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Selective Reductive Dimerization of CO_2 into Glycolaldehyde

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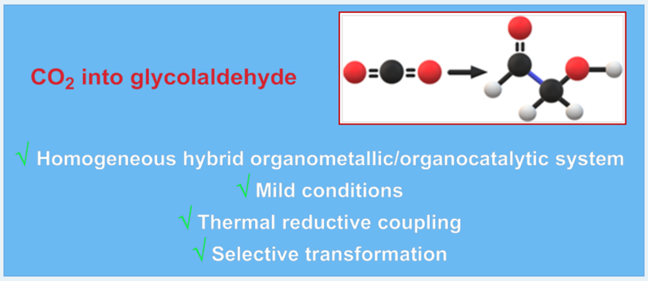
ABSTRACT: The selective dimerization of CO_2 into glycolaldehyde is achieved in a one-pot two-step process *via* formaldehyde as a key intermediate. The first step concerns the iron-catalyzed selective reduction of CO_2 into formaldehyde *via* formation and controlled hydrolysis of a *bis*(boryl)acetal compound. The second step concerns the carbene-catalyzed C−C bond formation to afford glycolaldehyde. Both carbon atoms of glycolaldehyde arise from CO_2 as proven by the labeling experiment with $^{13}CO_2$. This hybrid organometallic/organic catalytic system employs mild conditions (1 atm of CO_2, 25 to 80 °C in less than 3 h) and low catalytic loadings (1 and 2.5%, respectively). Glycolaldehyde is obtained in 53% overall yield. The appealing reactivity of glycolaldehyde is exemplified (i) in a dimerization process leading to C_4 aldose compounds and (ii) in a tri-component Petasis−Borono−Mannich reaction generating C−N and C−C bonds in one process.



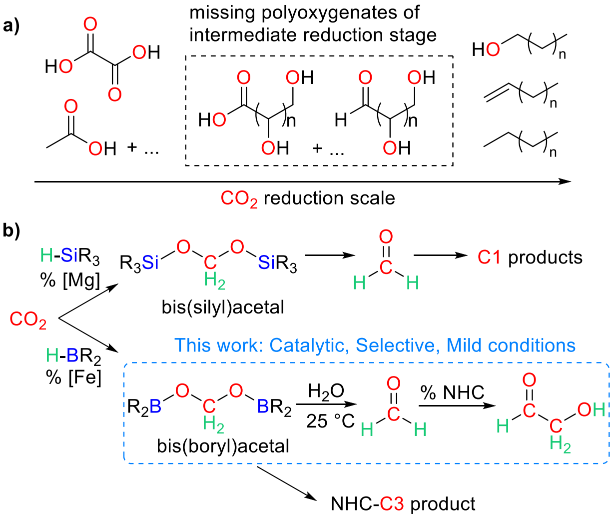
KEYWORDS: *CO_2 reduction, organocatalysis, Formose reaction, dimerization, carbohydrates*

INTRODUCTION

CO_2 reductions to $C_{n>1}$ products are much less developed than to C_1 compounds due to the intrinsic difficulty of combining two individually challenging steps in a single process: CO_2 reduction and C−C bond formation.[1] As a consequence, further developments of CO_2 utilization as the C_n source face two main issues: selectivity and limited scope of products.[1,2] Besides oxalate, acetate, and related products,[3] most of the obtained compounds are highly reduced products: aliphatic hydrocarbons, olefins, and alcohols (Scheme 1a). In these electroreduction or hydrogenation systems, CO is considered as the key bifurcation point toward C_n products. Because of their high energy density, the synthesized products are of interest as energy carriers. However, if one wants to use CO_2 as a sustainable C_n source, less reduced polyoxygenated compounds would be highly desirable (Scheme 1a) because such compounds, featuring multiple alcohol, ketone, and/or aldehydic functions, exhibit appealing molecular complexity leading to versatile reactivity. Their isolation from biomass is currently being explored for their use as a new chemical feedstock.[4] Finding a new access from CO_2 would offer a complementary sustainable alternative to biomass extraction. A thorough study on Cu-catalyzed electroreduction of CO_2 reported the detection of such C_2 and C_3 oxygenated compounds as minor species.[5] As indicated in the proposed mechanism and further complemented by an in-depth theoretical investigation,[6] these compounds cannot be accumulated because they are further reduced *in situ* (Scheme 1a) under the reaction conditions.

