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Protective carbon

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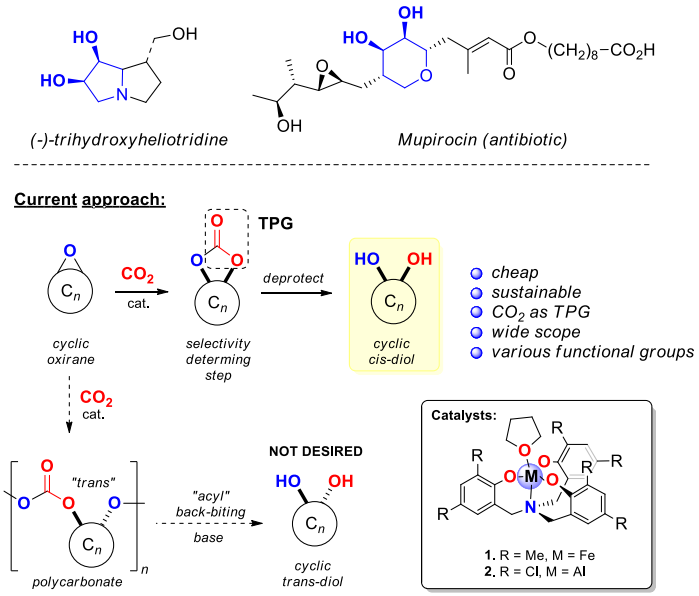
Carbon Dioxide as a Protecting Group: Highly Efficient and Selective Catalytic Access to Cyclic Cis-Diol Scaffolds**

Victor Laserna, Giulia Fiorani, Christopher J. Whiteoak, Eddy Martin, Eduardo Escudero-Adán, Arjan. W. Kleij**

***Abstract**: The efficient and highly selective formation of a wide range of (hetero)cyclic cis-diol scaffolds using powerful aminotriphenolate-based metal catalysts is reported. The key intermediates are cyclic carbonates that are derived in high yield and with high levels of diastereo- and chemo-selectivity from the parent oxirane precursors and carbon dioxide (CO_2). Deprotection of the carbonate structures affords synthetically useful cis-diol scaffolds with different ring sizes incorporating various functional groups. This atom-efficient methodology allows for simple construction of diol synthons using cheap and accessible precursors and green metal catalysts, and showcases the use of CO_2 as a temporary protecting group.*

Carbon dioxide (CO_2) represents an interesting carbon feed stock for organic synthesis, having a number of attractive features being renewable, cheap and readily available.[1] Recent progress in the area of CO_2 catalysis[2] has witnessed a spectacular increase in the application of this C_1 synthon providing access to important and functional chemical intermediates,[3] and precursors for (bio)renewable plastics.[4] One of the areas of high activity is the preparation of organic carbonates from oxirane/oxetane precursors giving rise to five- and six ring-membered cyclic structures.[5] Though this area has been developed to a sophisticated level,[6] important challenges remain to be resolved including the efficient conversion of internal cyclic epoxides[7] and their selective conversion towards the corresponding cyclic versus polycarbonate. The latter feature is especially vital to control the stereo-chemical outcome of the reaction as formation of the cyclic carbonate through a double inversion pathway leads to retention of the relative configuration at both carbon centers[8] whereas *poly*-carbonate formation followed by a depolymerization/hydrolysis pathway results in opposite stereochemistry (Scheme 1).[4b] We recently reported on powerful catalyst systems based on aminotriphenolate ligands (M = Fe, Al; Scheme 1, compounds **1-2**) which showed great versatility in the formation of both cyclic[7d,9] as well as polycarbonates.[10] Moreover, these systems proved to be highly efficient for the catalytic turnover of acyclic internal epoxides with ample functionality.



Scheme 1. Top: natural compounds with cyclic *cis*-diol scaffolds; below: synthetic approach towards *cis*-diols through intermediate carbonate formation using metal catalysts **1** and **2**.

