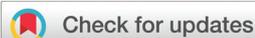


REVIEW

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Direct synthetic routes to functionalised crown ethers

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Crown ethers are macrocyclic hosts that can complex a wide range of inorganic and organic cations as well as neutral guest species. Their widespread utilization in several areas of fundamental and applied chemistry strongly relies on strategies for their functionalisation, in order to obtain compounds that could carry out multiple functions and could be incorporated in sophisticated systems. Although functionalised crown ethers are normally synthesised by templated macrocyclisation using appropriately substituted starting materials, the direct addition of functional groups onto a pre-formed macrocyclic framework is a valuable yet underexplored alternative. Here we review the methodologies for the direct functionalisation of aliphatic and aromatic crown ethers sporadically reported in the literature over a period of four decades. The general approach for the introduction of moieties on aliphatic crown ethers involves a radical mediated cross dehydrogenative coupling initiated either by photochemical or thermal/chemical activation, while aromatic crown ethers are commonly derivatised via electrophilic aromatic substitution. Direct functionalization routes can reduce synthetic effort, allow the later modification of crown ether-based architectures, and disclose new ways to exploit these versatile macrocycles in contemporary supramolecular science and technology.

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1. Introduction

Crown ethers (CE), in their most common form, are macrocyclic oligomers of ethylene oxide characterised by selective binding abilities toward cationic and neutral species. Although cyclic polyethers had been known since the early 1900s,¹ Charles J. Pedersen was the first in 1967 to discover an efficient strategy to prepare macrocyclic polyethers, and to systematically study their binding properties towards metal cations.² Pedersen named “crown ethers” this new class of compounds, inspired by the appearance of the molecular models of the complexes formed with cations, in which the ether host seems to crown the metal guest (Fig. 1).³ His seminal work led Pedersen, along with Donald J. Cram and Jean-Marie Lehn, to receive the Nobel Prize in Chemistry in 1987, for “the development and use of molecules with structure-specific interactions of high selectivity”.^{3–5} CE have been

instrumental for the advancement of the field of supramolecular chemistry^{6,7} and have found widespread application,⁸ so much so that currently many of them are commercially available.

CE can be divided into two groups: aliphatic and aromatic (Fig. 2). The most common aliphatic CE are cyclic oligomers of ethylene oxide, in which from four to a maximum of ten –

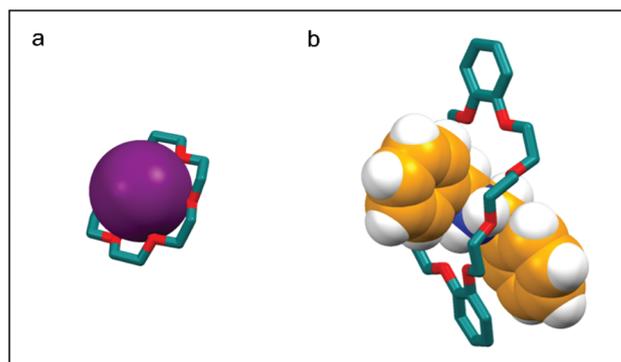


Fig. 1 Representative examples of crown ether-based supramolecular elements. Crystal structure of: (a) the supramolecular complex formed between the potassium cation and 18-crown-6; (b) the pseudorotaxane consisting of a dibenzylammonium axle threaded through dibenzo-24-crown-8.

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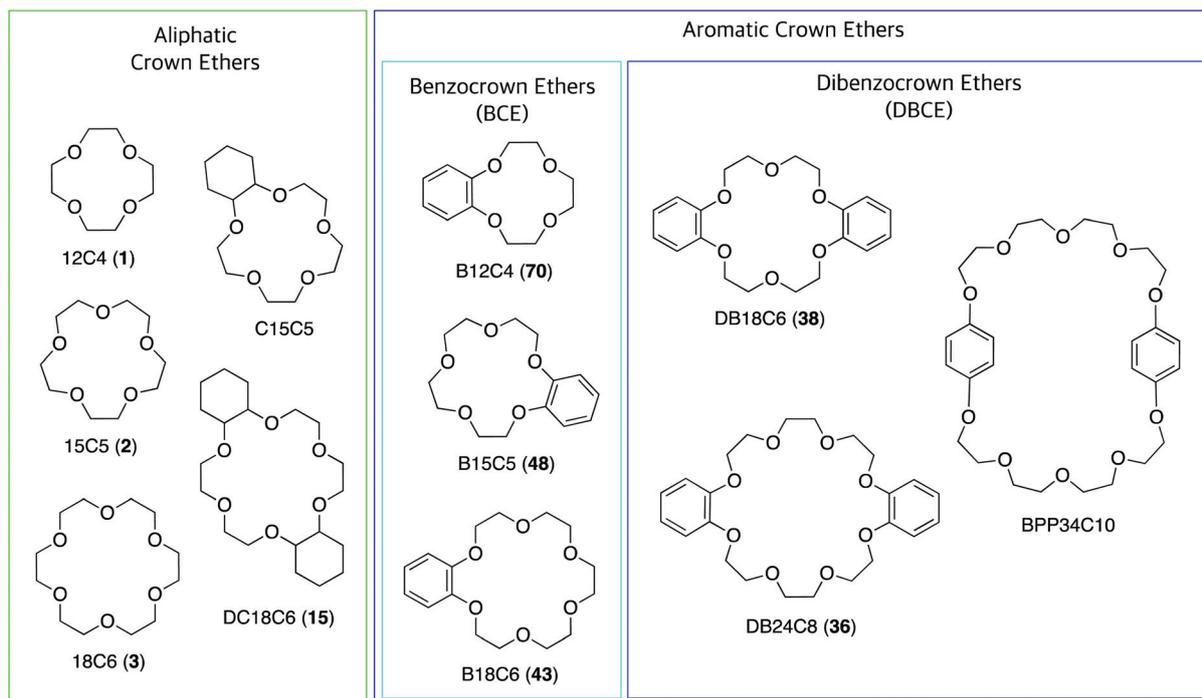
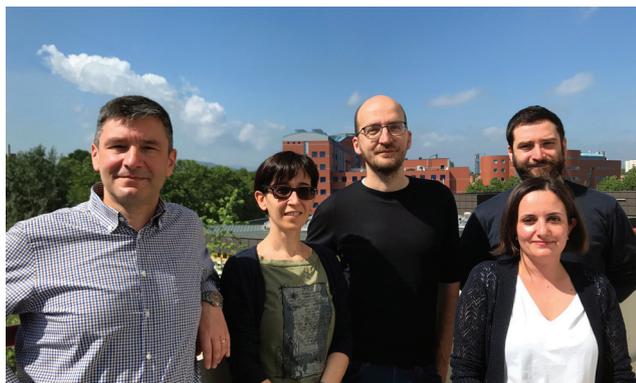


Fig. 2 Structure of commonly used crown ethers, most of which are commercially available. The numbers in parentheses are the compound labels used in this article.

(CH₂CH₂O)- repeating units are linked together; one or more ethylene groups of the macrocycle may be part of an aliphatic moiety such as cyclohexyl. Aromatic CE are characterised by the presence of endocyclic aromatic rings in their structure. Although a wide range of aromatic moieties has been incorporated in aromatic CE,⁹ the benzene ring represents by far the most common instance, giving rise to benzocrown (BCE) and dibenzocrown (DBCE) ethers. Crown ethers are conventionally

indicated as *x*-crown-*y* (abbreviated *x*C_{*y*}) in which *x* is the number of atoms in the macrocyclic cavity and *y* is the number of these atoms that are oxygen. Thus, 18-crown-6, or 18C6, is a crown ether with a cavity of 18 atoms, 6 of which are oxygen.

