β CAT	Yield (%) Pd(OAc) ₂
1			93	70
2			89	65
3			72	51
4			76	50
5			82	64
6			65	46
7			59	31



^a Sixteen reactions were performed simultaneously in the SynthWAVE reactor with a multi-position rack on a 2 mmol scale of (**1**), using 2 equiv of amine (**13-20**), 0.01 % of C β CAT and 3.5 equiv of Et₃N in the presence of CO (1 bar) and N₂ (9 bar) atmosphere (125 °C, 90 min).

The optimized protocol was tested over 10 simultaneous reactions which ranged from 1 to 10 mmol aryl iodide levels (**1**) (1, 2.5, 5, 7.5 and 10 mmol, respectively) in presence of amine (**2**) or (**14**) using 0.01% C β CAT. We flushed the MW reactor chamber first with the CO amount needed for the five reactions run simultaneously (56 mmol scale) (2 bar) and added up to 10 bar using N₂. During the course of the reaction, a drop in pressure to 2 bar was observed, this clearly indicated CO consumption. Upon reaction completion, the reactor cavity was cooled down to 40° C, before the residual pressure was released into a well-ventilated hood. Amide products (**3**) were obtained in yield ranges of 75-94% and 68-89%, which are in accordance with results obtained in our previous smaller-scale trials.

Table 6. Scaling up of the MW-assisted CO aminocarbonylation reactions in the presence of C β CAT.

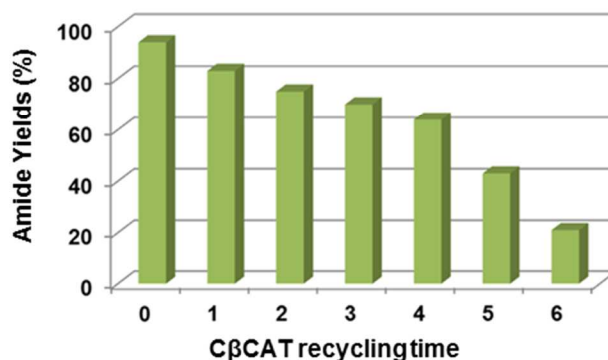
Entry ^a	Amine	mmol	Yield (%)
1	(2)	1	94
2	(2)	2.5	90
3	(2)	5	89
4	(2)	7.5	83

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 C β CAT, and 3.5 equiv of EtN₃ in the presence of MeCN. (Reaction condition: 125 °C, 90 min, CO (1.5 bar) and N₂ (8.5 bar).

2.1. C β CAT recycling

Key features of heterogeneous catalysts are recovery and reuse; essential considerations for green chemistry which looks to both the ecologic and economic. We also evaluated the activity and recycling of C β CAT in the MW-assisted aminocarbonylation of (1) with (2) in the presence of CO gas (reactions performed in MeCN at 125 °C for 90 min in the presence of CO (1.5 bar) and N₂ (8.5 bar). It should be pointed out that the C β CAT used was easily recovered by filtration after the completion of the reaction and washed with a Petroleum Ether 40-60/EtOAc (1:1) mixture, dried under vacuum and reused under the same reaction conditions. The recovered catalyst was reused at least five times and gave consistent isolated amide yields (3a) (83%, 75%, 70% and 64%, respectively) (Figure 1). The slight change may be due to a loss of catalyst during handling of the β -CD catalytic system.

Figure 1. C β CAT recycling.

In this context, it is worth noting 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 (C β CAT) has been applied to MW-assisted aminocarbonylation reactions under mild CO pressure for the first time. Several amide derivatives have been synthesized from an aryl iodide/nucleophilic amine 1:2 ratio in good yields, using a CO/N₂ mixture. This novel catalyst is well suited to MW-assisted reactions, 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 entrapped metal catalyst leaching. This inexpensive and effective catalyst should have a bright future in industrial applications and enable the MW production of multi-kg quantities of amides from CO gas in a safe 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).

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3 C β CAT was prepared following a previously reported procedure.⁵⁹
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5
6 Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized
7
8 by UV inspection and/or by heating after a spraying with 5% H₂SO₄ in ethanol or
9
10 phosphomolybdic acid. MW-promoted reactions were carried out in a multimode MW reactor
11
12 SynthWAVE (Milestone Srl, Italy; MLS GmbH, Germany).
13