Cyclic *cis*-diol scaffolds are key structural elements of various naturally occurring compounds such as (–)-trihydroxyheliotridine and Mupirocin (Scheme 1)[11] and are thus interesting synthetic targets. One of the most well-known methods for *cis*-diol formation is based on the Sharpless dihydroxylation of alkene precursors using osmium catalysis.[12] We envisaged that the catalytic formation of organic carbonates from cyclic oxiranes and CO_2 using earth-abundant and cheap metal catalysts followed by deprotection under basic conditions could offer a useful and alternative sustainable approach towards cyclic *cis*-diols.[13] Using this methodology, CO_2 has a dual role acting as a temporary protecting group (TPG; Scheme 1) that helps to stir the process stereo-selectivity, and as an oxygen source. Though various reports exist on diol formation from organic carbonates,[14] the substrate scope to date remains limited and has been primarily based on terminal epoxides which are relatively facile to convert, though cyclic *cis*-diol formation using CO_2 as a key reagent has rarely been studied.[15] Here we present a general approach towards functional cyclic *cis*-diol synthons using a versatile catalytic strategy that allows for efficient conversion of (internal)

[*] V. Laserna, Dr. G. Fiorani, Dr. C. J. Whiteoak, Dr. E. Martin, E. Escudero-Adán, Prof. Dr. A. W. Kleij
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans 16, 43007 – Tarragona (Spain)
Fax: (+)34-977920823
E-mail: akleij@iciq.es; chriswhiteoak@googlemail.com
Homepage: www.iciq.es

Prof. Dr. A. W. Kleij
Catalan Institute for Research and Advanced Studies (ICREA)
Pg. Lluís Companys 23, 08010 Barcelona (Spain)

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(hetero)cyclic oxirane substrates, suppressing undesired polycarbonate formation and thus controlling the stereo-selectivity. Further, this CO_2-based methodology allows for a broad substrate scope and good functional group tolerance, providing a wide range of accessible and functional *cis*-diol scaffolds in good to excellent yields.

Our first efforts focused on the chemo-selective conversion of some benchmark substrates including cyclopentene oxide and cyclohexene oxide (see Table S1; **1** as catalyst, Supporting Information) that have previously been shown to easily form polycarbonates;[10,16] this screening stage afforded useful information about the required reaction conditions and nature of (co)catalysts and their loadings to achieve high and selective conversions towards the *cyclic* carbonate.[17] Whereas for the conversion of cyclopentene oxide (Table S1, entries 1–9) both high selectivity for the cyclic carbonate and appreciable conversion levels were obtained at 70ºC (entries 4–6), for cyclohexene oxide under similar reaction conditions (entries 10–14, 18–21) high selectivity towards the (undesired) polycarbonate was noted. Two important requisites for selective conversion to the *cyclic* organic carbonates were revealed upon further variation of the reaction medium and the relative ratio between complex **1** or **2** and the nucleophile (NBu_4Br), see entries 15–17. The use of a co-solvent (2-butanone) and relative *excess* of nucleophile (NBu_4**X**: bromide was generally found to be the best nucleophile) suppressed multiple, alternate CO_2 and/or epoxide insertions that would lead to undesired polycarbonate formation with the opposite stereochemistry in the carbonate unit (Scheme 1 and Table 1). Once the reaction conditions had been optimized,[18] a series of cyclic oxiranes were screened as substrates to form their respective bi-, tri- and tetracyclic organic carbonates **3a-3q** (Figure 1).