We believe that (i) new pathways need to be developed for the generation and accumulation of these reactive intermedi-

Scheme 1. (a) C_n Products Obtained from Electroreduction and Hydrogenation of CO_2 and (b) Synthesis and Utilization of $4e^-$ Reduction Products as the C1 Source from CO_2 Hydrosilylation[7] and as the Cn Source from CO_2 Hydroboration[8]



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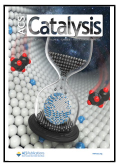

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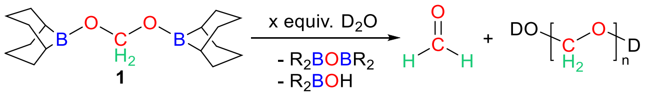
ates, (ii) homogeneous thermal transformations of CO_2 into C_n compounds would have a key role to play in this objective,[9] and (iii) HCHO could be an alternative bifurcation point toward the C_n products. Mild operating conditions should be pursued to favor *in situ* characterization and control of the reaction. In the field of CO_2 reduction, hydrosilane and hydroborane reductants enabled to use particularly mild conditions and make significant progress in understanding the mechanisms as well as in the characterization and functionalization of reactive intermediates.[10] More specifically, it enabled the reduction of CO_2 to the formaldehyde level with the selective generation of *bis*(silyl)[11] and *bis*(boryl)acetal[12] compounds (Scheme 1b). These reactive intermediates were proven particularly versatile for the synthesis of a large scope of different C_1 products.[8,11c,12d,f,13] While these acetal compounds were used as formaldehyde surrogates, it is only in a recent example where Parkin *et al.* reported the actual release of formaldehyde from a *bis*(silyl)acetal compound by adding CsF at 25 °C or heating the solution to 120 °C in DMF.[7] The *in situ* generated formaldehyde was then involved in C_1 transformations (Scheme 1b).

In the last 10 years, we developed $4e^-$ reductions of CO_2 with hydroboranes[14] and applied it to C_1 chemistry.[12f,15] More recently, we aimed at using this process for the transformation of CO_2 into C_n products. A first example of the synthesis of a C_3 compound was reported from the stoichiometric reaction of an *N*-heterocyclic carbene (NHC) with a *bis*(boryl)acetal compound.[8] However, the coupling step was not catalytic and the yield (30%) remained modest. Herein, we present the first catalytic system enabling to generate selectively glycolaldehyde from the CO_2 reductive dimerization in 62% yield from a *bis*(boryl)acetal compound.

RESULTS AND DISCUSSION

Step 1: Formaldehyde Release from *bis*(Boryl)acetal. As reported earlier, *bis*(boryl)acetal **1** (Scheme 2) is generated from the selective $4e^-$ reduction of CO_2 with 9-BBN using mild conditions (25 °C, 1 atm of CO_2, 45 min) and 1 mol % of the iron complex $Fe(H)_2(dmpe)_2$.[12f] The first objective was to find a pathway to generate formaldehyde from *bis*(boryl)acetal **1** under mild and compatible conditions for the subsequent organocatalyzed coupling step (vide infra). While partial release of HCHO was mentioned in the literature from a *bis*(boryl)acetal featuring pinacolboryl moieties,[12d,14b,16] no system actually reported quantitative generation of HCHO from the *bis*(boryl)acetal compound as in Parkin's example from a related *bis*(silyl)acetal.[7] In this context, compound **1** was subjected to 1, 2, and 10 equivalents of water (Scheme 2). While 1 and 2 equiv led to partial release of formaldehyde in 24 and 72% yield, respectively (even after 24 h), the use of 10 equiv afforded formaldehyde in 94% yield within 30 min. Formaldehyde was detected by ^1H NMR analysis both as free formaldehyde (singlet at 9.58 ppm) and as hydrated or oligomeric formaldehyde (broad signals at 4.5−5.5 ppm). Both sets of resonances were measured against an internal standard to calculate the yield in formaldehyde (see Table S2 and Figure S1 in the Supporting Information for details).