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15 This instrument is equipped with a high-pressure stainless steel reaction chamber which can
16
17 work up to a maximum of 300 °C and 199 bar and enables microwave reactions both on a
18
19 simultaneous small-scale (mL) and a large scale (L). Moreover, integrated reactor sensors
20
21 continuously monitored the internal pressure, temperature and power applied inside the reactor
22
23 cavity during all runs and adjusted the applied microwave power in real time to follow a
24
25 predefined temperature profile.
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28
29 Product purification was performed via flash-chromatography (CombiFlash RfsTeledyne
30
31 ISCO) on appropriate silica cartridges. NMR spectra were recorded on a Bruker Avance 300
32
33 (operating at a magnetic field strength of 7T) at 25 °C; chemical shifts were calibrated to the
34
35 residual proton and carbon resonance of deuterated solvents: CDCl₃ (δ H=7.26, δ C=77.16). GC-
36
37 MS analyses were performed in a GC Agilent 6890 (Agilent Technologies - USA) that was fitted
38
39 with a mass detector Agilent Network 5973, using a 30 m long capillary column, i.d of 0.25 mm
40
41 and film thickness 0.25 μ m. GC conditions were: injection split 1:20, injector temperature 250
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43 °C, detector temperature 280 °C. Gas carrier: helium (1.2 mL/min), temperature program: from
44
45 70 °C (2 min) to 300 °C at 5 °C/min. HRMS was determined using a MALDI-TOF mass spectra
46
47 (Bruker Ultraflex TOF mass spectrometer). The metal content in solution was determined by
48
49 ICP-MS on a Quadrupole-ICP-MS X Series II (Thermo Fisher Scientific) after sample digestion
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51 in HNO₃ and *aqua regia*. The oxidation state of the adsorbed palladium or copper was measured
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3 by X-ray photoelectron spectroscopy (XPS) with a Quantum 2000 (PHI Co., Chanhassen, MN,
4 USA) with a focused monochromatic Al K source (1486.7 eV) for excitation.
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10 11 4.1. GENERAL PROCEDURES

12 13 *Single MW-assisted aminocarbonylation procedures using Pd(OAc)₂*

14
15 In a typical experiment, 4-iodoanisole (**1**) (1 mmol) was reacted in the SynthWAVE reactor
16 with *t*-butylamine (**2**) (2 mmol), 0.01% of Pd(OAc)₂, 0.1% of TPP and Et₃N (3.5 mmol) in
17 toluene or MeCN (5 mL), at 125 °C for 90 min (55 W average MW power) in the presence of
18 CO (1 bar) and N₂ (9 bar) atmosphere. The reaction mixture was magnetically stirred throughout
19 the run. Upon completion of the heating stage, the reaction chamber was cooled to 35 °C and
20 then slowly vented and opened, before the slow release of the internal residual pressure. The
21 reaction solvent was removed under vacuum; the residue was dissolved in EtOAc (20 mL) and
22 washed with HCl (2 x 20 mL, 1N), saturated NaHCO₃ (2 x 20 mL) and brine (2 x 20 mL). The
23 organic phase was finally dried over Na₂SO₄ and the solvent removed by distillation. Product
24 purification was performed by flash-chromatography (CombiFlash RfsTeledyne ISCO) on
25 appropriate silica cartridges (petroleum ether 40-60/EtOAc = 8:2 v/v) yielding amide (**3a**) and
26 ketoamide (**3b**).
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46 47 *4.1.1. Single MW-assisted aminocarbonylation procedure using CβCAT.*

48
49 In a typical experiment 4-iodoanisole (**1**) (1 mmol) was reacted in the SynthWAVE reactor
50 with *t*-butyl amine (**2**) (2 mmol), 0.01% of CβCAT and Et₃N (3.5 mmol) in toluene or MeCN
51 (7.5 mL) at 125 °C for 90 min in the presence of CO (1 bar) and N₂ (9 bar) atmosphere. The
52 reaction mixture was magnetically stirred throughout the run. Upon completion of the heating
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3 stage, the reaction chamber was cooled to 35 °C and then slowly vented and opened, before the
4
5 slow release of the internal residual pressure. The C β CAT was filtered off on a sintered-glass
6
7 Buchner funnel and washed twice with EtOAc. Organic solvents were removed under vacuum
8
9 and the residue was dissolved in EtOAc (20 mL) and washed with HCl (2 x 20 mL, 1N),
10
11 saturated NaHCO₃ (2 x 20 mL) and brine (2 x 20 mL). The organic phase was dried over Na₂SO₄
12
13 and the solvent removed by distillation. Product purification was performed by flash-
14
15 chromatography (CombiFlash RfsTeledyne ISCO) on appropriate silica cartridges (petroleum
16
17 ether 40-60/EtOAc = 8:2 v/v) yielding amide (**3a**) and ketoamide (**3b**). The crude products did
18
19 not require further purification for metal contamination as shown by ICP-MS analysis (Pd
20
21 content < 6-8 ppm in all cases).
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29 *4.1.2. Simultaneous MW-assisted aminocarbonylation of aryl iodides with different amines*
30
31 *with C β CAT.*
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34 All reagents and catalyst were added to each of twenty reaction vessels (15 mL capacity)
35
36 equipped with a magnetic stir bar and placed into a multiple-position rack: aryl halide (**1** or **4-12**)
37
38 (2 mmol), C β CAT (0.01%), 0.1 % of TPP, Et₃N (3.5 mmol) and the corresponding amine (**2** or
39
40 **13-20**) (2 mmol) in MeCN (7.5 mL). The multiple-position rack was immersed in a few cm of
41
42 ethylene glycol (250 mL) present in the reactor cavity (1L Teflon[®] vessel) as a moderating fluid.
43
44 The vessel was loaded and purged three times with N₂ then loaded with 1 bar CO (a near-
45
46 stoichiometric amount based on the twenty reactions tubes) and further pressurized by N₂ (9 bar),
47
48 giving a total pressure of 10 bar. An identical heating program was used as in previous single
49
50 experiments (MW heating at 125 °C for 90 min). After reaction completion, each product
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52 mixture was worked up individually using the same protocol as previously described in the
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3 single reaction procedure, thus giving amides (**21-34**) in good to excellent yields. The crude
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5 products did not require further purification for metal contamination, as shown by ICP-MS
6
7 analysis (Pd content < 6-8 ppm in all cases).
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10 11 12 13 4.2. C β CAT recycling 14