The peculiar characteristics of CEs originate from the graceful interaction between the chemically stable and conformationally flexible ethylene units, and the nucleophilic oxygen atoms symmetrically arranged around the ring. This combi-



From left to right: Alberto Credi, Serena Silvi, Massimo Baroncini, Jessica Groppi and Federico Nicoli

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nation generates an electron rich cavity able to accommodate suitable guests, as well as to endow the compounds with a relatively amphiphilic nature.^{3,10} Early complexation studies were focused on the interaction between CE and metal ions: it was demonstrated that the process is driven by several factors, including the relative sizes of the ether host and the cationic guest, the charge of the cation, the number and location of the oxygen atoms, the steric hindrance on the ring, and the competition by the solvent.^{2,3,6,7}

Indeed, CE are able to selectively bind alkali and alkaline earth ions (Fig. 1a), forming complexes which, owing to the lipophilic character, are soluble in non-polar solvents, thus acting as carriers of the charged species. For this reason, CE have been extensively used in phase transfer catalysis¹¹ and ion extraction;¹² more recently, they have been exploited as ion translocators and as components for synthetic channels through lipidic membranes.¹³ In the last three decades, it has been demonstrated that the complexing ability of CE is not limited to metal cations, as CE can generate stable supramolecular complexes with a wide variety of organic guests in aprotic solvents (Fig. 1b). Arenediazonium salts, which are readily complexed and stabilised by 18C6 and 21C7, were one of the first reported examples of non-metallic guests.¹⁴ Aromatic CEs, by virtue of their π -electron rich aromatic groups, act as hosts for different π -electron poor guests such as bipyridinium,¹⁵ diazapyrenium,¹⁶ bis-(pyridinium)ethane,¹⁷ imidazolium,¹⁸ and triazolium.¹⁹ Besides electrostatic effects, both donor-acceptor π - π interactions and strong hydrogen bonds contribute to the formation and stability of these complexes.

The complexes of primary alkylammonium ions (RNH_3^+) with DB18C6 have been extensively studied. The host and guest interact in a face-to-face orientation, with the formation of three alternating hydrogen bonds between the oxygen atoms of the macrocycle and the ammonium group, forming very stable supramolecular entities. A consequence of this binding motif is that the stability of complexes formed with secondary and tertiary ammonium ions is much lower.²⁰

Stoddart and co-workers first demonstrated that crown ethers with a larger cavity, such as DB24C8, form complexes with secondary alkylammonium ions in which the cation “pierces through” the cavity of the macrocycle (Fig. 1b).²¹ Secondary ammonium guests designed to have an axle-type structure are therefore able to thread appropriately sized crown ethers²² to generate pseudorotaxanes which are not only interesting *per se*,²³ but also useful supramolecular precursors to mechanically interlocked molecules (MIMs). CE, given their versatility as host molecules, have nowadays become a staple in the construction of MIMs and have been included in the design of hundreds of rotaxane architectures and catenane topologies.²⁴ A direct consequence of the inclusion of CE as components of MIMs, is their application in the development of artificial molecular machines:^{24–26} pH, redox, or light activated mechanical switches²⁷ and molecular pumps²⁸ are just a few examples of molecular devices incorporating CE. The interest in functionalising CE has grown in parallel to the number of their areas of application. Crown ethers have been deriva-

tised in order to couple the ability to form complexes with other functions such as catalysis,²⁹ self-assembly³⁰ and sensing,³¹ and to be introduced in dendrimers,³² polymers,³³ and covalent³⁴ or metal organic frameworks.³⁵ In the field of MIMs, functionalised CE have been used for the construction of interlocked polymers³⁶ and higher order structures,³⁷ molecular transporters,³⁸ mechanically planar chiral rotaxanes,³⁹ and dynamic crystalline materials.⁴⁰

Despite the extensive application of functionalised CE and the astounding number of reports dealing with the properties and uses of this class of macrocycles, to our best knowledge the only review article on the synthesis of modified CE was published by Bradshaw *et al.* in 1980.⁴¹ Homberg *et al.* recently described in a minireview an alternative approach to templated ring closure for the synthesis of chiral polyether macrocycles.⁴² To the present day, only one publication by Pluzhnik-Gladyr describes methodologies for the direct halogenation of CE.⁴³

This review will focus on direct synthetic routes to functionalised CE, encompassing publications until April 2021; the literature cited in previous reviews will not be included, unless it is necessary to better assess newer protocols. After a brief excursus regarding the main synthetic strategies for the preparation of functionalised crown ethers and their pro and cons, the discussion will move to direct functionalisation protocols and it will be organized according to the class of the CE substrate, either aliphatic or aromatic.

2. Synthetic approaches to functionalised crown ethers

The synthesis of functionalised crown ethers is performed following two main approaches: templated macrocyclisation, using pre-functionalised starting materials, or direct functionalisation of previously formed CE. Although templated macrocyclisation is the most used approach for the synthesis of functionalised CE, the introduction of substituents on pre-formed macrocycles represents a valid and, under some aspects, superior alternative. First of all, direct functionalisation routes are obviously the only option available when the CE to be functionalised is irreversibly embedded in a more extended architecture (*e.g.*, a MIM). Hence, identifying procedures to perform selective reactions on CE is important to enable the modification of multicomponent species *via* post-synthetic pathways.

The protocols for the synthesis and purification of non-functionalised crown ethers have been optimized for large scale production, and a number of CE are currently commercially available at reasonable prices. Therefore, the direct functionalisation of a purchased macrocycle may drastically reduce the synthetic effort necessary to prepare *ad hoc* CE. This is particularly true for aliphatic CE, for which the preparation of the derivatised precursors usually requires a significant number of steps, potentially resulting in a waste of time and resources compared to a one-step direct functionalisation. Moreover, in templated approaches, the introduced functional groups must



be very stable under the macrocyclisation reaction conditions. Specifically, they must be able to withstand basic conditions and heating, and they must be inert towards nucleophilic addition as well as not being nucleophiles themselves; if this is not the case, parasite processes will likely lead to low yields and challenging purification procedures. This stringent limitation is clearly overcome by performing the functionalisation directly as the final step.

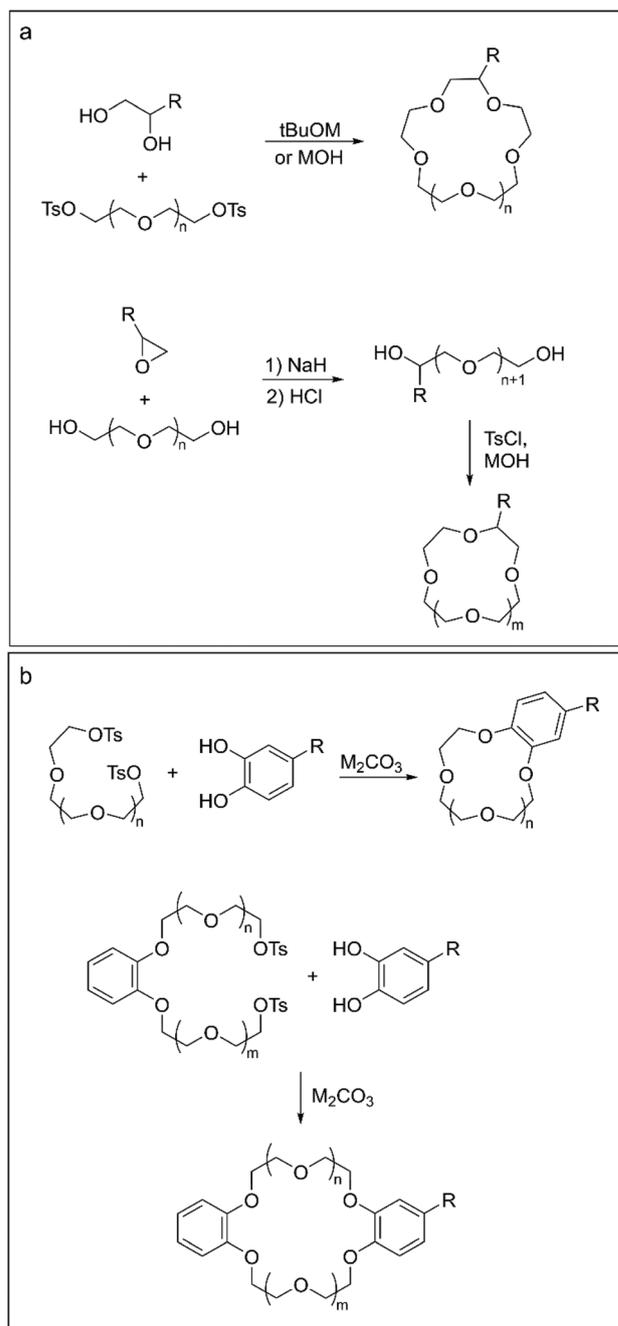
The principal limitation of direct approaches is indeed the lack of efficient, rigorously described and verified protocols and procedures. For example, direct reactions for mono-functionalisation of DBCE are characterised by poor yields, while those for bis-functionalisation suffer from scarce regioselectivity. Another drawback of direct functionalisation protocols is that an excess of the starting CE (or CE-containing substrate) must usually be employed to reach high yields of the final product; in most instances, however, the unreacted material can be recovered during purification. Surely, albeit direct functionalisation approaches are still underexplored, they can represent an advantageous and expedient synthetic strategy that deserves to be considered while confronting challenging CE-based synthetic targets.

