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# UNIVERSITÀ DEGLI STUDI DI TORINO

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# A new class of cationic cyclodextrins: synthesis and chemico-physical properties

Luisa Boffa,<sup>a</sup> Emanuela Calcio Gaudino,<sup>a</sup> Katia Martina,<sup>a</sup> Laszlo Jicsinszky<sup>b</sup> and Giancarlo Cravotto<sup>\*a</sup>

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A new class of positively charged triazole-bridged  $\beta$ -cyclodextrin ( $\beta$ -CD) derivatives have been synthesized in excellent yields (over 70%) through a copper-catalyzed azide-alkyne cycloaddition (CuAAC), starting from  $6^{I}$ -azido- $6^{I}$ -deoxy- $\beta$ -CD or its permethylated derivative and a series of 1-butyl-3-alkynylimidazolium salts. The regioselective azide/alkyne [3 + 2] cycloaddition was efficiently carried out using metallic copper as the catalyst, affording very clean products. Easy access to such hybrid molecules that combine the properties of CDs and ionic liquids, may pave the way to a number of new applications in analytical chemistry and catalysis.

## Introduction

One of the recent hot topics in organic synthesis, ionic liquids (ILs) play an ever important role. Mean while cyclodextrin (CD) derivatives have found a plethora of innovative applications in several fields of chemistry and biology. Owing to their unique chemico-physical properties, CD derivatives are the most common components of chiral phases for enantioseparation.<sup>1,2</sup>

The interactions between CDs and ILs have been deeply investigated. Recently, Shen et al. analysed the interaction of several imidazolium ILs with  $\beta$ -CD.<sup>3</sup> They demonstrated that the alkyl side chain on the imidazolium ring but not the imidazolium ring itself entered into the  $\beta$ -CD cavity. They presented a general scale of anion and cation binding strengths with  $\beta$ -CD: 1-dodecyl-3-methylimidazolium > NTf<sub>2</sub><sup>-</sup> (bis(trifluoromethylsulfonyl) imide).<sup>4</sup> This inclusion complex could even modify the chemico-physical properties and solubility of CD-polymers<sup>5</sup> or  $\beta$ -CD itself.<sup>6</sup> Recently, the combined use of chiral ionic liquids (CILs) (N-undecenoxycarbonyl-L-leucinol bromide) and CDs (2<sup>L-VII</sup>,3<sup>L-VII</sup>,6<sup>L-VII</sup>-O-permethyl- $\beta$ -CD) was proposed for the enantioseparation of anionic profen drugs which turned out to be applicable to the quantitative determination of ibuprofen in commercial samples.<sup>7</sup> In 2008, Desbe`ne et al. separated enantiomers of binaphtol derivatives using two different CILs and CD derivatives.<sup>8</sup> An application of ILs and CDs in gas chromatography (GC) was previously described by Berthod et al. in 2001.<sup>9</sup>

Chiral GC capillary columns were prepared by dissolving  $2^{I-VII}$ , $3^{I VII}$ , $6^{I VII}$ -O-permethyl- $\beta$ -CD and  $2^{I-VII}$ , $6^{I VII}$ -O- dimethyl- $\beta$ -CD in 1-butyl-3-methylimidazoilum chloride. The enantioseparation was restricted to a small number of cyclic compounds, this was probably due to the unfavorable interactions between the IL aliphatic chain with the CD cavity, however in a comparison with commercial equivalent columns, RTILs columns showed lower retention factors and higher peak efficiency.

 $\beta$ -CD derivatives are excellent chiral selectors for molecules containing an aromatic ring as well as amino or carboxyl groups. CDs can be modified with strongly charged moieties (e.g. sulfated or sulfoalkylether groups) or weakly charged functional groups (e.g. carboxymethyl, phosphate or amino groups). Besides the commonly used neutral CD derivatives, charged CDs gained much interest because they can perform fast chiral separations at low concentrations and give a better resolving power with oppositely charged analytes. In fact, the interactions between charged CDs and analytes are based not only on inclusion complexation but also on strong electrostatic interactions.<sup>10</sup> The interaction and recognition of ionic guests by ionic CDs has been well explained.<sup>11</sup> The cooperative work of inclusion can be considered to be the general mechanism for the complexation of a charged host with an oppositely charged guest.