Scheme 2. Step 1: Release of HCHO from the Reactivity of 1 with D_2O

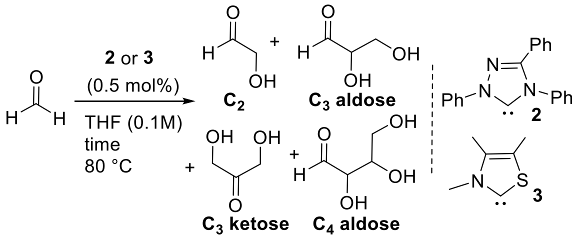


Step 2: Carbene-Catalyzed Formose Reaction of HCHO in the Presence of Water. We then turned our attention to the formation of short-chain carbohydrates from HCHO. The so-called formose reaction corresponds to the oligomerization of formaldehyde into carbohydrate compounds. While this powerful transformation was discovered in the 19th century,[17] it suffers from numerous side reactions, leading to mixtures of up to 30 different products when catalyzed by inorganic bases.[18] Net improvements in controlling side reactions and chain growth were achieved with the use of NHC-type catalysts, notably with thiazolium and triazolium precursors.[18,19] In these studies, it is clear that formose outcome is very sensitive to the reaction conditions (solvent, NHC, and reaction time); however, (i) beyond the accepted general mechanism *via* the Breslow intermediate, more defined rationales to explain such variations are lacking[19c−e] and (ii) THF and H_2O are two solvents that have been sparingly used.[19e,20]

In this context, NHC **2** and **3** were selected for initial tests with commercial *para*-formaldehyde in DMF, THF, and THF/H_2O media (Table 1). The results reported by Teles *et al.* in DMF were first reproduced with catalyst **2**, showing that 30 and 60 min were necessary to reach full conversion. Glycolaldehyde (C_2) was the main product after 30 min while a mixture of C_{2-4} carbohydrates was observed after 60 min with 0.5 mol % catalyst loading (Table 1, entries 1−3).[19e] Two formose reactions were reported in THF with triazolium precursors, slightly different from **2**, leading to the favored formation of glycolaldehyde in 62 and 46% yields.[19e,f] We thus explored the reaction in THF with catalysts **2** and **3**. The reaction was almost complete after 30 min: 88 and 93% total yield with **2** and **3**, respectively (Table 1, entries 5 and 11). Interestingly, **3** favored the dihydroxyacetone (C_3 ketose) with a measured 67% yield after 30 min, and **2** favored the C_4 aldoses (erythrose and threose) with combined yields of 72 and 78% after 30 and 60 min, respectively. C_4 ketoses were never detected. To the best of our knowledge, these latter results are the best yields and selectivity reported for C_4 aldoses. Teles *et al.* indeed reported two reactions in DMF in which the C_4 carbohydrates were the major products with yields of 50 and 16% with triazolium and imidazolium precursors as catalysts, respectively.[19e,f] We then probed the impact of the addition of H_2O which was reported detrimental for the reaction yield and the selectivity in DMF/H_2O thiamine-based catalysis.[20] In accordance with these data, we observed a general negative impact of H_2O on the yield. However, while the addition of 10 equiv of water completely shut down any conversion with catalyst **3** (Table 1, entry 12), we were pleased to observe a 56% total yield of C_{2-4} aldose products with catalyst **2** after 30 min in the same conditions. The addition of 20 and 40 equiv of water or 1 equiv of methanol afforded lower total yields (Table 1, entries 8−10). With these positive results from HCHO in the presence of water in hands, we then decided to explore this transformation from CO_2.

