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A green approach to heterogeneous catalysis using ligand-free, metal-loaded cross-linked cyclodextrins

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Abstract

In this work, we describe the application of a new series of solid cross-linked cyclodextrin (α-, β-, and γ-CD) based catalysts that are obtained by reticulation with hexamethylene diisocyanate (HDI) in solutions containing $Pd^{(II)}$ or $Cu^{(I)}$ cations. Diisocyanates are efficient cross-linking agents for CDs because of their high reactivity towards hydroxyl groups. Metal content in the polyurethane-bridged CD polymers has been analyzed using ICP-MS. $Pd^{(II)}$ based catalysts have been successfully used in C-C couplings (Heck and Suzuki reactions), and a $Cu^{(I)}$ based system has been used in alkyne/azide [3+2] cycloadditions. Because metal leaching is negligible, which allows it to be recycled, and preparation is facile, this protocol is truly sustainable. As confirmed by ICP-MS analysis, the crude products do not require further purification for metal contamination. This versatile catalyst, due to its polar structure, is particularly suitable for microwave (MW)-assisted reactions that, in this study, gave the best yields in shorter reaction times. Due to their polar structure, both native CDs and cross-linked derivatives are very sensitive to dielectric heating; this effect is enhanced by the embedded cations. The design of sustainable synthetic protocols can be efficiently accomplished using a multi-faceted strategy that combines innovative solid catalysts and suitable enabling technologies.

Keywords: click chemistry; cross-linked cyclodextrins; Heck and Suzuki reactions; heterogeneous catalysis; $Pd^{(II)}$/$Cu^{(I)}$ catalysts.

1. Introduction

Reticulated cyclodextrins (CDs) have been applied in several fields [1–3], and a wide range of reactive CD derivatives have been described [4]. In recent years, polycyclodextrin derivatives have found a number of applications as enzyme stabilizers [5], as solid-phase adsorbents of pollutants [6] and for the removal of $Cu^{(II)}$ in aqueous solutions [7]. We studied different reticulation methods with diisocyanates, arylcarbonates and epichlorohydrin [8]. CD reticulation in the presence of metal ions in solution is not unprecedented, and recently the preparation of superparamagnetic β-CD-functionalized composite nanoparticles via the epichlorohydrin cross-linking of carboxymethyl β-CD-modified magnetite (Fe_3O_4) nanoparticles has been reported [9]. The inclusion phenomenon can occur either in the CD cavity or in other larger cavities that are generated by the reticulation. The location of the inclusion depends on the radius of the cations [10] and the type of CD [11]. An alternative solid catalyst preparation method can be found in the simple physical mixture of the metal salt and the polyurethane-bridged CDs in a planetary ball mill. A similar approach has recently been described for chitosan based Pd-catalysts in which the simple physical mixture [12] was compared to metal-loaded cross-linked chitosan [13]. In addition, when used in MW-assisted reactions, this catalyst is strongly activated by ball milling [14], which allows the solid-state Suzuki cross-coupling of poorly reactive (hetero) aryl chlorides with phenylboronic acid to be performed [15]. Other authors have used several supported metals (Pt, Pd, Rh and Ru) integrated onto a β-CD polymer (epichlorohydrin) as catalysts. These metals were prepared by refluxing a suspension of the corresponding metal salt and a β-CD polymer in either a mixed methanol-water or methanol-NaOH solution [16]. These heterogeneous catalysts were applied in enantioselective olefin hydrogenation. We recently described the preparation and synthetic application of a new series of metal-loaded ($Pd^{(II)}$ and $Cu^{(I)}$) catalysts that are based on cross-linked native β-CD and reticulated with different diisocyanates under sonication [17]. Excellent yields were observed for Sonogashira reactions performed in water and glycerol, and the catalyst was easily recovered and reused three times without a significant loss in catalytic activity. In the present study, we extend ultrasound-promoted HDI reticulation in the presence of $Pd^{(II)}$ and/or $Cu^{(I)}$ salts to α- and γ-CD. These versatile catalysts were tested in several reactions, both under conventional heating and MW irradiation. The $Pd^{(II)}$ loaded polymers were used to perform Heck and Suzuki cross-couplings, whereas the catalysts that bear $Cu^{(I)}$ were used to carry out alkyne/azide [3+2] cycloadditions (CuAAC).