The main application of neutral and charged CD derivatives is as chiral mobile phase additives in capillary electrophoresis (CE) and high-performance liquid chromatography (HPLC).<sup>12–15</sup> The application of this chiral additive approach was limited by the large consumption of CD derivatives as mobile phases in HPLC and supercritical fluid chromatography (SFC). Pioneers in the synthesis of charged CDs as chiral selectors for pharmaceutical analysis were Tarabe and co-workers.13 They first achieved the separation of six dansyl amino acids enantiomers using a cationic CD, the 6I-(baminoethyl- amino)-6<sup>I</sup>-deoxy-β-CD.<sup>14</sup> In 1969, Parmeter et al. proposed the synthesis of 2hydroxypropyltrimethylammonio- $\beta$ -CD,<sup>15</sup> which was widely used and became a commercially available product. Its first application was proposed in 1996 by Bunke et al.<sup>16</sup> In 1993 Nardi et al. presented the synthesis of 6<sup>I</sup>-methylamino-6<sup>I</sup>-monodeoxy-β-CD and 6<sup>I,IV</sup>-dimethylamino-6<sup>I,IV</sup>dideoxy-β-CD and their applications in the enantiomeric resolution of some 2-hydroxyacids.<sup>17</sup> Some years later, the 6<sup>I</sup>-amino-6<sup>I</sup>-deoxy- $\beta$ - CD was tested to separate several neutral and anionic racemates,<sup>18</sup> and two hystamine moieties bearing CD derivatives were used in the separation of dansyl amino acids.<sup>19</sup> A wide variety of monosubstituted positively charged CD have been explored for chiral electrophoresis by introducing imidazolium, ammonium and pirydinium moieties with varied alkyl chain lengths and CD types by Ng and co-workers.<sup>20</sup> In a recent review they described four series of cationic CDs.<sup>21</sup> The alkyl imidazolium (Series 1) and the alkyl ammonium (Series 2) were obtained starting from 6<sup>I</sup>-tosyl-β-CD (or 2<sup>I</sup>-tosyl-β-CD) by nucleophylic substitution with alkyl

imidazole or alkyl amines. The same authors published a detailed protocol of this synthetic procedure.<sup>22</sup> For Series 3, the 6<sup>I</sup>/2<sup>I</sup>-amino-6<sup>I</sup>/2<sup>I</sup>- deoxy-b-CD hydrochlorides, they exploited a new synthetic method with the reduction with PPh<sub>3</sub> of the  $6^{I/2I}$ -azido- $6^{I/2I}$ - deoxy- $\beta$ -CD to obtain the amino derivatives in very high yields (90%). Methylated 6<sup>I</sup>- or 2<sup>I</sup>-ammonium compounds were also tested. The last Series includes  $\alpha$ - and  $\gamma$ -alkylammonium, alkyl imidazolium and amino derivatives.<sup>23</sup> Recently, Ng and Tan presented the synthesis of a new single-isomer CD derivative, the 6I-deoxy-6<sup>I</sup>-(3R,4R- dihydroxypyrrolidine)-β-CD chloride, and its applications as a chiral selector for CE in the enantioseparation of anionic and ampholytic acids.<sup>24</sup> Finally, a new pyridinium cationic CD has been presented for the preparation of a graphite electrode.<sup>25</sup> Only one synthetic application of a cationic CD was described by Chan and co-workers.<sup>26</sup> They achieved the asymmetric reduction of prochiral acetophenones with sodium borohydride using  $6^{I}$ -(1-methyl-3-imidazolium)- $6^{I}$ -deoxy- $\beta$ - CD tosylate. In the present paper we describe a new simple and reliable synthetic protocol involving a copper-catalyzed azide-alkyne cycloaddition (CuAAC)<sup>27</sup> for the preparation of a new class of cationic CDs. These charged CD adducts derive from the 1,3-dipolar cycloaddition between an azido CD derivative (methylated or not) and a 1-alkyl-3-alkynylimidazolium salt in the presence of metallic copper powder.<sup>28</sup> Our synthetic method leads to a 1,2,3-triazole bridged hybrid CD-IL adduct, whose properties can be tailored "ad hoc" by varying the spacer length, the type of counter-anion and heterocycle ring. The catalytic activity of metallic copper was established early on.<sup>29</sup> We recently described, in detail, an efficient green process in which metallic copper efficiently catalyzes azidealkyne cycloadditions under sonochemical conditions.<sup>30</sup>

