Temporary Protecting Groups | Hot Paper

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

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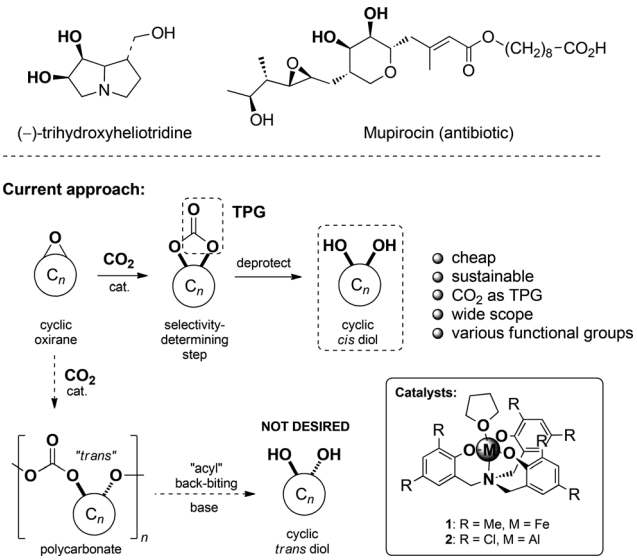
Abstract: *The efficient and highly selective formation of a wide range of (hetero)cyclic cis-diol scaffolds using aminotriphenolate-based metal catalysts is reported. The key intermediates are cyclic carbonates, which are obtained in high yield and with high levels of diastereo- and chemoselectivity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

Carbon dioxide (CO_2) is an interesting carbon feedstock for organic synthesis with a number of attractive features as a renewable, inexpensive, and readily available resource.[1] Recent progress in the area of catalytic transformations with CO_2[2] has led to 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 these intensively studied areas is the preparation of organic carbonates from oxirane/oxetane precursors giving rise to five- and six-membered cyclic structures.[5] Although this area has been developed to a sophisticated level,[6] important challenges remain to be solved, including the efficient conversion of internal cyclic epoxides[7] and their selective conversion into the corresponding cyclic carbonate rather than the polycarbonate. The latter selectivity is especially vital to control the stereochemical outcome of the reaction as the formation of the cyclic carbonate through a double inversion pathway leads to retention of the relative configuration at both carbon centers,[8] whereas polycarbonate formation followed by a depolymerization/hydrolysis pathway results in the opposite stereochemistry (Scheme 1).[4b] We recently reported powerful catalyst systems that are 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 catalyzed the conversion of acyclic internal epoxides with ample functionality and high turnover numbers.



Scheme 1. Natural compounds with cyclic *cis*-diol scaffolds and 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 inexpensive metal catalysts followed by deprotection under basic conditions could offer a useful and alternative sustainable approach towards cyclic *cis* diols.[13] In this method, CO_2 has a dual role as it acts both as a temporary protecting group (TPG; Scheme 1) that helps to steer the process stereoselectivity, and as an oxygen source. Although various methods for diol formation from organic carbonates have been reported,[14] to date, the substrate scope has

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remained limited and has been primarily based on terminal epoxides, which are relatively facile to convert, whereas cyclic *cis*-diol formation using CO_2 as a key reagent has rarely been studied.[15] Herein, we present a general approach towards functional cyclic *cis*-diol synthons using a versatile catalytic strategy that allows for the efficient conversion of (internal) (hetero)cyclic oxirane substrates, suppressing undesired polycarbonate formation and thus controlling the stereoselectivity. Furthermore, this CO_2-based method could be applied to a broad substrate scope and exhibits good functional group tolerance, providing a wide range of functional *cis*-diol scaffolds in good to excellent yields.

Our first efforts focused on the chemoselective conversion of some benchmark substrates, including cyclopentene oxide and cyclohexene oxide (using **1** as the catalyst; see the Supporting Information, Table S1), which have previously been shown to easily form polycarbonates.[10,16] This screening provided useful information about the required reaction conditions and the nature of the (co)catalysts and their loadings to achieve high and selective conversion into 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 70 °C (entries 4–6), for cyclohexene oxide under similar reaction conditions (entries 10–14, 18–21), high selectivity towards formation of the (undesired) polycarbonate was observed. Two important requisites for selective conversion into 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_4**X**, bromide was generally found to be the best nucleophile; entries 15–17). The use of a co-solvent (2-butanone) and an excess of the nucleophile suppressed multiple, alternate CO_2 and/or epoxide insertions, which would lead to undesired polycarbonate formation with the opposite stereochemistry in the carbonate unit (Scheme 1 and Table S1). Once the reaction conditions had been optimized,[18] a series of cyclic oxiranes were screened as substrates to form the corresponding 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 the nucleophile additive. It was eventually observed that catalyst **2** was slightly preferred.[18] In most cases, rather mild temperatures (70 °C) could be used whereas for 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 oxiranes were all smoothly converted into the targeted products (**3a–3p**), whereas the eight-membered-ring carbonate **3p** could only be isolated in 15% yield. The latter result suggests that activation of larger cycloalkenyl-based epoxides through coordination to the Lewis acid (such as **2**) is more difficult, and the ring-opening step[19] with the nucleophile is made more complicated by the rather unreactive conformation of the oxirane substrate. This hypothesis was further supported by the fact that the reaction with cyclooctadiene oxide as the