We were pleased to find that the optimized reaction conditions gave access to a wide range of organic carbonates in high yields and selectivities using catalysts **1** or **2** and NBu_4Br as nucleophile additive, with catalyst **2** being eventually preferred.[18] In most cases, rather mild temperatures (70ºC) could be used whereas in the synthesis of *bis*-carbonate **3h** (66% yield) a somewhat elevated reaction temperature was required to achieve high conversion of both oxirane fragments into their respective carbonates. Five-, six- and seven-membered ring oxiranes were all smoothly converted into their targeted products (**3a-3p**), whereas the eight-membered ring carbonate **3p** could only be isolated in 15% yield. This latter result suggests that activation of larger cycloalkenyl-based epoxides is more difficult through coordination to the Lewis acid (cf., **2**) with the nucleophilic ring-opening step[19] complicated by the presence of a relative non-reactive conformation of the oxirane substrate. This was further supported by using cyclooctadiene oxide as substrate successfully furnishing carbonate **3q** (63%): the presence of a double bond in the backbone is sufficient to result in significantly higher conversion and yield of the cyclic carbonate, and likely the result of a more rigid nature of the substrate backbone which appears to play an important role. It, however also (slightly) influences the *cis*/*trans* ratio of the carbonate unit (87:13) as testified by the NMR characteristic patterns of both *cis* and *trans* isomers. When the *bis*-oxirane derived from cyclooctadiene was used as substrate, the oxirane-derived *trans*-carbonate **3r** was isolated in 52% yield having, as in **3d**, a synthetically useful epoxide group incorporated. Surprisingly, the presence of the epoxide ring in **3r** (sp^3 versus sp^2 hybridized C-centres when compared to **3q**) thus directs the stereoselectivity towards the *trans*-carbonate.

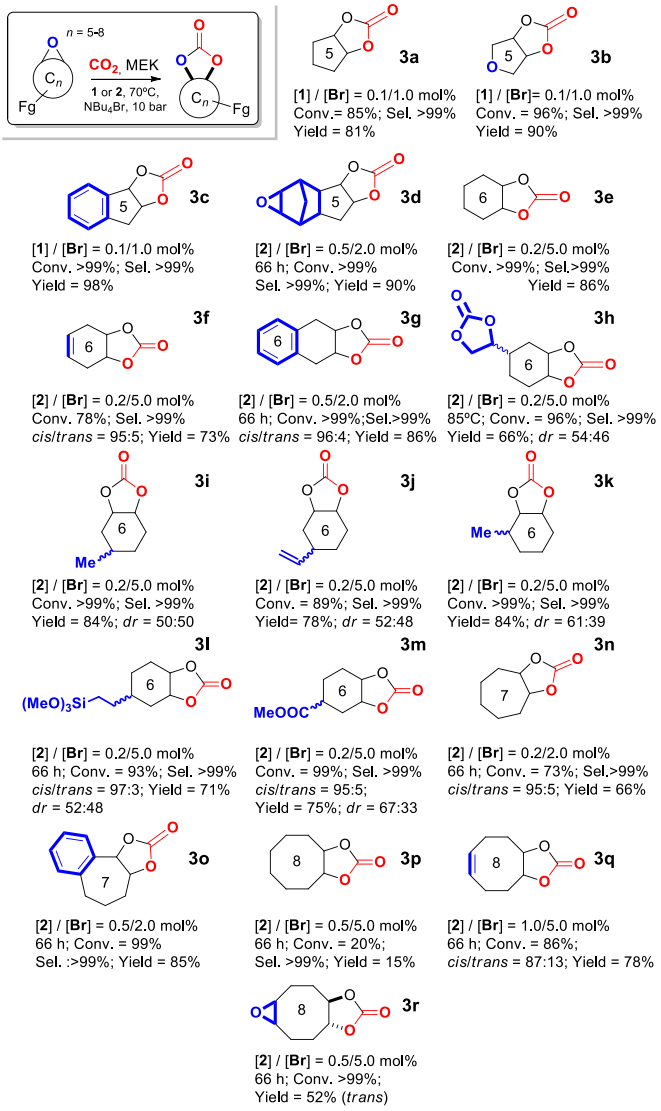

Figure 1. Substrate scope in the formation of cyclic carbonates **3a-3r**. General conditions used (deviations mentioned in the Figure): 18 h, 70ºC, $p(CO_2)$ = 10 bar, 2-butanone (MEK) as solvent (0.5-2.0 mL), NBu_4Br ([**Br**]) as co-catalyst using either **1** ([Fe]) or **2** ([Al]) as catalysts (amounts indicated). Reported yields are based on the isolated compounds. Apart from some indicated cases, the carbonate configuration was >98% *cis*. Fg stands for functional group. Reported *dr* values were calculated from analysis of ^1H and/or ^{13}C NMR spectra and relate to the relative configuration of the carbonate unit and C_6 ring substituent.