# Results and discussion

The synthesis of hybrid CD-IL adducts combines the chemical and physical properties of ILs with those of CDs and generates new chiral micro-environments with an high organisational degree which is a fundamental factor for chirality transfer. A new family of cationic CDs was obtained through a CuAAC  $6^{I}$ -azido- $6^{I}$ -deoxy- $\beta$ -CD.and that binds 1-alkynyl-3-butylimidazolium derivatives..Several.different derivatives.were synthesized, as shown in Scheme.1. As first, the 1butyl- imidazolium was.alkylated with propargyl bromide or 5-chloropentyne using a solvent-free procedure under MW irradiation.<sup>31</sup> 1-Butyl-3-propargylimidazolium.bromide (BuPrImBr).was obtained.in 1.h at 60.°C.(84%), while 1-butyl-3-(4-pentynyl)imidazolium.chloride (BuPeImCl) in 1 h at 110 °C.(94%). An example of alkene and alkyne- substituted methylimidazolium ILs was reported by Drake et al.<sup>32</sup> The second generation ILs, 1-butyl-3-propargyl- imidazolium and 1-butyl-3-(4-pentynyl)imidazolium hexafluoro- phosphate.(BuPrImPF6 and BuPeImPF6), were obtained following a one-pot procedure<sup>33</sup>.under MW irradiation in 3 h at 60 °C (65 and 57%, respectively).



#### Scheme 1

 $6^{I}$ -Azido- $6^{I}$ -deoxy-β-CD (**2**) was prepared from  $6^{I}$ -O-tosyl- β-CD (**1**) by nucleophilic substitution with NaN3 under MW irradiation at 85 °C..The alkylation of 2 with MeI in the presence.of.NaH.in.DMF,<sup>34</sup> afforded the. $6^{I}$ -azido- $6^{I}$ - deoxy- $2^{I-VII}$ , $3^{I-VII}$ , $6^{II-VII}$ -O-permethyl-β-CD (**7**) in excellent yield (85% after chromatography.purification).(Scheme 2). The first hybrid molecule of.this type, 1-butyl-3-[1- ( $6^{I}$ -deoxy- $6^{II-VII}$ , $2^{I-VII}$ , $3^{I-VII}$ -O-permethyl-β-CD- $6^{I}$ -yl)triazol- 4-ylmethyl] imidazolium.bromide (**8**), was obtained from 1-butyl-3-propargylimidazolium.bromide and **7**.(Table 1, entry I).



Scheme 2

Table 1. CuAAC with CuSO<sub>4</sub>

Entry <sup>a</sup>	Substrate	IL	Time/h	Yield(%) <sup>b</sup>
Ι	7	BuPrImBr	1.5	79 ( <b>8</b> )
II	7	BuPeImCl	1.5	68 ( <b>9</b> )
III	7	BuPrImPF <sub>6</sub>	2	80 ( <b>10</b> )
IV	2	BuPrImBr	2	75 ( <b>3</b> )
V	2	BuPeImCl	2	90 (4)

<sup>*a*</sup> Experimental conditions: CD, IL (5 equiv.), 0.4 equiv. of CuSO<sub>4</sub> and 1.2 equiv. of L-ascorbic acid in *t*-But-OH/H<sub>2</sub>O 1:1 at 80 °C under MW irradiation <sup>*b*</sup> Isolated yields by flash chromatography