Templated strategies rely on the size complementarity between the cavity of the target macrocycle and an added metal cation. The latter acts as a template by pre-organising the polyether chain precursor into the correct conformation required for efficient cyclisation, hence minimising the formation of polymeric side products.^{7,10} Thus, Li^+ templates the macrocyclisation of 12-membered CE, whereas Na^+ , K^+ and Cs^+ favour 15-, 18- and 24-membered cycles, respectively.⁴⁴⁻⁴⁷

Aliphatic CE can be obtained either by closure of the ether macrocycle by nucleophilic addition of a functionalised diol to an *n*-ethyleneglycol-ditosylate (Scheme 1a, top)⁴⁴ or by a two-step procedure involving the reaction between an *n*-ethyleneglycol and a derivatised epoxide to produce the open functionalised (*n* + 1)-ethyleneglycol chain. The latter is then converted to the final crown ether *via* a one-pot tosylation-macrocyclisation reaction (Scheme 1a, bottom).⁴⁵ The yield of the isolated products could vary significantly according to the final ring size and the nature of the functional group, ranging from 12% to 72%.

Templated macrocyclisation represents the go-to approach for the synthesis of BCE and DBCE presenting functional groups on the aromatic portion of their structure. In a typical procedure, a functionalised catechol is reacted with either an *n*-ethyleneglycol-ditosylate (or di-halogen) chain, to obtain BCE (Scheme 1b, top),⁴⁶ or with a benzo-di-*n*-ethyleneglycol-ditosylate precursor, in the case of DBCE⁴⁷ (Scheme 1b, bottom). Aromatic CE are routinely obtained in 40%–50% yield following such synthetic routes.

The methodologies for direct functionalisation will be thoroughly discussed in the upcoming sections of this review. In brief, functional groups can be introduced on aliphatic CE mainly *via* radical-mediated cross dehydrogenative coupling (CDC), while aromatic CE are generally functionalised *via* electrophilic substitution reactions of the aromatic moieties.



Scheme 1 Methodologies for the templated synthesis of functionalised aliphatic (a) and aromatic (b) crown ethers.

3. Methodologies for direct functionalisation

3.1. Aliphatic crown ethers

As introduced in the previous paragraph, most of the literature describing the direct functionalisation of aliphatic CE relies on the use of CDC for the introduction of a variety of functional groups: the selective oxidation of the $\alpha\text{-C}(\text{sp}^3)\text{-H}$ bond to $\alpha\text{-C}(\text{sp}^3)\text{-X}$ ($\text{X} = \text{C}, \text{N}, \text{F}$) bond is achieved *via* radical inter-

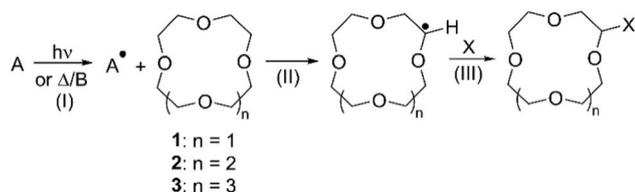


mediate mechanism.⁴⁸ The process can be divided in three distinct steps: (I) generation of an electrophilic radical; (II) hydrogen abstraction from the CE by the electrophilic radical, with formation of a radical at the electron-rich α -carbon; (III) reaction of the radical with the coupling partner to yield the functionalised crown (Scheme 2).

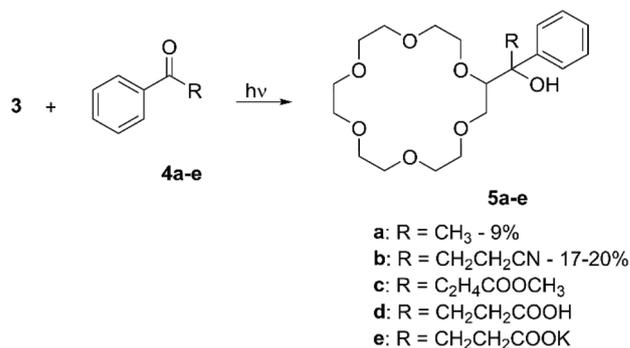
The routes for direct functionalisation of aliphatic CE can be divided in two groups, according to the method used for the generation of the electrophilic radical (step I). As the latter can be produced by either photochemical or thermal/chemical activation, this section will be organised accordingly. Peculiarities will be dealt with in due course, but some general remarks can be made. All the examples found report mono-functionalisation, although a large excess of the starting CE is usually needed. Reactions are normally performed under inert atmosphere and the purification of the derivatives is typically straightforward, achieved either by fractional distillation or chromatography. Finally, higher yields are reported for procedures that rely on photochemical radical generation compared to thermal/chemical one. The implications related to the generation of one or more chiral centres on the crown ether upon introduction of functional groups are frequently overlooked. Indeed, the functionalization of aliphatic CE leads to the formation of enantiomers, or diastereomeric pairs if a chiral centre is also present on the grafted functional group. Although such stereoisomers could be separated and might exhibit different recognition properties, they are usually isolated and characterized as mixtures (*e.g.* racemates).

3.1.1. Direct functionalisation by photochemical activation. One of the earliest examples of direct functionalisation of aliphatic CEs is represented by the photochemical derivatisation of 18-crown-6 (**3**) with alkyl aryl ketones reported by Tada *et al.*⁴⁹ Irradiation with a Hg lamp of a 1 : 1 mixture of **3** and a ketone for several hours produced the corresponding mono-functionalised derivatives in yields comprised between 7% and 21%, according to the nature of the R group present on the keto moiety. It is interesting to note that higher yields were obtained for those ketones able to generate complexes with **3**, *i.e.* **4b** and **4e** (Scheme 3). Similarly, aliphatic CE were directly functionalised with 1,4-benzoquinones by photoirradiation.⁵⁰

More recently, Kamijo *et al.* exploited the ability of photochemically generated oxyl radicals to abstract a hydrogen atom by homolytic C–H bond cleavage, to develop a general methodology for the conversion of electron-rich C(sp³)–H into C(sp³)–

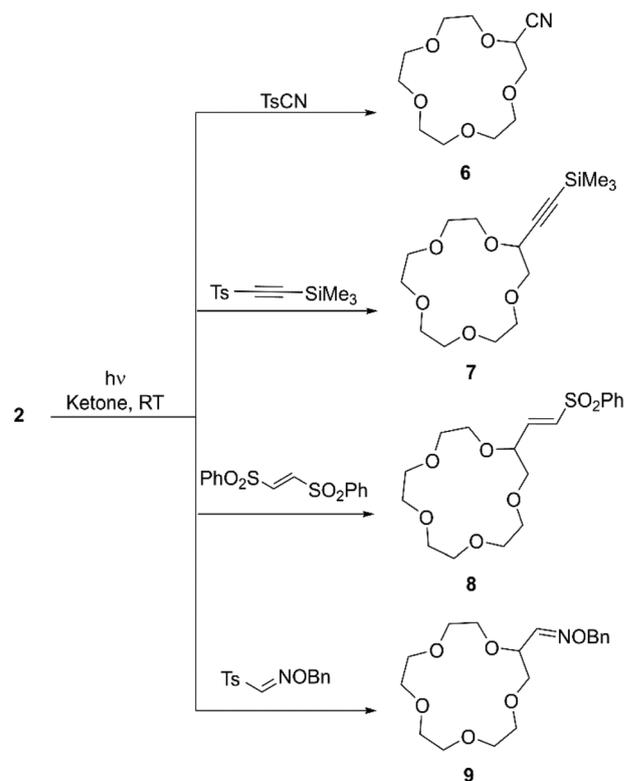


Scheme 2 Functionalisation of aliphatic crown ethers via cross dehydrogenative coupling (CDC).



