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TITLE:

Versatile CO_2 Transformations into Complex Products: a One-pot Two-step Strategy

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KEYWORDS:

CO_2, one-pot two-step, 4e$^-$ reduction, hydroboration, bis(boryl)acetal, versatile reactivity, chirality.

SUMMARY:

CO_2 transformations are conducted in a one-pot two-step procedure for the synthesis of complex molecules. The selective 4 e$^-$ reduction of CO_2 with a hydroborane reductant affords a reactive and versatile bis(boryl)acetal intermediate which is subsequently involved in condensation reaction or carbene-mediated C-C coupling generation.

ABSTRACT:

CO_2 transformations using a one-pot two-step method are presented herein. The purpose of the method is to give access to a variety of value-added products and notably to generate chiral carbon centers. The crucial first step consists in the selective double hydroboration of CO_2 catalyzed by an iron hydride complex. The product obtained with this 4 e$^-$ reduction is a rare bis(boryl)acetal, compound **1**, which is subjected in situ to three different reactions in a second step. The first reaction concerns a condensation reaction with (diisopropyl)phenylamine affording the corresponding imine **2**. In the second and third reaction, intermediate **1** reacts with triazol-5-ylidene (Enders' carbene) to afford compounds **3** or **4**, depending on the reaction conditions. In both compounds, C-C bonds are formed, and chiral centers are generated from CO_2 as the only source of carbon. Compound **4** exhibits two chiral centers obtained in a diastereoselective manner in a formose-type mechanism. We proved that the remaining boryl fragment plays a key role in this unprecedented stereocontrol. The interest of the method stands on the reactive and versatile nature of **1**, giving rise to various complex molecules from a single intermediate. The complexity of a two-step method is compensated by the overall short reaction time (2 h for the larger reaction time), and mild reaction conditions (25 °C to 80 °C and 1 to 3 atm

of CO_2).

INTRODUCTION:

In light of the large interest in using CO_2 as a sustainable carbon source[1-3], the purpose of the method is to transform CO_2 into a variety of value-added products.

Intense researches aim at functionalizing CO_2[4,5] or reducing it into formic acid (2 e^- reduction), carbon monoxide (2 e^- reduction), methanol (6 e^- reduction) or methane (8 e^- reduction)[1,6]. The interception of the 2 e^- reduction product with amine, notably, gives rise to formamide and methylamine[7-9]. These areas of research are the most advanced so far. However, the scope of accessible functions and the added value of products formed compared to the starting materials remains rather minimal.

To circumvent this limitation, we focused i) on the **4 e^- reduction of CO_2** and ii) on applying a **one-pot two-step procedure**. The interest of the one-pot two-step procedure is to limit compatibility issues between the two steps and consequently to broaden the type of reactivity which could be conducted after the first step of reduction. We targeted the 4 e^- reduction of CO_2 because formaldehyde –the simplest 4 e^- reduction product– is a particularly reactive and versatile carbon source[10,11]. It is used in condensation reaction as a methylene source and can be polymerized into carbohydrates. The latter –called formose reaction– is an impressive transformation generating carbon chain and chiral carbon centers solely from formaldehyde and is of high interest for synthetic-[12,13] and prebiotic-chemistry[14-16]. While we are able to observe free formaldehyde from CO_2 hydroboration,[17] its selective generation under homogeneous conditions is still unprecedented. Instead of formaldehyde, we developed the synthesis of bis(boryl)acetal compound **1** from the selective double hydroboration of CO_2[18,19].

In one-pot two step processes we prove herein that, in the same pot, this intermediate **1** i) reacts as a surrogate of formaldehyde in condensation reactions[18] or ii) gives rise to a modified formose-type reaction[20]. In this latter reaction, C-C coupling and chiral carbon centers are obtained.

PROTOCOL:

CAUTION: Please consult material safety data sheets (MSDS) of the chemicals before use. Please use appropriate safety practices when performing the following reactions and personal protective equipment. A special attention must be dedicated to the use of the vacuum line and gas pressure system.