The CuAAC reaction was carried out in the presence of an excess of IL, CuSO<sub>4</sub>.and L-ascorbic acid; the final product was isolated by flash chromatography.(79%). In the same way, the products..1-butyl-3-[3-(1(6<sup>I</sup>-deoxy-6<sup>II-VII</sup>,2<sup>I-VII</sup>,3<sup>I VII</sup>-O-permethyl- $\beta$ -CD-6<sup>I</sup>-yl)triazol-4-yl)propyl]imidazolium.chloride (**9**) and 1-butyl-3-[1-(6<sup>I</sup>-deoxy-6<sup>II-VII</sup>,2<sup>I-VII</sup>,3<sup>I VII</sup>-O-permethyl- $\beta$ -CD-6<sup>I</sup>-yl)triazol-4-ylmethyl]imidazolium..hexa- fluorophosphate. (**10**) were obtained.respectively.in a 68% and 80% yield (Table 1, entries II and III). When the CuAAC was performed with 2, the reaction afforded 1-butyl-3-[1-(6<sup>I</sup>-deoxy- $\beta$ -CD-6I-yl)triazol-4-ylmethyl]imidazolium bromide (**3**) and 1-butyl-3-[3-(1-(6<sup>I</sup>-deoxy- $\beta$ -CD-6I-yl)triazol-4-ylmethyl]imidazolium bromide (**4**) in good yield after purification with reverse-phase chromatography.(Table 1, entries IV and V).

The melting points of the final methylated.products.are below 110 °C, while the unprotected CDs melt at temperatures over 200.°C..The synthetic.protocol employing.soluble copper(II) salts requires careful purification.due to the high content of residual.metal; native and substituted CDs are efficient complexing agents for copper ions.<sup>35</sup> Starting from our previous investigations<sup>36</sup> and from a few recent examples in the literature,<sup>37</sup>.we chose copper powder as the catalyst for the CuAAC.

Our synthetic.protocol based.on Cu(0) was previously optimized.on the.reaction with 1azidoheptadecane and phenylacetylene, using a dioxane/water 8:2 mixture as solvent and comparing different reaction conditions.(conventional heating, power ultrasound (US) and microwave (MW) alone or combined)<sup>32</sup>. Powerful sonication strongly promoted the reaction, giving high yields in a very short reaction time. On the other hand MW irradiation.alone did not provide any significant effect on reaction rates. US promotes the depassivation (CuO) of the metal surface, and the disproportion.of Cu(0) and Cu(II) into Cu(I), the effective catalyst of the cycloaddition. Owing to the easy removal of Cu(0) at the end of reaction by simple filtration, we used a high catalyst load (7.85 mmol per g of starting material or 0.5 g per 1 g).

Table 2. CuAAC on 7 employing Cu powder.

Entry	IL	Solvent	Temp./ °C	Time/h	Yield
VI	BuPeImCl	THF/H <sub>2</sub> O 8:2	80	18	67 ( <b>9</b> )

VII	BuPeImCl	diox/H <sub>2</sub> O 8:2	100	20	71 ( <b>9</b> )
VIII	BuPeImCl	diox/H <sub>2</sub> O 2:8	100	3	76 ( <b>9</b> )
IX	BuPrImBr	diox/H <sub>2</sub> O 2:8	100	3	79 ( <b>8</b> )
Х	BuPeImPF <sub>6</sub>	H <sub>2</sub> O/Prop-OH 1:1	100	3	72 (11)
XI	BuPrImPF <sub>6</sub>	H <sub>2</sub> O/Prop-OH 1:1	100	3	80( <b>10</b> )

<sup>*a*</sup> Experimental conditions: CD (7), Cu powder (7.85 mmol g<sup>-1</sup>) and IL (5 equiv.), dissolved in the indicated solvent mixture, were heated in oil bath under magnetical stirring at the temperature and for the time indicated. <sup>*b*</sup> Isolated yields by flash chromatography

We started from 7; due to the different solubilities of the ILs and CDs, the choice of the solvent mixtures was critical. The classic organic solvent for click reactions, *t*-But-OH, was first replaced by THF.then by dioxane in order to reach the temperature of 100 °C.(Table 2, entries VI–IX). These low-polar.solvents were mixed with H<sub>2</sub>O in the initial ratio 8:2 (Table 2, entries.VI and VII). After several trials the optimal solvent mixture found was dioxane/H<sub>2</sub>O 2:8, that gave the final products **9** and **8**, in about 3 h in 76% and 79% yields respectively (Table 2, entries VIII and IX).