Over the last decade, a huge effort has been made in the search for cost-effective, ligand-free Pd or Cu catalysts and new activation techniques to perform highly efficient C-C couplings [18] and click reactions [19]. Simple metal salts, metals supported on active charcoal or metal-loaded polymers have been efficiently used under ultrasound [20] and MW irradiation [12, 13], and even under simultaneous irradiation [21–23], which tends to give better results. Although high turnover numbers (TONs) have been attained using heterogeneous catalysts coupled with sophisticated recycling strategies, it would be enormously simpler to use catalysts that are effective at such low levels that, in principle, they may not need to be recovered and recycled. In addition to cost considerations, an important concern is product contamination by the metallic catalyst, which in the case of pharmaceuticals must be strictly controlled (usually not to exceed 10 ppm). Problems of cost and contamination could be solved with catalysts that display TONs of 10^5 or higher [24]. Thus, any Pd-based technique with TONs of 10^5–10^6 and adequate turnover frequency (TOF) will be of great practical interest for fine chemical and pharmaceutical production [25]. An outstanding contribution to this ambitious task can be found in so-called "enabling technologies" that are able to strongly enhance reaction rates even at very low catalyst loads [22]. This is mainly made possible by the optimization of heat and mass transfer and the strict control of all reaction parameters.

2. Experimental

2.1. Chemicals and reactors

Commercially available reagents and solvents were used without further purification unless otherwise noted (Sigma Aldrich Srl, Milan, Italy). All native CDs were kindly provided by Wacher Chemie (Germany). The commercially available sonochemical reactor (high-power cavitating tube working at 21.5 kHz) was developed in collaboration with Danacamerini s.a.s. (Turin, Italy). All critical parameters (power, frequency, reaction temperature and the modified atmosphere) were monitored [26].

2.2. Analytics

GC-MS analyses were performed on a gas chromatograph Agilent 6890 (Agilent Technologies-USA) fitted with a mass detector Agilent Network 5973 using a capillary column with the following characteristics: 30 m length, 0.25 mm ID and 0.25 μm film thickness. The metal content in solution was determined by ICP-MS on a Quadrupole-ICP-MS X Series II (Thermo Fisher Scientific) after the samples had been digested in HNO_3 and aqua regia (1 HNO_3/3 HCl). The oxidation state of the adsorbed palladium or copper was measured using 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.

2.3. Catalyst preparation

In a typical poly-α-/β- or γ-CD/Pd/Cu catalysts preparation, $Pd(OAc)_2$ (25 mg, 0.22 mmol) or CuCl (25 mg, 0.5 mmol) and α-/β- or γ-CD (1 g, β-CD=0.78 mmol) were dissolved in DMF (25 ml) under sonication in a thermostatted sonochemical reactor at room temperature. Hexamethylene diisocyanate (HDI) (1.4 ml, 8.7 mmol) was then added portion-wise, and the reaction mixture was kept under sonication at 60°C (21.1 kHz, 60 W) for 30 min. The compact gel was crushed and washed with water (100 ml), acetone (100 ml) and methanol (100 ml). The product was filtered on a sintered glass Buchner funnel and dried overnight under vacuum at 75°C to produce a brownish or brownish-green powder (with $Pd^{(II)}$ or $Cu^{(I)}$, respectively).

The average metal content in the various cross-linked CDs catalysts was analyzed by ICP-MS, using three different samples from three different preparation batches for each catalyst. The Pd content was 0.53%±0.02 in α-CD 0.67%±0.03 in β-CD and 0.48%±0.08 for γ-CD, whereas the Cu content in β-CD was 0.88%±0.04.

2.4. Catalysts application

2.4.1. Heck and Suzuki reactions with 4-bromoacetophenone Styrene (1.5 mmol), 4-bromoacetophenone (1 mmol), K_2CO_3 (1.5 mmol), TBAB (1 mmol) DMA (10 ml) and the polymeric CD catalyst (200 mg) were stirred 3 h at 120°C. The mixture was cooled at room temperature under stirring. After filtration and neutralization (dil. HCl), *t*-butylmethylether or dichloromethane (25 ml) was added, and the organic layer was recovered and evaporated under vacuum, giving a high yield of the product (Tables 1 and 2).

Phenylboronic acid (1 mmol), 4-bromoacetophenone (1 mmol), Na_2CO_3 (1.5 mmol) (or TEA), water or water:dioxane 9:1 (10–15 ml) and the CD catalyst (50 mg) were stirred 3 h at 65°C. The mixture was cooled at room temperature under stirring. After filtration and neutralization (dil. HCl), *t*-butylmethylether or dichloromethane (25 ml) was added, and the organic layer recovered and evaporated under vacuum, giving a high yield of the product (Table 3).

Table 1 Heck reaction with styrene and 4-bromoacetophenone: oil bath vs. MW heating.

CD-cat	Oil bath (3h) yield (%)			MW (1 h) yield (%)		
	Conversion	*Trans*	*Cis*	Conversion	*Trans*	*Cis*
β	97	94	3	100	96	4
α	92	91	1	99	97	2
γ	96	93	3	100	94	6

Table 2 Heck reaction: MW under pressure with different amount of β-CD/$Pd^{(II)}$ catalyst.