Synthesis of Glycolaldehyde from CO_2. We combined the two reactions developed above in a one-pot system. The conditions deduced from these independent studies are as follows: *bis*(boryl)acetal **1** generated *in situ* in THF was hydrolyzed with 10 equiv of water at 25 °C in 1 h. NHC **2** (0.5%) was then added to catalyze the formose reaction at 80

Table 1. Step 2: Formose Reaction in DMF, THF, and THF/H_2O Media with Catalysts 2 and 3[a]

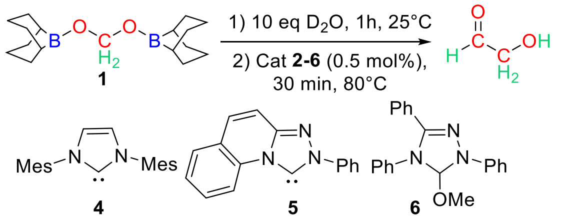


entry	time min	NHC	solvent	C_2[b], %	C_3[b], %	C_4[b], %	total yield %
1	10	2	DMF	33			33
2	30	2	DMF	62	34		96
3	60	2	DMF	38	28	34	100
4	10	2	THF	16			16
5	30	2	THF	16		72	88
6	60	2	THF	17	5	78	100
7	30	2	THF + H_2O[c]	27	18	11	56
8	30	2	THF + H2O[d]	31			31
9	30	2	THF + H2O[e]	17			17
10	30	2	THF + MeOH[f]	37	3		40
11	30	3	THF	12	67	4	93
12	30	3	THF + H2O[c]				0

[a] Reaction conditions: 0.5 mmol of paraformaldehyde, 0.0025 mmol of carbene, 5 mL of THF (0.1 M), and 80 °C. [b] GC yields obtained after derivatization reactions. [c] 10 equiv of water was added relative to the HCHO amount. [d] 20 equiv of water was added relative to the HCHO amount. [e] 40 equiv of water was added relative to the HCHO amount. [f] 1 equiv of MeOH was added relative to the HCHO amount.

°C in 30 min (Scheme 3). To our delight, glycolaldehyde was generated in 37% yield under these standard conditions. The yield is the average yield of four runs with a measured maximum deviation (Δmax) of 7%. C3 and C4 carbohydrates were detected in 0.4 and 0.6% yield, respectively. The reaction was thus particularly selective since no other carbohydrate was detected, although the yield remained modest. The reaction took place only in the presence of carbene catalyst **2** or its triazolium precursor **6**. Their absence or the use of carbenes **3**−**5** did not afford any detectable C2, C3, or C4 products.[21] Future work will be dedicated to understand the specificity of carbene **2** in protic media, keeping in mind the recent questioning about organocatalyzed Umpolung reactions.[22]

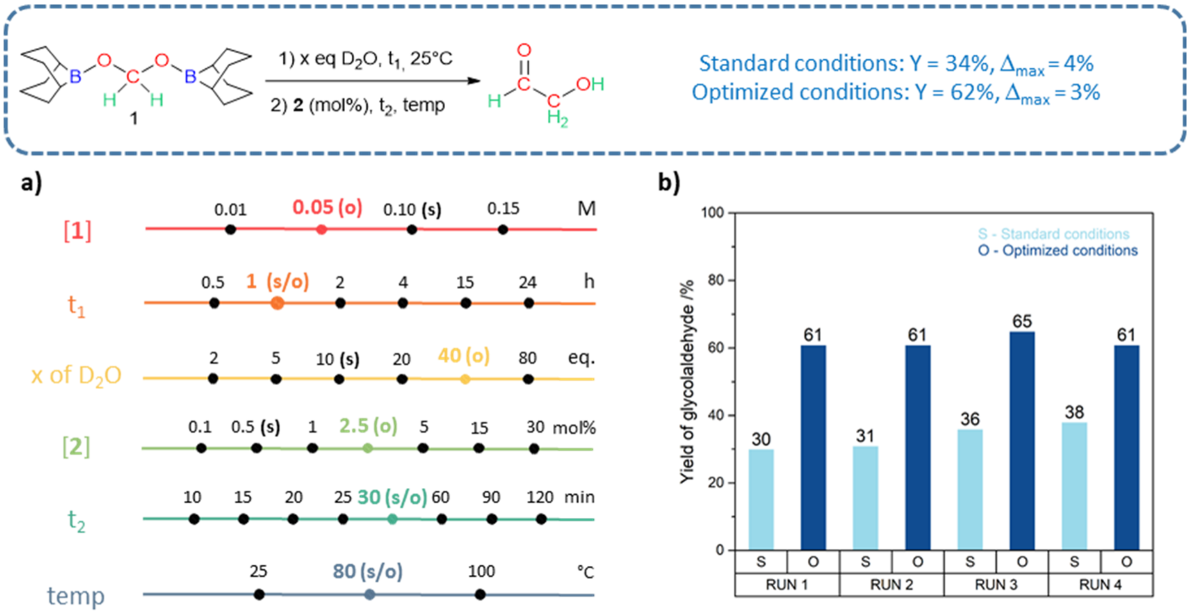
Scheme 3. One-Pot System under Initial Standard Conditions with Catalysts 2−6