The role of H2O in the copper disproportion, particularly in the presence of ILs, is worthy of a mention. In our published synthetic protocol which was cited before, dioxane/water 5: 5 or 2:8 mixtures instead did not give better results. For the reaction with BuPeImPF<sub>6</sub> and BuPrImPF<sub>6</sub> a mixture of H<sub>2</sub>O/Prop-OH 1:1 was used, affording **11** and **10**, in 72% and 80% yield in 3 h at 100 °C (Table 2, entries X and XI).

Entry	IL	Solvent	Temp.	Time	Method	Yield
XII	BuPeImCl	H <sub>2</sub> O	70 °C	0.5 h	o.b.	91
XIII	BuPeImCl	H <sub>2</sub> O	70 °C	0.5 h	MW/US	93
XIV	BuPeImCl	H <sub>2</sub> O	70 °C	0.5 h	o.b./US	89
XV	BuPrImBr	H <sub>2</sub> O	70 °C	0.5 h	o.b.	85
XVI	BuPrImBr	H <sub>2</sub> O	70 °C	0.5 h	MW/US	83
XVII	BuPrImPF <sub>6</sub>	H <sub>2</sub> O/THF 3:2	70 °C	2 h	o.b.	69
XVIII	BuPeImPF <sub>6</sub>	H <sub>2</sub> O/THF 3:2	70 °C	2 h	o.b.	64

**Table 3.** Reagents:  $6^{I}$ -azido- $6^{I}$ -deoxy- $\beta$ -CD and Cu powder.

<sup>*a*</sup> Experimental conditions: CD (2), Cu powder (7.85 mmol  $g^{-1}$ ) and IL (5 equiv.), dissolved in the indicated solvent mixture, were treated at 70 °C as indicated in the table. <sup>*b*</sup> Isolated yields after flash chromatography <sup>*c*</sup> Oil Bath



Fig. 1 <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O) of 1-butyl-3-[1-( $6^{I}$ -deoxy- $\beta$ -CD- $6^{I}$ -yl)triazol-4-ylmethyl]imidazolium bromide (7) with the signals assignment; on the left, the complete product structure; on the right, a particular of the bidimensional <sup>1</sup>H–<sup>13</sup>C HSQC spectrum



Fig. 2 TGA of derivatives 3, 6, 8, 11 and  $\beta$ -CD



Fig. 3 DSC of 9

 $H_2O$  was the solvent of choice for the CuACC between 2 and BuPeImCl or BuPrImBr, due to the high solubility of these substrates (Table 3, entries XII–XVI). The reaction was much faster.even.when performed.at only 70 °C,.100% conversion of 2 in products 3 and 4 was achieved in 30 min. A.mixture. $H_2O$ –THF.3:2.was.used.with BuPrImPF<sub>6</sub> or BuPeImPF<sub>6</sub>,.affording 5.and 6.in good yields in 2.h (Table 3, entries XVII and XVIII).

In all cases using these substrates, MW and US alone orcombined did not afford a remarkable improvement in reactions rate and yield. Some examples.were reported.in Table 3 (entries XIII, XIV and XVI).

# Uses and applications

All the products (**3–6**, **8–11**) have been tested either pure or in solutions in several reactions. Among them: the addition of 4-hydroxycoumarin to enals,<sup>38</sup> allylation of aldehydes,<sup>39</sup> reduction of acetophenones with NaBH<sub>4</sub>.<sup>28</sup> Although we had fast and efficient conversions, our hybrid CD derivatives did not induce enantioselectivity. Excellent yields and chemo- selectivity were obtained in Heck reactions<sup>40</sup> by complexing Pd(OAc)<sub>2</sub> on **3** and **10** as a first step. Stereoselection however, did not differ significantly from that obtained with normal solvents (E/Z ratio 13.5:1 *vs.* 12:1).<sup>41</sup> Work is in progress in the analytical field by testing permethylated derivative **11** as a stationary phase in chiral GC.

# Chemico-physical properties

#### Solubility and polarity

Permethylated CDs are lipophilic like the hybrid derivatives:permethylated CD-ILs, soluble in common organic solvents as such  $CH_2Cl_2$ ,  $CHCl_3$ , acetone, MeOH and quite soluble in diethyl ether. The counter anion influences the polarity and hygroscopy. In particular bromide and chloride confer a higher polarity and relatively high hygroscopy to permethylated CD-ILs, while hexafluorophosphate anion makes them considerably less polar. In any case this whole family of compounds is insoluble in water.