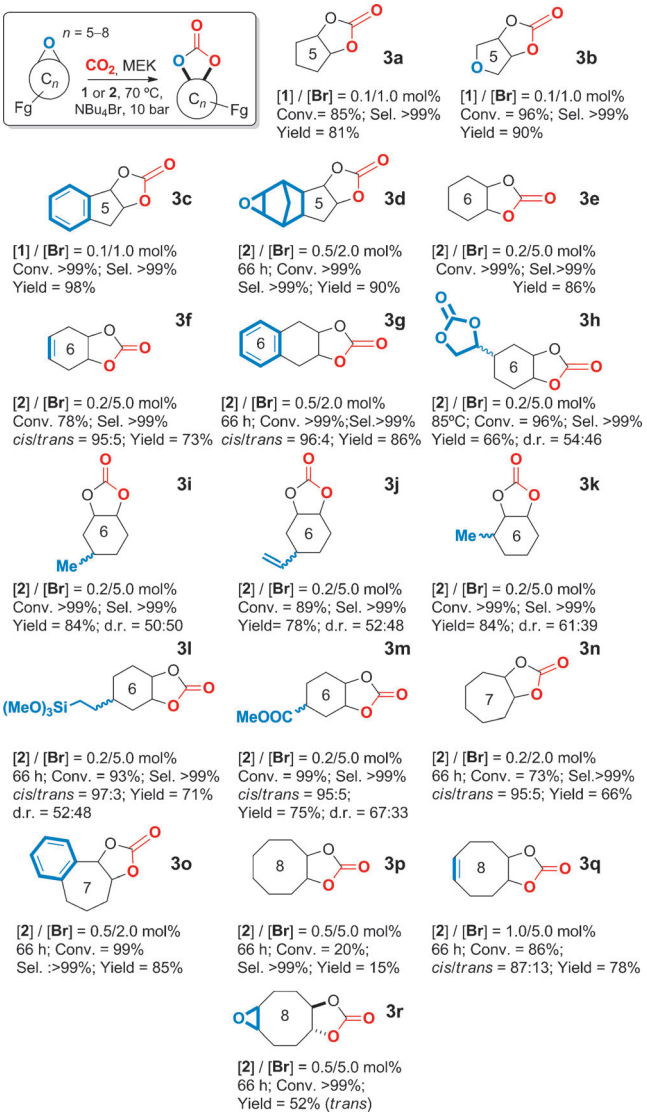

Figure 1. Substrate scope for the formation of cyclic carbonates **3a–3r**. Reaction conditions, unless otherwise noted: **1** ([Fe]) or **2** ([Al]) as the catalyst, NBu_4Br ([**Br**]) as a co-catalyst in 2-butanone (MEK; 0.5–2.0 mL), 18 h, 70 °C, $p(CO_2) = 10$ bar. Yields of isolated products are given. Unless otherwise indicated, the carbonate configuration was >98% *cis*. Reported d.r. values were determined by ^1H and/or ^{13}C NMR spectroscopy and relate to the relative configuration of the carbonate unit and the C_6 ring substituent. Fg = functional group.

substrate successfully furnished 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, which is likely to be the result of a more rigid nature of the substrate backbone, which appears to play an important role. However, it also (slightly) influenced the *cis*/*trans* ratio of the carbonate unit (87:13) as testified by the characteristic NMR patterns of the *cis* and *trans* isomers. When the bis(oxirane) derived from cyclooctadiene was used as the substrate, the oxirane-derived *trans* carbonate **3r**, which, as **3d**, bears a synthetically useful epoxide group, was isolated in 52% yield. Surprisingly, the presence of the epoxide ring in **3r** (sp^3- versus sp^2-hybridized carbon centers

when compared to **3q**) thus directed the stereoselectivity towards the *trans* carbonate.