Interestingly, the catalyst system based on **1** or **2** tolerates a number of useful functionalities including ether (**3b**), oxirane (**3d**, **3r**), *endo*- and *exo*-cyclic double bonds (**3f**, **3j** and **3q**), trimethoxysilyl (**3l**) and ester (**3m**) groups. Remarkably, the tetracyclic carbonate product **3d** is obtained from its corresponding *bis*-oxirane derivative without affecting the other epoxide unit and thus provides clean access to a difunctional intermediate.[20] Of further note are the preparation of the substituted bicyclic carbonates **3h**-**3m** for which straightforward analysis by NMR spectroscopy was more challenging due to the presence of three stereocentres in these molecules; however, for a representative example we were able to separate the set of diastereoisomers (**3m**) by column chromatography (Figure S1) and have analysed one of these (i.e., the minor isomer **3ma**; ester group

equatorial) by X-ray analysis;[21] the other, major diastereoisomer **3mb** (ester group axial) was isolated as a viscous liquid (see for details Supporting Information). The combined data was used to assign both isomers present in the isolated product, and also confirmed the *cis* nature of the carbonate unit.

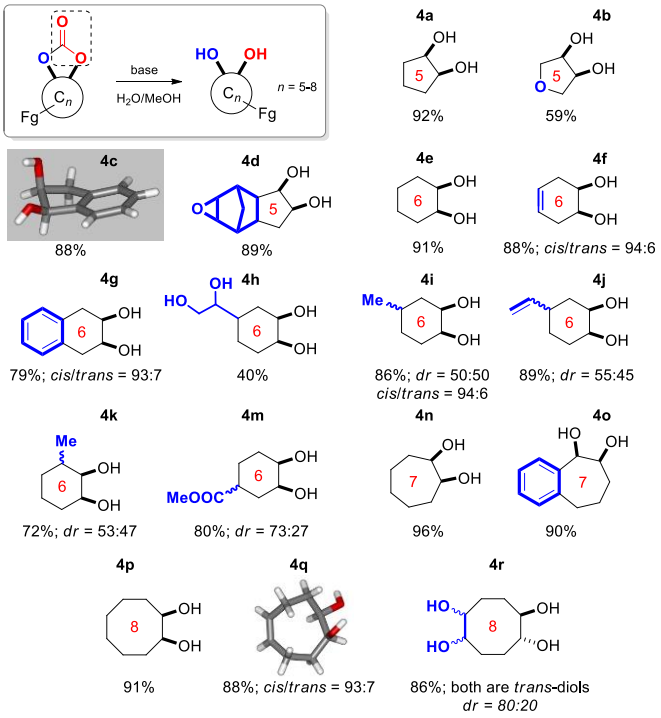

Figure 2. Formation of *cis*-diol products **4a-4r** from precursors **3a-3r**. General conditions used: 3 h, rt, NaOH (5 equiv) in H_2O; for **4m** K_2CO_3 (3 equiv. in MeOH) was used. Reported yields are based on the isolated compounds. Apart from some indicated cases, the diol configuration was >98% *cis*. Fg stands for functional group. Reported *dr* values were calculated from analysis of ^1H and/or ^{13}C NMR spectra and relate to the relative configuration of the carbonate unit and C_6 ring substituent, except for **4r**. Note that further details for the analysis of **4r** are provided in the Supporting Information.

The next step involved the formation of the *cis*-diol products from the carbonate precursors **3a-3r** by treatment with a suitable base and most diol targets were readily formed in good to excellent yields (Figure 2). The deprotection of carbonate **3l** was complicated as the resulting product was a difficult to interpret mixture of rather insoluble components. Likely, the silyloxy fragment gives rise to insoluble gels through cross-hydrolysis. However, basic deprotection of **3m** could be carried out with a weaker base (K_2CO_3) giving *cis*-diol **4m** selectively in high yield (80%). The yield of tetraol **4h** (40%) was lower than generally observed for the other diol products as its isolation was obviously more difficult. The oxirane group in **4d** (89%) remained surprisingly unaffected under basic conditions showing again its high stability. The relative *cis*-configuration in these diols was further supported by X-ray analysis of diol derivatives **4c** and **4q** (see inserts Figure 2).[21] These results clearly show the generality of this approach toward potentially useful cyclic *cis*-diol scaffolds.