Entry	Aryl-X	β CD-cat (mg)	Conversion (%)
1	4-Br-acetophenone	25	30
2	4-Br-acetophenone	50	34
3	4-Br-acetophenone	100	51
4	4-Br-acetophenone	125	54
5	4-Br-acetophenone	150	72
6	4-Br-acetophenone	175	87
7	4-Br-acetophenone	200	100
8	4-Br-anisole	150	89
9	4-Cl-nitrobenzene	150	39
10	4-Cl-acetophenone	150	8
11	4-Cl-acetophenone	300	19

MW irradiation at 120°C for 1 h.

Table 3 Suzuki reaction: oil bath vs. MW irradiation under pressure with different amount of β-CD/Pd$^{(II)}$ catalyst.

Entry	Aryl-X	β CD-cat (mg)	Oil bath conv. yield (%)	MW conv. yield (%)
12	4-Br-acetophenone	25	60	64
13	4-Br-acetophenone	30	61	68
14	4-Br-acetophenone	35	70	75
15	4-Br-acetophenone	40	84	86
16	4-Br-acetophenone	45	93	97
17	4-Br-acetophenone	50	99	100
18	4-Br-anisole	45	93	99
19	4-Br-anisole	50	98	100
20	4-Cl-nitrobenzene	45	10	22
21	4-Cl-acetophenone	45	6	15
22	4-Cl-acetophenone	90	25	34

2.4.2. MW-assisted procedures for Heck and Suzuki reaction under pressure (Tables 1–3) The same Heck and Suzuki reactions have been performed in a MW reactor SynthWAVE-Milestone, under N_2 pressure (20 bar) and stirring at 120°C for 1 h (power 130 W) and 65°C for 45 min (power 100 W), respectively. The crude products do not require further purification for metal contamination; in fact, ICP-MS analysis showed a Pd content lower than 6–8 ppm in all cases.

2.4.3. Alkyne/azide [3+2] cycloaddition Cu$^{(I)}$ cross-linked β-CD (150 mg) was added to a solution of H_2O/dioxane 8:2 of benzyl azide (1 mmol) and phenylacetylene (1.5 mmol). The solution was stirred at 70°C for 10 min under MW irradiation (100 W) and then cooled and filtered off. The filtrate showed complete conversion and the presence of the triazole in high yield (96%–98%). The residue catalyst was washed with H_2O and dioxane, dried over night at 75°C and reused twice with a moderate reduction of activity (about 6%–8% less each run) though a Cu content roughly constant (from 0.88% to 0.86%–0.87%).

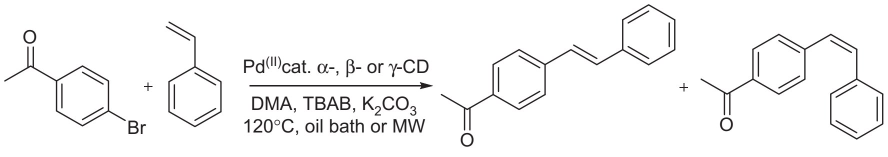
3. Results and discussion

Several outstanding authors have shed light on the enormous potential of enabling technologies from the smallest lab scale all the way up to industrial production [25–30]. Our approach, which combines a catalyst where the metal is tightly embedded in the cavities of the polymeric CD net and physical activation with MW irradiation, results in a winning green approach to process intensification. First we studied the catalytic differences between the three Pd-loaded cross-linked CD catalysts obtained from α-, β- and γ-CD. This study was conducted with the Heck reaction using styrene and 4-bromoacetophenone, both under conventional heating and under MW irradiation (Scheme 1).

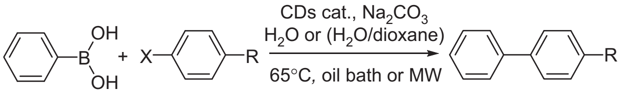
Figure 1 The rack with several test tubes in the MW reactor (*Synth*WAVE Milestone).

Following the standard procedure described in the experimental section with the same amount of α-, β- and γ-CD/Pd$^{(II)}$ catalyst for each reaction (200 mg), we observed little conversion and yield differences with the three catalysts (Table 1). This led us to proceed with the β-CD/Pd$^{(II)}$ catalyst because native β-CD is much cheaper and more easily available. The MW reactor SynthWAVE, (Milestone) equipped with a rack with several test tubes (Figure 1), facilitated the search for the optimal catalyst load, solvent ratio and type. MW irradiation brought the reaction to completion in 1 h with all the catalysts. In the search for optimum conditions, the reaction was performed with a series of aryl halides varying the catalyst amount (Table 2).