Scheme 3 Photochemical functionalisation of 18C6 (**3**) with alkyl-aryl ketones.

C bonds. In this instance the ketone only acts as a photosensitiser in the process and the coupling partner is added as a tosyl derivative. Such an approach (Scheme 4) allowed to introduce cyano,⁵¹ alkynyl,⁵² alkenyl⁵³ and aldoxime (as formyl precursor)⁵⁴ functional groups on alkanes, benzylic compounds, ethers, alcohols and amines, generating derivatives suitable for conversion to synthetically relevant synthons. 15-crown-5 (**2**) was included in the substrate scope: irradiation with a Hg lamp of a mixture containing an excess of **2**, the ketone (1 equiv.) and the coupling partner (1 equiv.) at room temperature for periods that depend on the coupling partner (Table 1)



Scheme 4 Functional groups introduced on 15C5 (**2**) according to the methodology reported by Kamijo *et al.*



Table 1 Reaction conditions reported by Kamijo *et al*

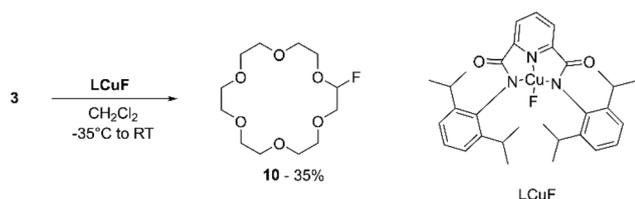
Product	Equiv. of 2	Ketone	Solvent	<i>t</i> (h)	Yield (%) ^{ref}
6	8	Ph ₂ CO	CH ₃ CN	3	84 ⁵¹
7	8	Ph ₂ CO	<i>t</i> -BuOH	1	82 ⁵²
8	5	Ph ₂ CO	CH ₃ CN	5	71 ⁵³
9	8	4-BzPy	CH ₂ Cl ₂	24	58 (89) ^{a,54}

^a Yield determined by ¹H NMR.

leads to mono-functionalisation in high yield, despite the presence of multiple reactive sites on the molecule (Scheme 4).

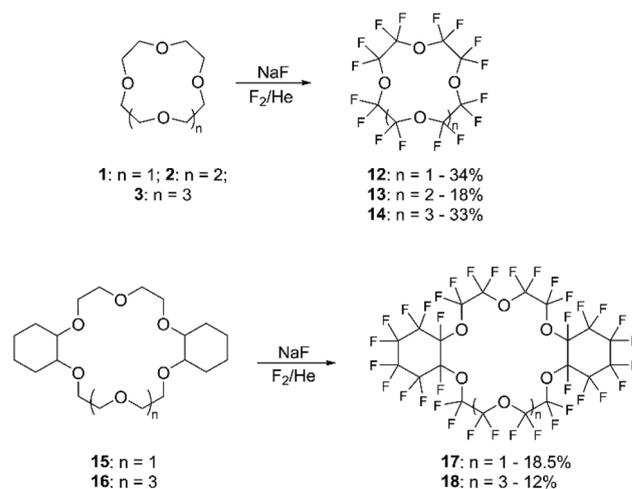
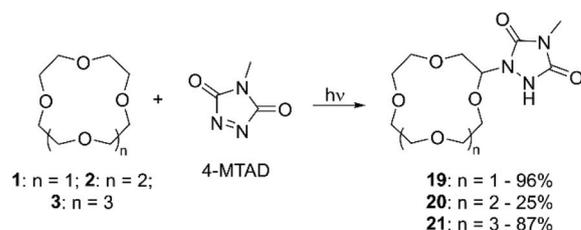
This work motivated Beniazza *et al.* to apply a similar approach to the mono-fluorination of cyclic ethers to obtain derivatives suitable for further modification by nucleophilic substitution.⁵⁵ The optimised procedure, consisting of a two-step one-pot protocol, was applied to the functionalisation of **3** with benzyl alcohol. First, a CHCl₃ solution containing **3** (1 equiv.), a catalytic amount of benzophenone (2% mol), and *N*-fluorobis(phenyl)sulfonimide (NFSI) (0.5 equiv.) as a fluorine source, is irradiated at 320–390 nm for 20 minutes at room temperature. This process generates a transient mono-fluorinated macrocycle (**10**) in 74% yield, which, by addition of benzyl alcohol in the second step of the reaction, undergoes nucleophilic substitution affording product **11** in 56% yield (Scheme 5). The transient nature of the monofluorinated adduct was explained by the formation of sulfonimide acid as a side product, which catalyses fluoride elimination.

Compound **10** was also reported by Bower *et al.*⁵⁶ In this work, a formally copper(III) fluoride complex (LCuF) performed both the hydrogen atom abstraction and radical capture roles. Upon mixing **3** and LCuF in a 8 : 1 ratio in dichloromethane, product **10** was obtained in 35% yield (Scheme 6). The reactivity of the monofluorinated crown ether, however, was not further investigated.

**Scheme 5** Direct fluorination of 18C6 (**3**) and subsequent nucleophilic addition of benzyl alcohol.**Scheme 6** Direct fluorination of 18C6 (**3**) using copper complex LCuF.

Previous to these recent studies on direct mono-fluorination, only per-fluorination of aliphatic CE, including cyclohexano derivatives, had been carried out.⁵⁷ The general procedure consisted in coating NaF with the chosen CE followed by exposing the solid mixture to a flow of fluorine gas in a cryogenic fluorination reactor under inert conditions (Scheme 7). The yields, that range between 12% and 35%, were highly affected by several parameters, including fluorination conditions, the exposed surface area of the starting materials, as well as the initial purity of the reagents.

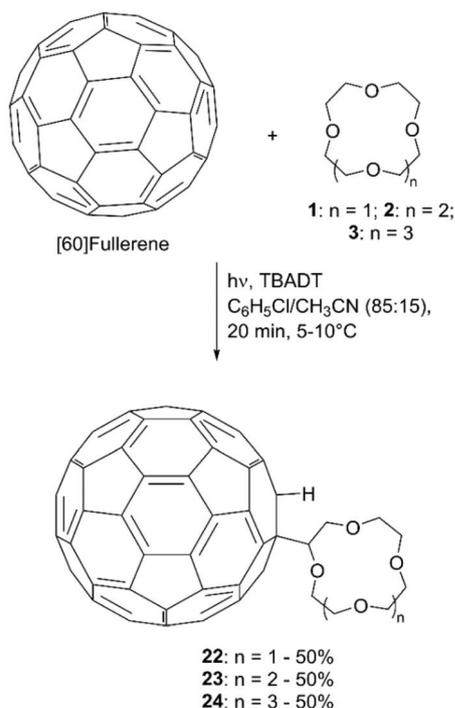
Risi *et al.* studied the photochemical coupling reaction between cyclic ethers and 4-methyl-1,2,4-triazoline-3,5-dione (4-MTAD).⁵⁸ The interest in such a specific functionalisation originates from the wide application of triazolinedione compounds in the fields of polymer science and click chemistry.⁵⁹ Slow addition of 4-MTAD to an excess of CE 12-crown-4 (**1**), **2** or **3** under continuous laser irradiation at $\lambda = 514.5$ nm for several days, allowed for the formation of the corresponding α -urazolyl derivatives. While in the case of **2** and **3** only the mono-functionalised product was isolated, for **1** also the bis-urazolyl compound was obtained, for which the authors suggest either a symmetrical 1,3 or 1,7 substitution pattern according to the simple ¹H NMR and ¹³C NMR spectra. (Scheme 8). The reaction mechanism, elucidated by ESR and computational calculations, involves the photoreduction of

**Scheme 7** Perfluorination of aliphatic crown ethers.**Scheme 8** Direct functionalisation of aliphatic crown ethers with 4-MTAD.

4-MTAD to generate an urazolyl radical, followed by abstraction of a hydrogen atom from the polyether, and terminated in the coupling of the two intermediates. The reaction yields were excellent for products **19** and **21** while only 25% was reported for compound **20**; no further investigation was carried out to elucidate the reason behind the different reactivities of the three CE.