Interestingly, the catalyst systems based on **1** or **2** tolerate a number of useful functional groups, including ether (**3b**), oxirane (**3d**, **3r**), *endo*- and *exo*-cyclic double bonds (**3f**, **3j**, and **3q**), trimethoxysilyl (**3l**), and ester (**3m**) moieties. Remarkably, the tetracyclic carbonate product **3d** was obtained from the corresponding bis(oxirane) derivative without affecting the other epoxide unit and thus provides clean access to a bifunctional intermediate.[20] The preparation of the substituted bicyclic carbonates **3h**–**3m** is noteworthy; for these products, analysis by NMR spectroscopy was more challenging owing to the presence of three stereocenters in these molecules; however, for a representative example, we were able to separate the set of diastereoisomers (**3m**) by column chromatography (Figure S1) and analyzed one of these (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 (for details, see the Supporting Information). The combined data was used to assign the configurations of both isomers that are present in the isolated product and also confirmed the *cis* nature of the carbonate unit.

The next step involved the formation of the *cis*-diol products from the carbonate precursors **3a**–**3r** by treatment with a suitable base. 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 difficult to analyze because it was formed as a mixture of rather insoluble components. It is likely that the silyloxy fragment gave rise to insoluble gels through cross-hydrolysis. However, basic deprotection of **3m** could be carried out with a weaker base (K_2CO_3), selectively giving *cis* diol **4m** in high yield (80%). The yield of tetraol **4h** (40%) was lower than generally observed for the other diol products as its isolation was more difficult. The oxirane group in **4d** (89%) surprisingly remained 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** (Figure 2, insets).[21] These results clearly show the generality of this approach towards potentially useful cyclic *cis*-diol scaffolds.

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

The current approach is characterized by the use of easily accessible, air-stable, and powerful catalysts that are derived from aminotriphenolate complexes and incorporate inexpensive 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 method (no special precautions required) 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.

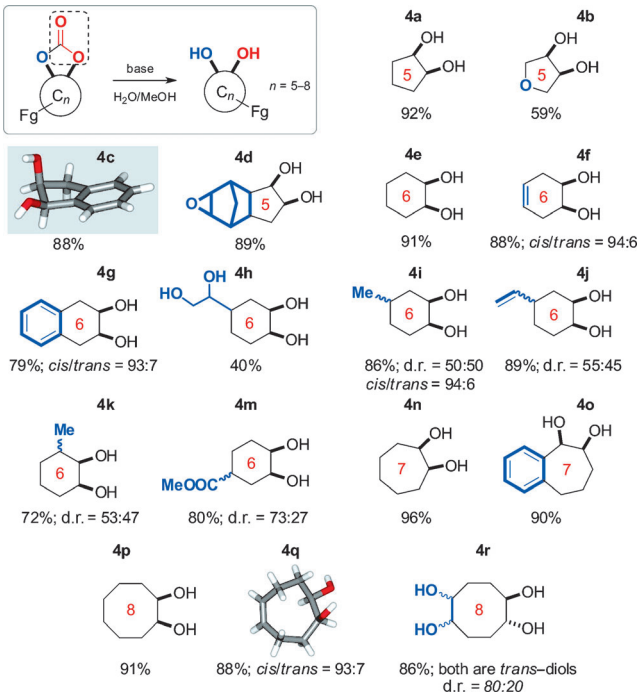

Figure 2. Formation of the *cis*-diol products **4a**–**4r** from precursors **3a**–**3r**. Reaction conditions: NaOH (5 equiv) in H_2O, 3 h, RT. For **4m**, K_2CO_3 (3 equiv in MeOH) was used. Yields of isolated products are given. Unless otherwise specified, the diol configuration was >98% *cis*. Reported d.r. values were determined by ^1H and/or ^{13}C NMR spectroscopy and relate to the relative configuration of the carbonate unit and the C_6 ring substituent, except for in the case of **4r**. Further details for the analysis of **4r** are provided in the Supporting Information. Fg = functional group.

Experimental Section

Typical procedure for organic carbonate formation: A 30 mL stainless steel autoclave was charged with the epoxide precursor (0.5 g) along with the correct loadings of catalyst, 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 pressure stabilization (1.0 MPa, 10 bar). The autoclave was sealed and heated to the required temperature for 18–66 hours. Afterwards, 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 by filtration through a silica pad or by column chromatography on silica gel.

Typical deprotection procedure: The respective carbonate (1 mmol) was dissolved in NaOH (5 mL, 1M). The mixture was left stirring for 2–3 hours until complete dissolution of the starting material and formation of a homogeneous, pale yellow solution was

achieved. Hereafter, the diol was extracted with EtOAc and isolated by removal of the solvent in vacuo.

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[21] CCDC 1005696 (**3ma**), 1005695 (**4c**), and 1009477 (**4r**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[22] See, for instance, Ref. [7a], [7d], and [19].