A scale of polarity was determined by TLC: for bromide and chloride derivatives, a mixture of CHCl<sub>3</sub>/MeOH 8:2 was used as eluent, while for hexafluorophosphate derivatives, a mixture of CHCl<sub>3</sub>/MeOH 95:5. On the other hand the "unprotected" CD-ILs derivatives are quite soluble in water and MeOH, while insoluble in CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, acetone, diethyl ether. The hexafluorophosphate anion makes them less polar and more soluble in MeOH than water. Impurities of unreacted IL (bromide and chloride anions) may act as a co-solvent, dramatically increasing its solubility in water.

#### **Melting points**

The melting points of permethylated products (8–11, Scheme 2) are close to the parent monoazido derivative 7 (107 °C). After evaporation under vacuum, a good crystallization can be obtained in some cases by digesting the products with diethyl ether avoiding amorphous and vitreous aspects. All the CD-ILs deriving from native CDs (with unprotected OH) undergo progressive degradation/decomposition over 220 °C before the melting point.

#### NMR analyses

The <sup>1</sup>H NMR spectra of these cationic compounds show a down-fielded H-6' diasterotopic signal, composed of two multiplets (H-6<sup>'a</sup> and H-6<sup>'b</sup>) which can show quite a high ppm difference (0.4 ppm in the Fig. 1). The H-6<sup>'a,b</sup> shows a confirmed by bidimensional spectra, i.e. COSY and <sup>1</sup>H–<sup>13</sup>C HSQC (see Fig. 1, right). In particular, in the HSQC spectrum it is possible to discriminate the C6' (up-fielded to 51.8 from 60) and C5' (up-fielded to 70.8 from 73). The <sup>1</sup>H NMR spectrum shows the signals of imidazole (I<sub>2,4,5</sub>) and triazole (T) structures in the aromatic region and the aliphatic signals of the butyl group (from A to D). The <sup>1</sup>H NMR spectra of these compounds proved itself to be susceptible to a proton/deuterium exchange. The spectra of permethylated products were first recorded in CDCl<sub>3</sub>, and showed very broad signals, particularly in the aromatic region. Moreover some signals i.e H-6<sup>'a,b</sup>, T, I<sub>2,4,5</sub> and E showed a different chemical shift. Better spectra and sharper signals were obtained with CD<sub>3</sub>OD In some cases, when using CD<sub>3</sub>OD or D<sub>2</sub>O, the I<sub>2</sub> signal disappeared or decreased in intensity, proving its acidic nature.

#### Thermogravimetric analysis

The TGA thermograms are shown in Fig. 2.  $\beta$ -CD shows mass loss in three different temperature regions. A first mass loss at around 90 °C due to the dehydration of the samples, the second and third mass loss around 300 °C and 367 °C due to the melting and decomposition of the glucose unit in b-CD. TGA of compounds **3**, **6**, **8** and **11** showed that the shape of degradation curves does not differ too much from  $\beta$ -CD. The first mass loss is at around the same temperature but the second mass loss is at a lower temperature due to the modification of the CD unit.

#### **DSC** analysis

The first two thermograms have been recorded on two samples of native  $\beta$ -CD (one dried under high vacuum at 80 °C) as a control to the experiment. In the dried sample the endothermic peak at 85 °C disappeared. This can be attributed to the evaporation of water molecules. Full thermal degradation occurred at about 325 °C, the process started at 220 °C. The DSC thermograms of unprotected  $\beta$ -CD derivatives (samples **3–7**) showed similar behaviour. Differently the per-O-methyl  $\beta$ -CD derivatives (samples **8–11**; see the example in Fig. 3) exhibit a characteristic endothermic peak in the range 94–109 °C that corresponds to the melting point. Thermograms are influenced by the anion structure. All samples showed a similar degradation curve from 235 up to 275 °C, the phenomenon was complete at about 300 °C.