The covalent attachment of CE to [60]fullerene (C_{60}) has attracted attention for the photophysical and electrochemical properties of the resulting adducts and their potential applications in ion sensing and fluorescence switching devices. Tzirakis *et al.* first described the direct coupling of CE to C_{60} , achieved photochemically using tetrabutylammonium decatungstate $[(nBu_4N)_4W_{10}O_{32}]$, TBADT as a photosensitiser (Scheme 9).⁶⁰ The procedure, applied to the functionalisation of **1**, **2** and **3**, consisted in the irradiation with a xenon lamp of a mixture of the CE (100 equiv.), C_{60} (1 equiv.) and TBADT (0.5 equiv.) in C_6H_5Cl/CH_3CN (85:15) for 20 minutes at 5–10 °C. The yield was reported to be 50% for all the three isolated products. The authors also mentioned that the more common photosensitiser benzophenone was tested, but lower yields (20%) were obtained despite the use of 100 equiv. of ketone.

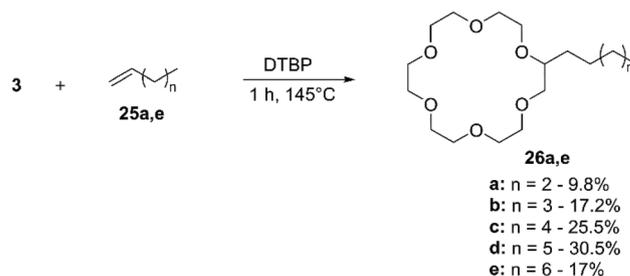
In a recent publication, compound **23** was synthesised with the aim to study its reactivity toward sodium and bis(arene) chromium compounds.⁶¹ The coupling between C_{60} and 15C5 (**2**) was performed photochemically in presence of benzophenone at 50 °C, irradiating a solution of the reagents in DCB for 5 hours. The reported yield was 30%.



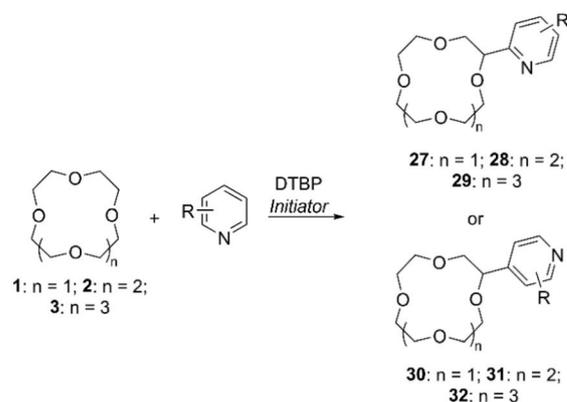
Scheme 9 Photochemical functionalisation of [60]fullerene with aliphatic crown ethers.

3.1.2. Direct functionalisation by thermal/chemical activation. The optimisation of a route for the addition of CE to olefins was attempted by Zeleconok *et al.*⁶² The approach consisted in the treatment of crown ether **3** with di-*t*-butylperoxide (DTBP) at high temperature to generate a radical, that would then attack the double bond of the substrate, thus yielding the alkylated final product (Scheme 10). The fast mixing of the reaction components **3**:olefin:DTBP in 10:2:1 molar ratio led to very low conversion of **3** and formation of telomers, highlighting the poor control over the process. On the other hand, the slow addition of peroxide and olefin to a very large excess of **3** (**3**:olefin:DTBP = 20:2:1) led to a slight improvement of the yield, reaching values up to 30%. Nonetheless, the methodology has been applied to the functionalisation of **1**, **2** and **3** with allyl chloride for the introduction of 8-hydroxyquinoline⁶³ and to synthesise alkyl-CE for the development of antifungal agents.⁶⁴

DTBP in presence of radical initiators was also used as a hydrogen abstractor in protocols for the functionalisation of CE with N-aromatic bases (Scheme 11). Early procedures relied on the use of metals such as Fe(II) and Ti(III) to generate the peroxy radical,⁶⁵ while in a recent more “green” approach DTBP was activated by photoirradiation with a higher control on the regioselection of the final products (Table 2).⁶⁶ In all cases, functionalised CE were obtained in good yields.



Scheme 10 Alkylation of 18C6 (**3**) with chains of variable length.



Scheme 11 Functionalisation of aliphatic crown ethers with aromatic bases.



Table 2 Reaction conditions for the functionalisation of aliphatic crown ethers with aromatic bases

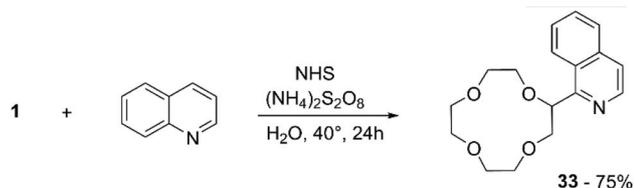
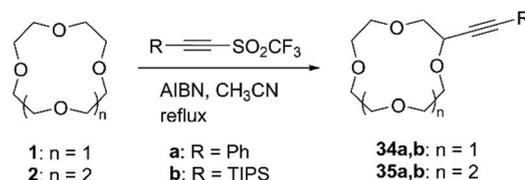
CE	N-aromatic base	Init.	Solv.	<i>t</i> (h)	<i>T</i> (°C)	Yield (%) [Prod] ^{ref}
3	2-Methylquinoline	FeSO ₄	DMSO	1	RT	70–90 [32] ^{65a}
3	Quinoxaline	TiCl ₃	H ₂ O	—	RT	— [29] ^{65b}
3	2-Methylquinoline	TiCl ₃	H ₂ O	—	RT	— [32] ^{65b}
3	2,6-Lutidine	TiCl ₃	H ₂ O	—	RT	— [32] ^{65b}
3	4-Methylquinoline	TiCl ₃	H ₂ O	—	RT	— [29] ^{65b}
3	Quinoline	FeSO ₄	DMSO	0.5	RT	20 [19] ^{65c} 30 [32] ^{65c}
3	Quinoxaline	FeSO ₄	DMSO	0.5	RT	85 [29] ^{65c}
3	2-Methylquinoline	FeSO ₄	DMSO	1	RT	65 [32] ^{65d}
1	2-Methylquinoline	FeSO ₄	DMSO	1	RT	69 [30] ^{65d}
2	2-Methylquinoline	FeSO ₄	DMSO	1	RT	65 [31] ^{65d}
3	4-Methylquinoline	hν	EDC	23	40	71 [29] ⁶⁶
2	4-Methylquinoline	hν	EDC	23	40	61 [28] ⁶⁶
3	Isoquinoline	hν	EDC	23	40	68 [29] ⁶⁶
2	Isoquinoline	hν	EDC	23	40	61 [28] ⁶⁶

An alternative to peroxy radicals for the direct attachment of N-aromatic bases to CE is represented by N-hydroxysuccinimide (NHS)-mediated C α -heteroarylation.⁶⁷ The reaction consists in the formation of a reactive N-radical form of NHS by oxidation with ammonium persulfate (APS); the generated radical carries out hydrogen abstraction on the ether, which in turn proceeds to attack the heteroaromatic base in a regioselective fashion (Scheme 12). Following this method, **1** was selectively introduced onto position 1 of isoquinoline to obtain compound **33** in 75% yield.

The serendipitous discovery that acetylenic triflones spontaneously react with THF at room temperature to afford the α -alkynylated product in almost quantitative yields brought Fuchs *et al.* to establish a methodology which exploits the reactivity of the trifluoromethyl radical towards C–H hydrogen abstraction for the introduction of alkyne functional group on several classes of compounds.⁶⁸ Subsequently, the reaction was successfully applied for the direct alkylation of **1** and **2** (Scheme 13).⁶⁹ Heating an excess of CE and acetylenic triflone (1 equiv.) in CH₃CN in presence of a catalytic amount of azobisisobutyronitrile (AIBN) (20% mol) as the radical initiator, led to the conversion to the corresponding mono-alkynylated product in good yields (Table 3).