In summary, we here present an efficient and practical methodology towards formation of cyclic *cis*-diols with ample scope and functional group tolerance affording these synthons in high yield and (diastereo)selectivity with the preparation of their *cis* organic carbonate precursors being the key to success. The selective formation of cyclic carbonate versus poly(carbonate) (cf., Scheme 1) from cyclic epoxides infers that two consecutive S_N2 reactions take place preserving the initial relative configuration of the two carbon centers in the oxirane unit leading to *cis*-diol formation after basic treatment. This double inversion mechanistic pathway leading to the carbonate intermediate has been studied and suggested independently by various groups.[22]

The current approach is characterized by the use of accessible, air-stable and powerful catalysts derived from aminotriphenolate complexes incorporating cheap and earth-abundant metals, and the use of carbon dioxide as a temporary protecting group. These attractive features combined with the simple operational characteristics of this catalytic methodology (no special precautions warranted) may give a valuable starting point for the synthesis of tri- and even tetra-substituted *cis*-diol synthons, and may stimulate the advancement of alternative asymmetric preparations of this important class of organic compounds.

Experimental Section

Typical procedure for organic carbonate formation: A 30 ml stainless steel autoclave was charged with epoxide precursor (0.5 g) along with the correct loading of catalyst and co-catalyst and MEK (0.5 mL). The autoclave was subjected to three cycles of pressurization and depressurization with CO_2 (0.5 MPa, 5 bar), before final stabilization of pressure to 1.0 MPa (10 bar). The autoclave was sealed and heated to the required temperature for 18-66 h. After this time, an aliquot of the crude reaction mixture was collected and analyzed by ^1H NMR spectroscopy to determine the reaction conversion (solvent: $CDCl_3$). Then, the product was isolated/purified through a silica pad or column chromatography.

Typical deprotection procedure: The respective carbonate (1 mmol) was dissolved into 1 M NaOH (5 mL). The mixture was left stirring for 2-3 h, until complete dissolution of the starting material and formation of a homogeneous, pale yellow solution was achieved. Hereafter, the diol was extracted with various portions of EtOAc and isolated by removal of the solvent *in vacuo*.

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[18] Although Fe-complex **1** was initially used, we found that complex **2** resulted consistently in slightly higher yields and selectivities, and thus the latter was used throughout the rest of the scoping studies. See also Table 1, entry 16 versus 15.

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[21] Details for structure determined for **3ma** (CCDC 1005696), for **4c** (CCDC 1005695) and for **4r** (CCDC 1009477) are available from the CCDC upon request or from the author.

[22] See for instance reference 7a and 19, and the reference in footnote 17.

Entry for the Table of Contents:

Protective carbon

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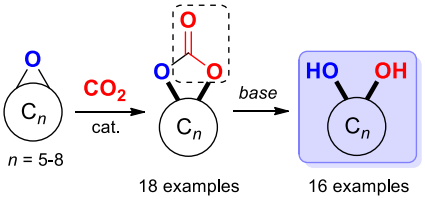
Carbon Dioxide as a Protecting Group: Highly Efficient and Selective Catalytic Access to Cyclic Cis-Diol Scaffolds



- *cheap and sustainable*
- *CO_2 as protecting group*
- *excellent FG tolerance*
- *high selectivities and yiels*

Aminotriphenolate complexes of Fe^{III} and Al^{III} are presented as highly efficient and selective catalysts for the conversion of functional, cyclic oxiranes into their organic, *cis*-carbonates. Basic hydrolysis of the latter provides a wide series of useful cyclic *cis*-diol scaffolds in high yield. This work demonstrates the dual use of CO_2 as a temporary protecting group and an oxygen donor furnishing compounds of potential use in chemical synthesis.