#### Conclusions

In summary, we described the synthesis of a new class of positively charged triazole-bridged CDs through CuAAC protocols in the presence of metallic copper. In all cases these hybrid CD-ILs adducts were easily obtained in excellent yield (over 70%). Their chemico-physical properties can be tailored "ad hoc" by varying the spacer length, the type of counter- anion and the heterocycle ring. Easy access to positively charged triazole-bridged CD derivatives that may pave the way to a number of new applications in analytical chemistry and catalysis has been described. To this end, the reaction scale-up is described in detail.

## Experimental

#### General

Commercially available reagents and solvents were used without further purification unless otherwise noted. $\beta$ -CD was kindly provided by Wacker Chemie (Germany).

Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized by UV inspection and/or by heating after being sprayed with 5% H<sub>2</sub>SO<sub>4</sub> in ethanol or phosphomolybdic

acid. The purification was performed by flash-chromatography (CombiFlash Rfs Teledyne ISCO) on appropriate columns (silica or RP18).

Thermogravimetric analyses (TGA) were performed by a TA Instrument TGA 2050 operating under nitrogen atmosphere with alumina crucibles containing 15–20 mg of polymer. The runs were carried out at a constant heating rate of 10 °C min<sup>-1</sup>. Differential Scanning Calorimetry (DSC) was performed by a TA Instrument with TA2010 DSC cell operating under a stream of nitrogen and a constant heating rate of 10 °C min<sup>-1</sup>. All the sonochemical apparatuses were developed in our laboratory in collaboration with Danacamerini sas (Torino, Italy), viz. a model with immersion titanium horn (21.4 kHz) and a non-metallic horn made in Pyrex<sup>®</sup> to be inserted in a professional oven, MicroSYNTH-Milestone (Italy) for simultaneous irradiation. MW-promoted reactions were carried out in a professional oven, MicroSYNTH-Milestone (Italy). IR spectra were recorded with a Shimadzu FT-IR 8001 spectrophotometer. Melting points (uncorrected) were determined on a Buchi SMP-20. NMR spectra were recorded on a Bruker 300 Avance (300 MHz and 75 MHz for <sup>1</sup>H and <sup>13</sup>C, respectively) at 25 °C; chemical shifts were calibrated to residual proton and carbon resonances of the solvents, viz. CDCl<sub>3</sub> ( $\delta$ H = 7.27,  $\delta$ C = 77.16), DMSO-D<sub>6</sub> ( $\delta$ H = 2.50,  $\delta$ C = 39.52) and (CD<sub>3</sub>)<sub>2</sub>CO ( $\delta$ H = 2.05,  $\delta C = 29.84$  and 206.26), CD<sub>3</sub>OD  $\delta = 3.31$ ,  $\delta C = 49.0$ ), D<sub>2</sub>O ( $\delta H = 4.79$ ). Chemical shifts ( $\delta$ ) are given in ppm and coupling constants (J) in Hz. ESI-mass spectra were recorded on a Waters Micromass ZQ equipped with an ESI source.

#### General procedure for CuAAC with CuSO4

Compound 7 (200 mg, 0.139 mmol), CuSO<sub>4</sub> 5H<sub>2</sub>O (13.9 mg, 0.0556 mmol, 0.4 equiv.), L-ascorbic acid (29.4 mg, 0.167 mmol, 1.2 equiv.) and the desired IL (5 equiv.) were placed in a 25 mL two-necked round-bottomed flask and dissolved in a mixture of t-BuOH/H<sub>2</sub>O (10 mL, 1 : 1). The mixture was irradiated with MW for 1.5 h at 80 1C (50 W, mean power). The reaction outcome was monitored by TLC. The reaction mixture was evaporated under vacuum. The crude product was purified by flash chromatography on silica gel using the following eluents in gradient: CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 98:2, 95:5, 9:1, 8:2, CH<sub>3</sub>OH, affording the pure product in the yield indicated in the tables.