In order to improve the glycolaldehyde yield, reaction conditions were optimized using catalyst **2**. The optimization was conducted in two stages: (i) variation of one parameter at a time (Scheme 4a) and (ii) combination of optimal conditions and careful comparison of the obtained yields between standard (s) and optimized (o) conditions (Scheme 4b).

First stage (Scheme 4a): six parameters were optimized: the initial concentration of compound **1** in THF, the time t_1 of the hydrolysis, the number of equivalents of D_2O added for hydrolysis, the catalyst loading in **2**, and the time (t_2) and temperature (temp) of formose reaction. For each parameter, standard (s) and determined optimal (o) conditions are indicated among the different conditions tested (in black color). Details on observed trends for each parameter are described hereafter in the order indicated in Scheme 4a, while detailed yields are given in the Supporting Information. A significant yield improvement of about 10% was observed when the initial concentration of **1** in THF was divided by half ([**1**] = 0.05 M). This observed trend is consistent with the common observation of lower chain length selectivity with lower concentration of formaldehyde in formose reaction.[19c−e] The hydrolysis time of the acetal **1** (t_1) had a negligible impact on the yield when it was varied from 30 min to 24 h. It indicates that compound **1** is readily hydrolyzed in these conditions. However, we observed improved yields in glycolaldehyde when 40 equiv of water were used instead of 2, 5, 10, 20, or 80. Since the hydrolysis time of the acetal **1** (t_1) had no impact on the yield, we believe that the increased yield with 40 equiv of H_2O was not due to a better hydrolysis process but rather to a dilution factor. Adding 40 equiv of H_2O indeed led to a decrease of the concentration by about half, which was shown to be beneficial. We confirmed this assumption by varying the amount of equiv of H_2O added while maintaining [**1**]. In this case, yield improvement was attenuated but still in favor of the addition of 40 equiv of H_2O. Although the observed +4% increase is marginal, we kept 40 equiv of H_2O as an optimized condition, while maintaining concentration [**1**] = 0.05 M. When catalyst loading [**2**] was varied from 0.1 to 30 mol %, a narrow variation of 10% was observed between the highest and the lowest yields. Catalyst (2.5 mol %) loading was found to be optimal. It first indicates that the catalyst is very active under these conditions. It also shows that if H_2O has a detrimental impact, its excess compared to the amount of catalyst (3−4 orders of magnitude) is too large to be compensated by a 10-fold increase of the catalyst loading. Finally, the standard conditions

Scheme 4. Optimization for the Synthesis of Glycolaldehyde: (a) One-Factor-at-a-Time Study over Six Parameters: (s) Indicates the Standard Condition and (o) Indicates the Optimal Condition; and (b) Comparison of Yields between Standard and Optimized Conditions