1. Synthesis of compound 2 from CO_2 in a nuclear magnetic resonance (NMR) tube

1.1. Stock solution of $Fe(H)_2(dmpe)_2$: dissolve 4.6 mg of $Fe(H)_2(dmpe)_2$[21,22] in 1 mL of tetrahydrofuran (THF)-d^8.

NOTE: dmpe = 1,2-bis(dimethylphosphino)ethane

1.2. In a glove box, charge an NMR tube with 15.9 mg of 9-borabicyclo[3.3.1]nonane (9-BBN) and 100 µL of a stock solution of $Fe(H)_2(dmpe)_2$ (1 mol%).

1.3. Add 0.5 mL of tetrahydrofuran (THF)-d^8.

1.4. Close the tube and bring it outside the glove box.

1.5. Connect the tube to a gas system and place it at 25 °C for 15 min to equilibrate the temperature of the solution inside the tube.

NOTE: The gas system connects the CO_2 bottle to both the vacuum line and the NMR tube. The connections are with Teflon tube and Swadgelock connectors (see **Figure 1** for a scheme of the setup). This system enables to add the pressure defined at the regulator at the desired temperature.

1.6. Add 1 atm of CO_2.

1.7. Leave for 3 min under a dynamic pressure of CO_2 and close the tube.

1.8. Leave the tube at 25 °C for 45 min.

NOTE: At this step bis(boryl)acetal **1** is generated inside the NMR tube in 85% yield (see representative results for the NMR analysis).

1.9. Stock solution of amine: dissolve 177.3 mg of 2,6-(diisopropyl)phenylamine in 1 mL of THF-d^8.Once compound **1** is generated, open the NMR tube inside a glove box and add 55 µL of a stock solution of the 2,6-(diisopropyl)phenylamine, corresponding to 1 equivalent of the generated bis(boryl)acetal **1**.

1.10. Close the tube and hand shake it for 10 s.

1.11. After 20 min, confirm the formation of imine **2** by ^1H NMR analysis (**Figure 2**). Use hexamethylbenzene (roughly 10 mol% vs 9-BBN) as an internal standard to determine the NMR yield.

2. Synthesis of compound 3 from CO_2 in a Fisher Porter

2.1. Charge a Fisher Porter with 320 mg of 9-BBN, 9.4 mg of $Fe(H)_2(dmpe)_2$ and a magnetic stirring bar[21,22].

2.2. Add 10 mL of THF.

2.3. Close the Fisher Porter and bring it outside the glove box.

2.4. Place it at 25 °C for 15 min to equilibrate the temperature of the solution.

2.5. Connect the Fisher Porter to the gas system and add 1 atm of CO_2.

NOTE: The gas system connects the CO_2 bottle to both the vacuum line and the Fisher Porter. The connections are with Teflon tube and Swadgelock connectors (see **Figure 1** for a scheme of the setup). This system enables to add the pressure defined at the regulator at the desired temperature.

2.6. Leave for 3 min under a dynamic pressure of CO_2, close the tube and stir it at 25 °C for 45 min.

NOTE: This stage corresponds to the selective generation of bis(boryl)acetal **1** from CO_2 hydroboration in 85% yield.

2.7. After 45 min, open the Fisher Porter in a glove box and add a solution of 380 mg of triazol-5-ylidene in 6 mL of THF.

2.8. Outside the glove box, charge the Fisher Porter with 3 atm of CO_2.

2.9. Stir the solution at 60 °C for 60 min under a dynamic pressure of 3 atm of CO_2.

2.10. Let the solution cool down to room temperature.

2.11. Remove the volatiles under vacuum and wash the residue with 3x 2 mL of diethylether (Et_2O) at 0 °C to obtain CO_2 adduct **3** as a white powder (**Figure 3**).

2.12. To generate monocrystals, place a concentrated THF/pentane solution at -37 °C for 24-48 h.

3. Synthesis of compound 4 from CO_2 in a Fisher Porter

3.1. In a glove box, charge a Fisher Porter tube with 159 mg of 9-BBN, 4.7 mg (1 mol%) of $Fe(H)_2(dmpe)_2$ and a magnetic stirring bar.