Compound 2 (200 mg, 0.172 mmol), CuSO<sub>4</sub> 5H<sub>2</sub>O (17.2 mg, 0.0688 mmol, 0.4 equiv.), L-ascorbic acid (36.4 mg, 0.206 mmol, 1.2 equiv.) and the desired IL (5 equiv.) were placed in a 25 mL two-necked round-bottomed flask and dissolved in a mixture of t-BuOH/H<sub>2</sub>O (10 mL, 1 : 1). The mixture was irradiated with MW for 1.5 h at 80 °C (60 W, mean power). The reaction outcome was monitored by TLC. The reaction mixture was evaporated under vacuum. The crude product was purified by flash chromatography on RP18 using the following eluents in gradient: H<sub>2</sub>O, H<sub>2</sub>O/CH<sub>3</sub>OH 98:2, 95:5, 9:1, 8:2, CH<sub>3</sub>OH, affording the pure product in the yield indicated in the tables.

#### General procedure for CuAAC with Cu(0)

Compound 7 (200 mg, 0.139 mmol), copper powder (100 mg, 1.57 mmol, 11.3 equiv.) and the desired IL (5 equiv.) were placed in a 25 mL two-necked round-bottomed flask and dissolved in a solvent mixture and treated as indicated in the tables. The reaction outcome was monitored by TLC. The reaction mixture was filtered on paper and evaporated under vacuum. The crude product was purified by flash chromato- graphy on silica gel using the following eluents in gradient:  $CH_2Cl_2$ ,  $CH_2Cl_2/CH_3OH$  98:2, 95:5, 9:1, 8:2,  $CH_3OH$ , affording the pure product in the yield indicated in the tables.

Compound 2 (200 mg, 0.172 mmol), copper powder (100 mg, 1.57 mmol, 9.1 equiv.) and the desired IL (5 equiv.) were placed in a 25 mL two-necked round-bottomed flask and dissolved in a solvent mixture and treated as indicated in the tables. The reaction outcome was monitored by TLC. The reaction mixture was evaporated under vacuum. The crude product was purified by flash chromatography on RP18 using the following eluents in gradient:  $H_2O$ ,  $H_2O/CH_3OH$  98:2, 95:5, 9:1, 8:2, CH<sub>3</sub>OH, affording the pure product in the yield indicated in the tables.

#### Preparation scale-up for 3 and 9

Compound **7** (2 g, 1.39 mmol) and 1-butyl-3-(4-pentynyl)- imidazolium chloride (1.57 g, 6.95 mmol, 5 equiv.) were placed in a 250 mL two-necked round-bottomed flask and dissolved in 100 mL of dioxane/H2O 2 : 8 and copper powder (1 g, 15.7 mmol, 11.3 equiv., 7.85 mmol g 1) was added. The reaction mixture was sonicated for 1 min with a titanium horn (21.4 kHz, 80 W) then magnetically stirred at 100 1C for 1 h and the outcome was monitored by TLC. The reaction mixture was filtered on paper and evaporated under vacuum. The crude product (3.04 g) was purified by flash chromatography on silica gel using the following eluents in gradient: CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 98:2, 95:5, 9:1, 8:2, CH<sub>3</sub>OH, affording 1.1 g of 1-butyl-3-(4-pentynyl)imidazolium chloride and 1.78 g of pure product 9 (1.07 mmol, 77%).

Compound 2 (2 g, 1.72 mmol) and 1-butyl-3-propargyl- imidazolium bromide (2.08 g, 8.6 mmol, 5 equiv.) were placed in a 500 mL two-necked round-bottomed flask and dissolved in 150 mL of H<sub>2</sub>O and copper powder (1 g, 15.7 mmol, 9.1 equiv., 7.85 mmol g 1) was added. The reaction mixture was sonicated for 1 min with a titanium horn (21.4 kHz, 80 W) then magnetically stirred 1 h at 70 1C. The outcome was monitored by TLC. The reaction mixture was filtered on paper and evaporated under vacuum. The crude product (4.4 g) was purified by flash chromatography on RP18 using the following eluents in gradient: H<sub>2</sub>O, H<sub>2</sub>O/CH<sub>3</sub>OH 98:2, 95:5, 9:1, 8:2, CH<sub>3</sub>OH, affording 1.52 g of 1-butyl-3-propargylimidazolium bromide and 2.1 g of pure product 3 (1.5 mmol, 87%).

All building block preparation, full characterization off all products, NMR spectra and DSC thermograms are reported in the ESI.

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