3.2. Aromatic crown ethers

The optimisation of synthetic protocols for production upscaling and the straightforward access to functionalised catechols enabled the preparation of a large variety of aromatic CE characterised by a wide range of properties. Moreover, the ease

**Scheme 12** NHS mediated functionalisation of 12C4 (**1**) with isoquinoline.**Scheme 13** Alkylation of aliphatic crown ethers with acetylenic triflones.**Table 3** Reaction conditions for the functionalisation of aliphatic crown ethers with acetylenic triflones⁶⁹

Product	CE equiv.	<i>t</i> (h)	Yield (%)
34a	10	3	70
34b	5	6	70
35a	10	2	80
35b	5	5	70

of handling and the solubility in most organic solvents brought this class of crown ethers at the center of many basic and applied investigations. The direct functionalisation of BCE and DBCE is usually achieved by electrophilic substitution on the aromatic portion. Hence, this part of the review will be organised according to the introduced functional groups. Albeit procedures have been adapted from general methodologies used for the derivatisation of aromatic compounds, the outcome can be affected by electronic and steric effects related to ring size and conformation. The weak points of this approach are the lack of control on the number of groups introduced in the crown ether framework (specifically, mono-functionalised adducts are obtained in low yields, since bis-functionalisation frequently proceeds in parallel) and, relatively to DBCE, poor regioselectivity (both *syn* and *anti* di-substituted products are obtained and their separation is not straightforward).

3.2.1. Functionalisation with halides. In 2016 Pluzhnik-Gladyr published a review on halogenated BCE, focusing on three main approaches for direct halogenation.⁴³ The first one

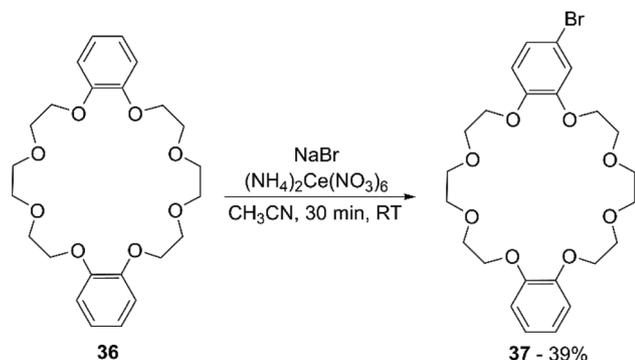


involves the use of molecular halogens. Such a technique is suitable for obtaining di-halogenated BCE and tetra-halogenated DBCE in good yields; the high reactivity of elemental halogen species however precludes the synthesis of mono-functionalised derivatives. The second methodology relies on N-halosuccinimides: while BCE can be easily halogenated with these reagents in aqueous media (the reaction can be catalysed by addition of acid), DBCE react only in organic solvents (CHCl_3 or CCl_4) or in mixtures of ethanol and water. Finally, direct halogenation can be achieved using hypohalites in water. Because of solubility reasons, this approach can only be used for the halogenation of BCE. Interestingly, acidic conditions lead to the addition of multiple halogen atoms, while basic pH allows to control the reaction and obtain the mono-halogenated product.

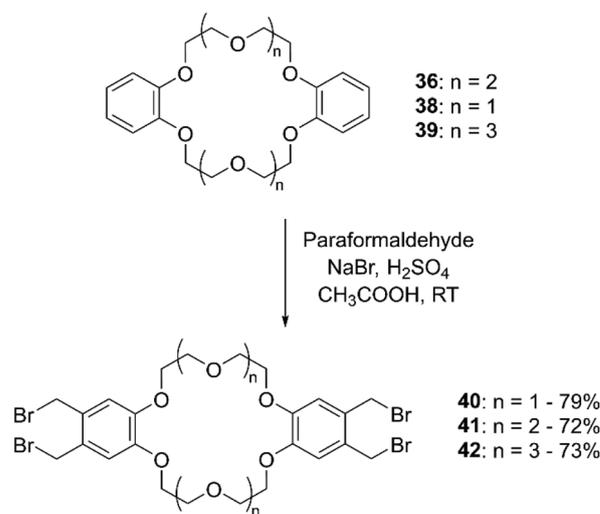
The reported methodologies were applied only for the direct addition of chlorine, bromine and iodine to BCE and DBCE. The author pointed out the lack of relevant literature focused on the direct fluorination of aromatic crown ethers.⁴³ In general, direct bromination of BCE is the most successful reaction among the protocols mentioned above, with yields that can exceed 90%; chlorination and iodination are less performing due to either selectivity or stability reasons. Indeed, the most challenging aspect of the direct halogenation of DBCE is selectivity: the mono-substituted derivative is usually obtained in low yields since the reaction leads to the formation of mixtures of mono- and di-substituted species. Moreover, di-substituted derivatives could be obtained both as *anti* and *syn* isomers which can only be separated by fractional crystallisation. Higher yields (80–90%) could be achieved in the preparation of the tetra-substituted derivatives.

Recently, Mobian *et al.* reported the bromination of DB24C8 (**36**) using sodium bromide (NaBr) and cerium(IV) ammonium nitrate $[(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6]$ in acetonitrile (Scheme 14).⁷⁰ The reaction proceeds fast at room temperature and both mono- and di-functionalised adducts are formed. A yield of 39% was only reported for the mono-brominated derivative **37**.

The addition of (halogen)methyl groups is briefly described in the review cited at the beginning of this section,⁴³ where the approach reported by Biernat *et al.*,⁷¹ involving the use of par-



Scheme 14 Direct bromination of DB24C8 (**36**) with NaBr.

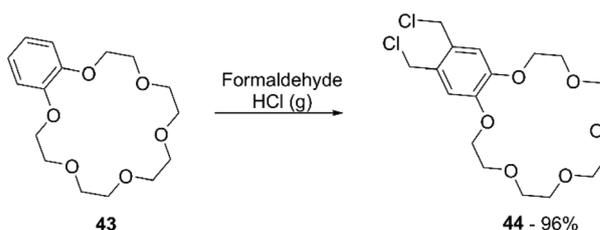


Scheme 15 Bromomethylation of DBCE.

aformaldehyde and hydrogen bromide in CH_3COOH , is given as an example for the bromomethylation of BCE and DBCE. An alternative procedure to obtain the tetra-bromomethyl-functionalised DBCE was reported by Nakamura *et al.*, substituting HBr with a combination of sodium bromide (NaBr) and H_2SO_4 (Scheme 15).⁷² Both methodologies led to yields that routinely exceeded 70%.

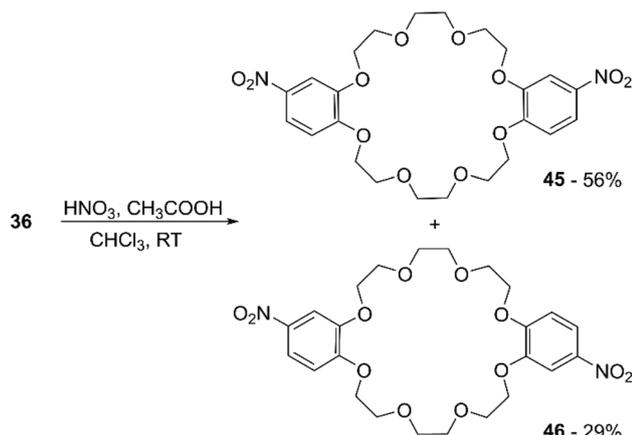
Chloromethylation has been performed in a similar way, using formaldehyde and gaseous HCl (Scheme 16). Following this procedure, a 90% yield of bis-chloromethylated B18C6 (**43**) was reported,⁷³ while for DB18C6 a conversion of 70% was obtained, with the formation of 80% of the mono-chloromethylated derivative and 20% of the bis-chloromethylated product.⁷⁴

3.2.2. Functionalisation with nitro- and amino- groups. The routes to the direct functionalisation of aromatic crown ethers with nitro groups follow the many standardised protocols for the nitration of aromatic compounds. They typically involve the reaction of the substrate with nitric acid (HNO_3) in presence of either CH_3COOH or H_2SO_4 , to generate the electrophilic species, in CHCl_3 at room temperature. The first example was reported by Feigenbaum *et al.*⁷⁵ The procedure, which used a mixture of HNO_3 and CH_3COOH as nitrating solution, allowed to obtain the di-nitro derivative of **36** as both the *syn* (**45**) and *anti* (**46**) isomers, which were easily separated



Scheme 16 Chloromethylation of B18C6 (**43**).