15 In a typical experiment, 4-iodoanisole (**1**) (1 mmol) was reacted in the SynthWAVE reactor
16
17 with *t*-butyl amine (**2**) (2 mmol), 0.01% of C β CAT and Et₃N (3.5 mmol) in MeCN (7.5 mL) at
18
19 125 °C for 90 min in the presence of a CO (1.5 bar) and N₂ (8.5 bar) atmosphere.
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22 The previous reaction procedure was followed and the C β CAT was filtered off on a sintered-
23
24 glass Buchner funnel and washed with a petroleum ether 40-60/EtOAc (1:1) mixture (3 x 20
25
26 mL), dried under vacuum and reused in the next run under the same reaction conditions. Using
27
28 the same work up protocol, the amide (**3a**) was obtained in 83%, 75%, 70%, 64%, 43% and 21%
29
30 yields, respectively, after each recycle.
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6
7
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9
10 Framework Program.
11

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15 ASSOCIATED CONTENT
16

17 The product characterization is reported in the supporting information. This material is available
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19 free of charge via the Internet at <http://pubs.acs.org>.
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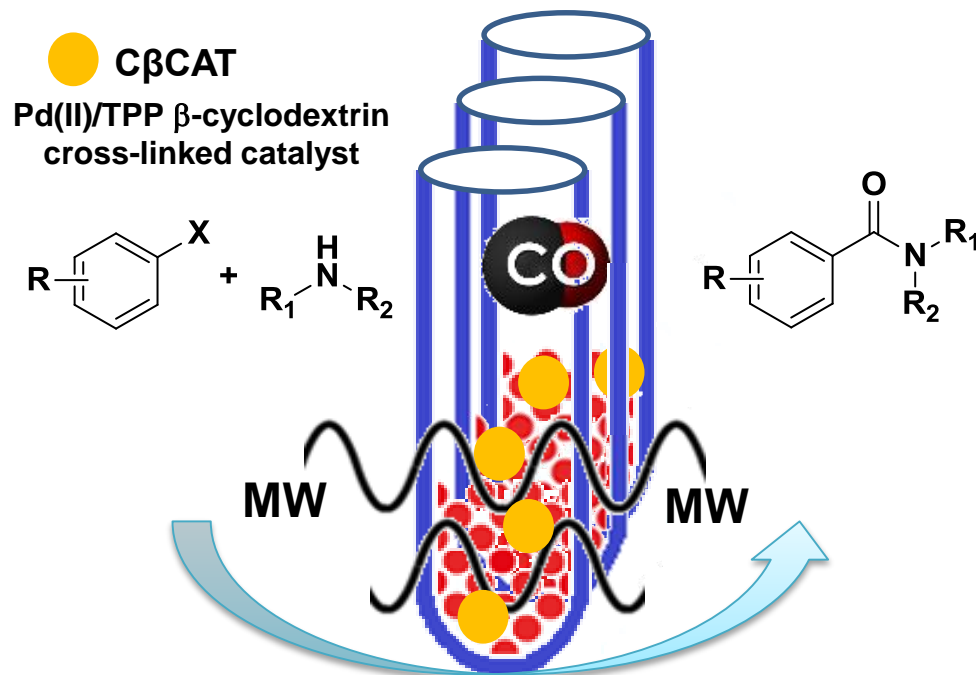


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