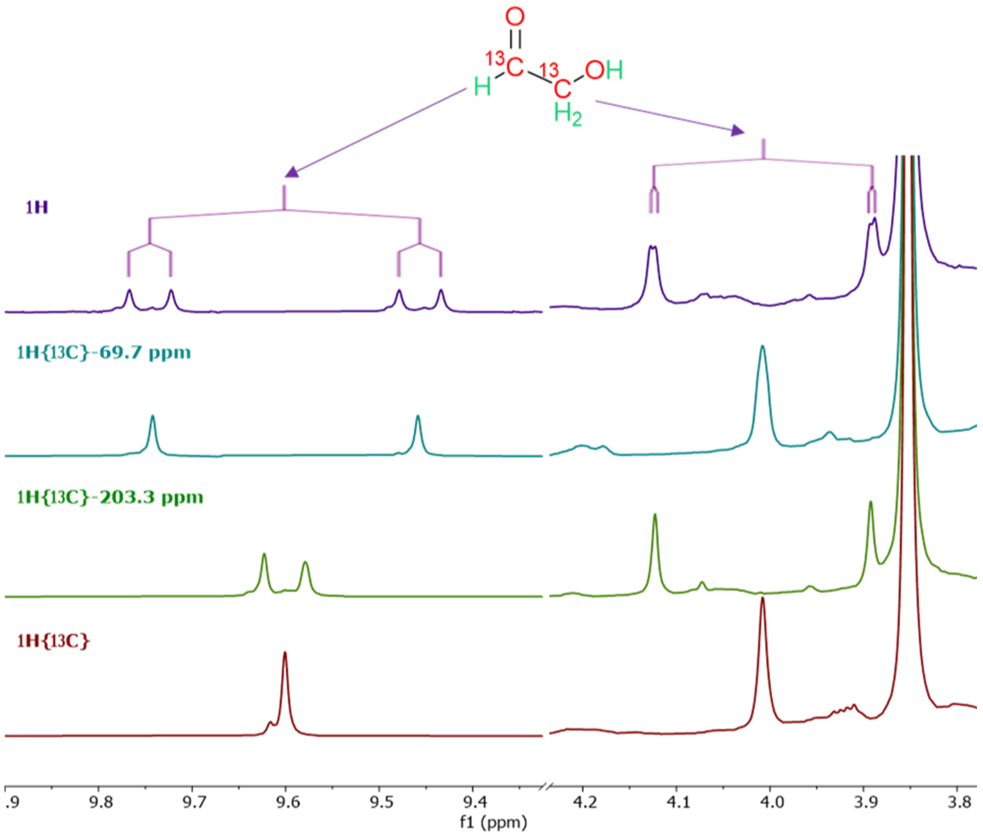


Figure 1. Selected areas of ^1H and $^1H\{^{13}C\}$ NMR analyses of the crude mixture obtained from the developed $^{13}CO_2$ reductive coupling process.

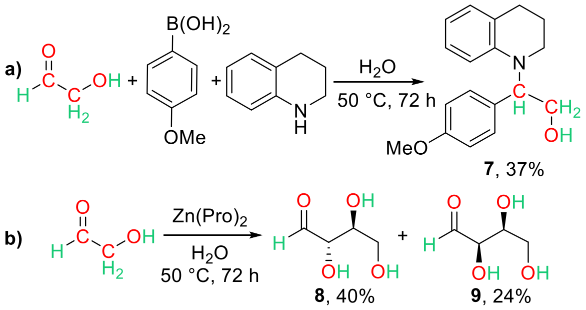
for formose reaction time and temperature (t_2 = 30 min, temp = 80 °C) are also the optimal conditions in accordance with the literature. t_2 = 25 or 30 min enabled to record the best yields, while shorter or longer reaction time had a negative impact. We confirmed that the reaction took place at 100 °C but with a slightly lower yield, while expectedly, it did not proceed at room temperature.

Second stage (Scheme 4b): The presented general optimization methodology relies on a classical one-factor-at-a-time method. Although this is a classical method, combinations of effect are then not considered.[23] In order to properly assess the impact of the optimized conditions, the given yields are the average of four runs. In each of them, the solution containing the *in situ* generated **1** was split into two containers which were then subjected in parallel to the standard conditions (s) for one container and to the optimized conditions (o) for the other one. With these experiments, a 34% yield (Δmax = 4%) was measured under the standard conditions in the same range as that initially obtained (*i.e.*, 37%, Δmax = 7%). Gratifyingly, the yield obtained under the optimized conditions is calculated to be 62% with a maximum deviation of 3%. The optimization study thus led to almost doubling the product yield. Considering the system including the CO_2 reduction step, we developed herein a hybrid one-pot organometallic/organic system transforming CO_2 into glycolaldehyde in an overall 53% yield based on hydroborane used under mild conditions in less than 3 h.