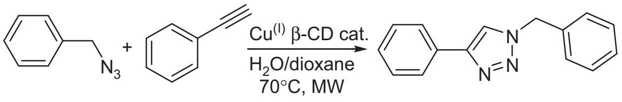
The reaction in oil bath was monitored every 30 min, reaching a complete conversion after 3 h. Our investigation



Scheme 1 General conditions for Heck reaction.



Scheme 2 General conditions for Suzuki cross-coupling.



Scheme 3 General conditions for the click reaction (CuAAC).

showed that the optimal amount of β-CD/Pd$^{(II)}$ catalyst in the Heck reaction was four times higher than the Suzuki coupling (200 vs. 50 mg). The β-CD/Pd$^{(II)}$ catalyst was then tested in Suzuki cross-couplings (Scheme 2), both under conventional heating (3 h) and MW irradiation (45 min); conversion yields are listed in Table 3.

A series of recycling trials using the catalyst recovered from Heck and Suzuki reactions was performed after the catalyst itself was washed and dried under vacuum. Considering that approximately 10%, in weight, was lost during the entire process, the addition of 20% of new catalyst to the recovered portion gave roughly the same yield as the first run (only 2%–3% less) in both reactions. The moderate reduction of activity does not derive, however, from Pd leaching; in fact, ICP-MS analysis showed a roughly constant metal content in the reused samples (0.5%–1.5% less).

The β-CD/Cu$^{(I)}$ catalyst was successfully applied in the most common click reaction, namely the alkyne/azide [3+2] cycloaddition with benzyl azide and phenylacetylene. In previous papers, we explored the possibility of entrapping Cu$^{(I)}$ in other solid supports, such as charcoal [31] and cross-linked chitosan [11], and the possibility of generating this species *in situ* from the sonochemical red/ox between the metallic copper and the copper oxide on the surface was also investigated [32]. The new β-CD/Cu$^{(I)}$ catalyst, under MW irradiation (70°C, 100 W), brought the reaction to completion in only 10 min (Scheme 3).

4. Conclusion

We have herein reported a case of ligand-free, metal-loaded polycyclodextrin catalysts effectually applied in C-C couplings under MW irradiation. The flexible combination of facilitating technologies and suitable supported catalysts enables efficient and sustainable synthetic protocols. This multi-faceted strategy may pave the way to the environmentally friendly intensification of several synthetic processes.

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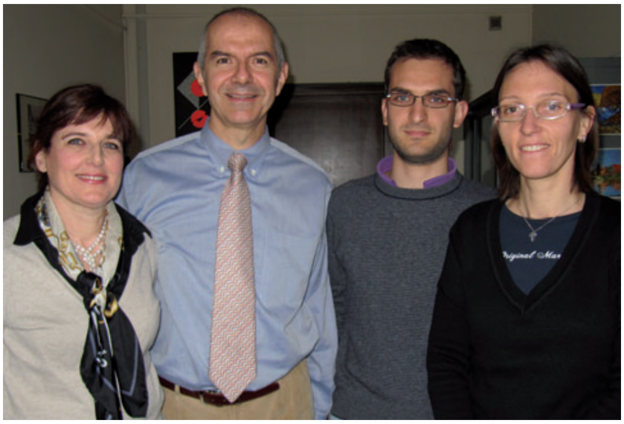

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Cravotto's group is known for its research activity in the field of non-conventional enabling technologies applied to organic synthesis, to the degradation of persistent organic pollutants, to plant extraction and flow chemistry. The group has developed several chemical processes and protocols for microwave, ultrasound and hydrodynamic cavitation and mechanochemical activation, and has also worked on the design of innovative reactors. These green procedures exploited new supported catalysts for use in water, glycerol, ionic liquids or in solventless reactions. The groups's main synthetic targets are bioactive compounds, fine chemicals, cyclodextrin derivatives and functionalized carbon nanotubes.

Prof. Cravotto is European Editor of *Ultrasonics Sonochemistry* (Elsevier) and Editor of *Green Processing and Synthesis* (De Gruyter).

Prof. Antonio Procopio (Full Professor, University of Magna Græcia – Catanzaro, Italy). The group of Prof. Procopio is working in the field of non-conventional technologies applied to organic synthesis and extraction and chemical manipulation of natural compounds. The group has developed several chemical processes and protocols using eco-friendly homogeneous and heterogeneous Lewis acid catalysts, often under microwave and ultrasound activation. These green procedures exploited the applications of these catalysts for use in water or in solventless reactions. The group's main synthetic targets are bioactive compounds, fine chemicals, natural antioxidants and functionalized mesoporous silica materials.