Scheme 17 Nitration of DB24C8 (36) according to the conditions reported by Feigenbaum *et al.*

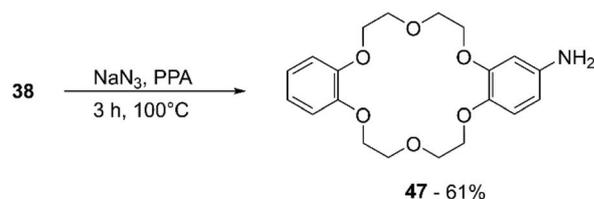
by fractional crystallisation. The overall yield of the nitration reaction was 85%, with an isolated yield of 34% for 46 (Scheme 17).

Slight variations of this protocol were adopted to convert B12C4, B15C5 and B18C6 into their mono-nitro⁷⁶ and di-nitro⁷⁷ derivatives in decent yields. Duggan *et al.* reported the synthesis of tetra-nitro derivatives of various DBCE in excellent yields, using H₂SO₄ instead of CH₃COOH in the nitrating solution.⁷⁸ Grebenyuk *et al.* described an alternative method for the nitration of BCE and DBCE with KNO₃ and polyphosphoric acid (PPA).⁷⁹ The process was carried out using a large excess of PPA, and different stoichiometric ratios between crown ether and KNO₃ were tested; however, mixtures of mono- and di-nitro derivatives were obtained in all cases.

Nitro derivatives are important compounds since they can be easily and quantitatively reduced to amino compounds, which in turn can be converted to other functional groups either for further derivatisation with chromophores or to be introduced in polymers.^{75–77} It is worth noting, however, that amino functionalised CE undergo fast oxidation, particularly the di- and tetra-modified derivatives; thus, they must be handled under a controlled atmosphere and cannot be stored for a long time.^{77,78}

A methodology for the direct amination of DB18C6 (38) was reported by Lyakhovnenko *et al.* using sodium azide (NaN₃) in PPA.⁸⁰ Heating at 100 °C of an equimolar mixture of 38 and NaN₃ in neat PPA led to the formation of the mono-functionalised derivative (47) in 61% yield (Scheme 18).

3.2.3. Functionalisation with formyl groups. Direct formylation of B15C5 was first achieved by Hyde *et al.* by means of the Vilsmeier reaction.⁸¹ Treating BCE with N-methylformanilide in presence of POCl₃ at 90 °C for 4 h yielded the mono-functionalised derivative in 30% yield. The demanding purification, which hampered the complete recovery of the product, pushed Wada *et al.* to resort to a different approach to functionalise B15C5 (48), B18C6 (43) and DB18C6 (38), adopting the classical Duff reaction for the formylation of



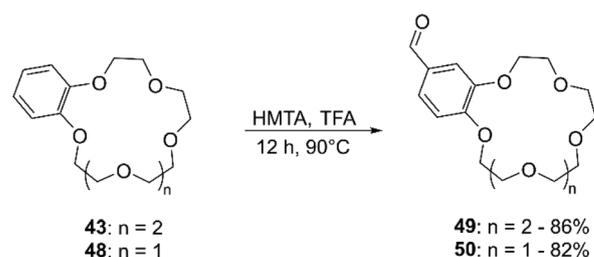
Scheme 18 Functionalisation of DB18C6 (38) with an amino group.

aromatics.⁸² Accordingly, CE were mixed with hexamethylenetetramine (HMTA) in presence of trifluoroacetic acid (TFA) and stirred at 90 °C for 12 hours. In these conditions, one formyl group is introduced in BCE while DBCE undergo difunctionalisation, both in excellent yields (Scheme 19). It is interesting to note that, while the nitration of DBCE results in the formation of *syn* and *anti* isomers, formylation leads to the exclusive formation of the *syn* isomer.

Formylbenzocrowns represent useful intermediates, since they can be easily converted to a wide range of functional groups. CEs modified according to Wada's procedure have been used for the synthesis of molecular tweezers containing cyclidene-Ni complexes⁸³ and BODIPY,⁸⁴ and derivatised with benzimidazole,⁸⁵ benzothiazolyl⁸⁶ and porphyrins.⁸⁷

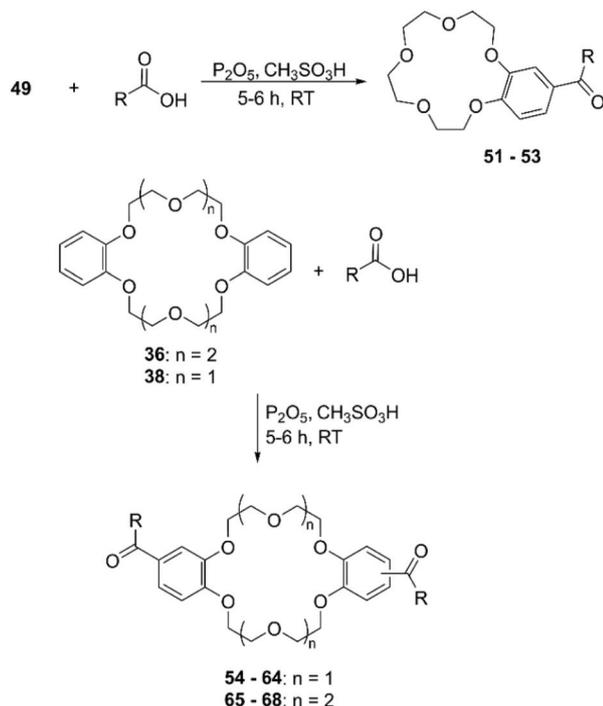
3.2.4. Functionalisation with acyl- and alkyl- groups. Direct acylation of BCE and DBCE has been achieved either using carboxylic acids in presence of Eaton's reagent (P₂O₅ and CH₃SO₃H) or with carboxylic acids/anhydride and PPA. The first approach to be optimised is illustrated in Scheme 20.⁸⁸ BCE were mono-functionalised with a wide range of acyl moieties in good yields, while modified DBCE were obtained as mixture of *syn* and *anti* isomers that could be separated by recrystallisation or exploiting their different solubilities in organic solvents (Table 4).

The functionalisation using PPA for the generation of the electrophile is the most frequently adopted methodology and reported yields are comparable with the ones obtained using Eaton's reagent (Scheme 21).⁸⁹ Saifullina *et al.* resorted to acetates as the source of acetyl group for the derivatisation of DBCE. It was demonstrated that there is a relation between the size of the counter cation of the acetate and the rate and regioselectivity of the reaction, due to the complexation between crown ether and cation.⁹⁰ Acyl derivatives, analogously to formyl ones, are suitable precursors for several functional



Scheme 19 Functionalisation of BCE with formyl groups.

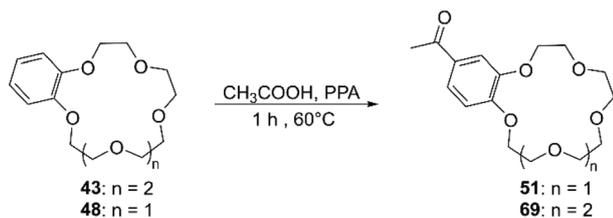




Scheme 20 Acylation of BCE and DBCE using Eaton's reagent.

Table 4 Products of the acylation using Eaton's reagent and yields⁸⁸

Prod.	R	Yield (%)	Prod.	R	Yield (%)
51	CH ₃	63	60	CH ₃ (CH ₂) ₇	84
52	CH ₃ (CH ₂) ₅	55	61	CH ₃ (CH ₂) ₈	75
53	CH ₃ (CH ₂) ₁₂	26	62	CH ₃ (CH ₂) ₁₀	79
54	CH ₃	86	63	CH(CH ₃) ₂	88
55	CH ₃ CH ₂	66	64	C(CH ₃) ₃	85
56	CH ₃ (CH ₂) ₂	72	65	CH ₃ (CH ₂) ₃	66
57	CH ₃ (CH ₂) ₃	100	66	CH ₃ (CH ₂) ₈	84
58	CH ₃ (CH ₂) ₄	78	67	CH ₃ (CH ₂) ₁₀	53
59	CH ₃ (CH ₂) ₅	86	68	CH ₃ (CH ₂) ₁₂	85



Scheme 21 Conditions for the acetylation of aromatic crown ethers.