Synthesis of ^{13}C-Labeled Glycolaldehyde. As a mean to prove that glycolaldehyde is indeed formed from the reductive coupling of two molecules of CO_2 and to generate valuable ^{13}C-labeled glycolaldehyde, we conducted the reaction using $^{13}CO_2$. The multiple forms adopted by glycolaldehyde in solution (monomeric, symmetrical, and unsymmetrical oligomeric and hydrated forms) complexify its NMR analysis (see the Supporting Information).[5,24] We present herein the characterization of the simple monomeric aldehydic form in the crude THF-d_8/D_2O mixture. In $^{13}C\{^1H\}$ NMR analysis, this species is characterized at δ 203.3 (d, $^1J_{C-C}$ = 41.1 Hz) and 69.7 (d, $^1J_{C-C}$ = 41.1 Hz). The two carbon centers correlate with the aldehydic and methylenic protons characterized at δ 9.60 (dd, 1H, $^1J_{H-C}$ = 173.2 Hz, $^3J_{H-C}$ = 26.9 Hz) and 4.01 (dd, 2H, $^1J_{H-C}$ = 140.9 Hz, $^3J_{H-C}$ = 4.0 Hz), respectively. Figure 1 discloses the stacking of ^{1}H NMR analysis as well as the selective and broad-band $^1H\{^{13}C\}$ spectra of the selected areas. It enables to visualize that each proton correlates with both carbon nuclei of the molecule with observed ^1J and ^3J scalar couplings, the selective ^{13}C decoupling further highlighting these correlations. Importantly, no ^{12}C-labeled glycolaldehyde was detected in the crude mixture by ^{1}H NMR, indicating that every molecule of glycolaldehyde quantified by GC analyses arises from CO_2 reductive coupling.

***In Situ* Transformation of Glycolaldehyde.** Carbohydrates and glycolaldehyde in this instance are attractive species because of their reactive nature.[4e,25] In order to exemplify this feature, glycolaldehyde *in situ* generated from CO_2 was engaged in two reactions depicted in Scheme 5a,b. The tricomponent Petasis−Borono−Mannich reaction was conducted in water to afford compound **7**, isolated in 37% yield in aqueous solution.[26] The dimerization of glycolaldehyde was then conducted with Zn(L-Pro)$_2$ as a catalyst.[27] Increasing the reaction temperature to 50 °C enabled to generate erythrose (**8**, 40%) and threose (**9**, 24%) for a total GC yield of 64% of C_4 aldoses.

Scheme 5. Reactivity of *In Situ* Generated Glycolaldehyde: (a) Synthesis of 7 by Petasis−Borono−Mannich Reaction and (b) Synthesis of C_4 Carbohydrates



CONCLUSIONS

In the present publication, the selective dimerization of CO_2 into glycolaldehyde is reported for the first time. To achieve such transformation, particularly mild conditions (1 atm of CO_2, 25 to 80 °C in <3 h) and low catalytic loadings (1 and 2.5%, respectively) were employed with a hybrid organometallic/organic catalytic process. The key aspects of the presented work rely on the quantitative release of formaldehyde from the hydrolysis of a *bis*(boryl)acetal compound compatible with the C−C coupling step. Intensive optimization led to the generation of glycolaldehyde in 62% yield from compound **1** and in 53% overall yield from CO_2 based on the amount of hydroborane engaged. The ultimate proof of CO_2 being the sole source of carbon was obtained with the labeling experiment using $^{13}CO_2$. This homogeneous thermal CO_2 process shows that (i) *bis*(boryl)acetal obtained from mild CO_2 reduction enables a selective and mild access to formaldehyde, (ii) acetal compounds can be involved in the generation of C_n compounds, and (iii) carbohydrates such as glycolaldehyde are valuable reactive feedstocks to be synthesized from CO_2.[4e,25] On a broader perspective, the presented strategy highlights that formaldehyde offers an appealing new synthetic access to the C_n products of intermediate reduction stage. Although, in the present case, the boron-based reductant system is not sustainable and the formose control only applies to the smallest carbohydrate, we believe that the strategy presented herein could stimulate different fields of CO_2 reduction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00412.

Experimental details, compounds' synthesis and characterization, and description of the optimization procedure (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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