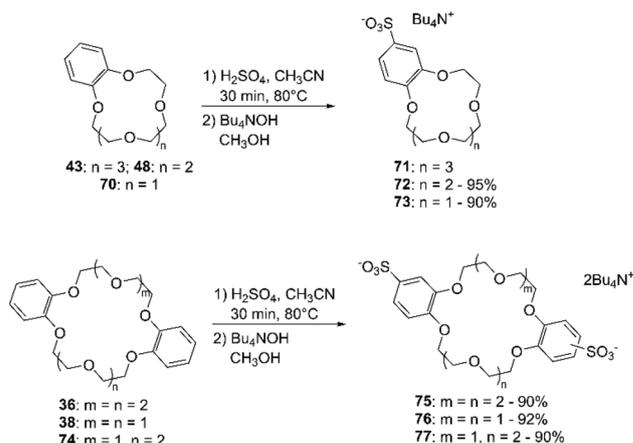
groups including vinyl,⁹¹ ester⁹² and α,β -unsaturated ketones.⁹³ Although acylated CE can be reduced in order to obtain alkyl derivatives, different procedures have been devised for the direct alkylation of BCE and DBCE. Alcohols in combination with PPA⁹⁴ or sulfuric acid (H₂SO₄)⁹⁵ have been used for the introduction of alkyl groups on aromatic CE. The outcome of the reaction proved to be dependent on the nature

of the alcohol used and the size of the CE. Moreover, in addition to the formation of regioisomers, these routes exhibited a poor control on the number of functional groups added to the CE substrate.

3.2.5. Functionalisation with sulfonate and sulfonyl chloride groups. Sasaki *et al.* described the sulfonation of BCE and DBCE using H₂SO₄ in acetonitrile.⁹⁶ While for both mono-sulfonation of BCE and di-sulfonation of DBCE high yields were reported (90%), more recent literature reports confirmed that di-sulfonated species are usually obtained as mixtures of isomers, whose properties could significantly vary from one another.⁹⁷ Sulfonated CE have been isolated as tetrabutylammonium salts, which are endowed with a better solubility in water and other protic solvents (Scheme 22).

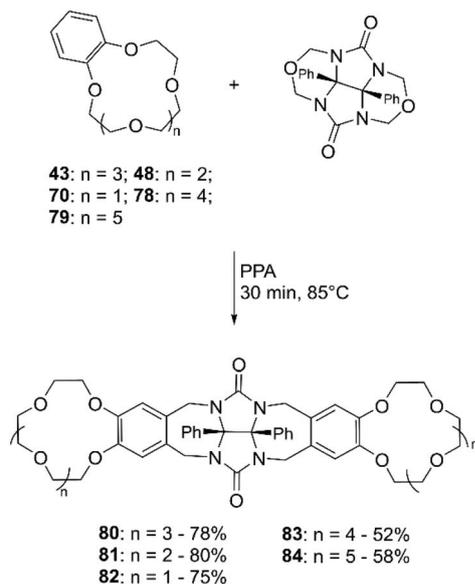
An alternative approach to sulfonation is based on the use of potassium sulfate in PPA.⁹⁸ This methodology afforded sulfonated BCE and DBCE in good yields. Sulfonated CE can be readily converted by treatment with sulfonyl chloride to their chlorosulfonate derivative, which in turn can be reduced to produce thiol-functionalised BCE.⁹⁹ A reported case of a good yielding direct chloro-sulfonation of aromatic CE involves the use of chlorosulfonic acid in chloroform.¹⁰⁰

3.2.6. Functionalisation with other groups. BCE have been functionalised with diphenylglycouril fragments to create molecular tweezers and clips characterised by a rigid backbone connecting two crown ether units. The original procedure by Nolte *et al.* envisaged the reaction of B15C5 with the tetrachloride derivative of diphenylglycouril in the presence of tin chloride (SnCl₄) to obtain the bis-functionalised derivative in 92% yield.¹⁰¹ Later, Bogaschenko *et al.* tried to reproduce the result, but reported lower yields which were in part ascribed to a challenging purification of the product. Hence, they tested a range of reaction conditions and diphenylglycouril derivatives in order to find an optimal procedure for the synthesis of molecular clips.¹⁰² The final proposed protocol relies on the use of bis(cyclomethoxymethylene)diphenylglycouril as a precursor in the presence of PPA. Higher yields (>70%) were reported for smaller CE (**80–82**), while macrocycles character-

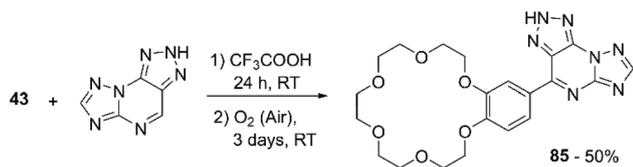


Scheme 22 Direct sulfonation of BCE and DBCE.





Scheme 23 Functionalisation of BCE with diphenylglycouril for the preparation of molecular clips.



Scheme 24 Functionalisation of B18C6 (43) with 8-azapurine analogues.

used by wider cavities (83, 84) were isolated in 50% yields (Scheme 23).

Gorbunov *et al.* developed a synthetic methodology for the introduction of aromatic ethers and thiophene onto H-azolo [1,5-*a*][1-3]triazolo[4,5-*e*]pyrimidines, analogues of 8-azapurines, aiming to develop compounds that present enhanced biological activity by the combination of multiple pharmacophore fragments.¹⁰³ The process involves a nucleophilic displacement of hydrogen (S_N^H) reaction characterised by a two-step addition-oxidation mechanism. B18C6 was considered for the scope of the reaction. Mixing the CE with the pyrimidine derivative in trifluoroacetic acid (CF_3COOH) allows the formation of the addition product, which is then oxidised to 85 in 50% yield by exposure to atmospheric oxygen over a three-day period (Scheme 24).

Conclusions

Crown ethers (CE) are a most prominent class of macrocyclic compounds in supramolecular science and technology. Their versatility as host molecules for cationic and neutral species allowed for their application in a wide range of fields including

catalysis, separation and purification, transport and delivery of ionic species, mechanically interlocked molecules and materials, and molecular machines. The growing complexity of systems of this kind and the interest in enriching the behaviour of CE as host compounds with other functions, has led to a growing need for the development of methodologies for the synthesis of derivatised macrocyclic polyethers that could be easily inserted into elaborated architectures.

Functionalised CE can be obtained either by templated macrocyclisation, using appropriately substituted starting materials, or through synthetic routes for the direct introduction of moieties on pre-formed macrocycles. Direct functionalisation of aliphatic CE is generally performed using cross dehydrogenative coupling (CDC) reactions: the process follows a radical mechanism initiated photochemically or thermally. Mono-functionalised aliphatic CE are thus obtained in good yields, albeit a large excess of the starting substrate is required. A wide range of functional groups has been introduced on BCE and DBCE *via* electrophilic aromatic substitution. Control over the number of moieties added on the product and regioselectivity represent the principal challenges in this case.

Despite the significant potential in the context of contemporary chemistry, the procedures dealing with the direct functionalisation of CE are quite scattered in the literature, and some of them are mere adaptations of general protocols. A focused optimisation of reaction conditions to fit the properties and structural characteristics of CE would allow a full exploitation of the opportunities offered by this approach, particularly with regard to the post-synthetic modification of sophisticated CE-based architectures. Indeed, the direct functionalisation of crown ethers could provide a valuable alternative to templated macrocyclisation, by reducing the synthetic effort and opening new routes to exploit this ceaselessly fascinating class of macrocycles.

Author Contributions

F. Nicoli: conceptualization, analysis, writing-original draft; M. Baroncini: supervision, writing-review and editing; S. Silvi: writing-review and editing; J. Groppi: conceptualization, analysis, writing-original draft; A. Credi: supervision, funding acquisition, writing-review and editing.

Conflicts of interest

The authors declare no conflict of interest.

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