3.2. Add 5 mL of THF.

3.3. Close the Fisher Porter and bring it outside the glove box.

3.4. Place it at 25 °C for 15 min to equilibrate the temperature of the solution.

3.5. Connect the Fisher Porter to the gas system and add 1 atm of CO_2.

3.6. Leave 3 min under a dynamic pressure of CO_2, close the Fisher Porter and stir it at 25 °C for 45 min.

NOTE: This stage corresponds to the selective generation of bis(boryl)acetal **1** from CO_2 hydroboration in 85% yield.

3.7. After the generation of 1, open the Fisher Porter in a glove box and add 54 mg of triazol-5-ylidene.

3.8. Outside the glove box, stir the solution at 80 °C for 40 min to generate a mixture of compounds containing compound **4**.

3.9. Remove the solvent and dissolve part of the residue in 0.6 mL of THF-d^8.

3.10. Filtrate the solution with a syringe equipped with a PTFE filter (0.2 µm) and place it in an NMR tube for analysis. Use hexamethylbenzene (roughly 10 mol% vs 9-BBN) as an internal standard to determine the NMR yields.

4. Alternative synthesis of compound 4 from D,L-Glyceraldehyde

4.1. In a glove box, charge a Schlenk tube with 50 mg of D,L-Glyceraldehyde, 135 mg of 9-BBN and a magnetic stirring bar.

4.2. Add 4 mL of THF.

CAUTION: Upon dissolution of the compound, H_2 evolution occurs.

4.3. Close the Schlenk with a septum and stick a needle into it to allow the constant release of H_2 formed.

4.4. Stir the white suspension at room temperature for 24 h inside the glove box.

4.5. Add 165 mg of triazol-5-ylidene.

4.6. Stir 3 h at room temperature. All residues solubilize during that time.

4.7. Remove the volatiles under vacuum.

4.8. Solubilize the residue in a minimum amount of Et_2O (1 mL) and place the solution at -37 °C for 12 h.

4.9. Compound **4** precipitates. Remove the filtrate by filtration and dry the precipitate under vacuum.

4.10. Isolate compound **4** as a white powder in 72% yield.

REPRESENTATIVE RESULTS:

Successful generation of bis(boryl)acetal compound **1** is assessed by ^1H NMR analysis with the characteristic methylene pick at 5.54 ppm in THF-d^8 (**Figure 4a**).Successful generation of compound **2** is assessed by ^1H NMR analysis with the characteristic AB signal (δ = 7.73 (d, 1H, $^2J_{H-H}$ = 18.4 Hz, CH_2), 7.30 (d, 1H, $^2J_{H-H}$ = 18.4 Hz, CH_2) for the two inequivalent protons of the methylene in THF-d^8 (**Figure 4b**). Successful generation of compound **3** is assessed by ^1H NMR analysis in THF-d^8 (**Figure 4c**). The most notable signals are the C*H*CO$_2$ at 5.34 ppm, and the C*H* of the BBN fragment at 0.26 and -0.65 ppm. Successful generation of compound **4** is assessed by ^1H NMR analysis in THF-d^8. As shown in **Figure 4d**, compound **4**, in situ generated from CO$_2$, is notably characterized by a doublet at 4.64 ppm ($^3J_{H-H}$ = 7.9 Hz, H^3) and a pseudo-t at 3.36 ($^2J_{H-H}$ = 9.7 Hz, $^3J_{H-H}$ = 9.5 Hz, 1H, H^{1b}). In the isolated compound **4** from D,L-Glyceraldehyde, the four proton signals of the C$_3$ chain are clearly observed (**Figure 4e**) and the three carbon atoms of the chain are characterized in the $^{13}C\{^1H\}$ NMR analysis at 76.9 (C2), 74.0(C3) and 71.5(C1) ppm (**Figure 5**).

FIGURE AND TABLE LEGENDS:

Figure 1: Gas system. Scheme of the gas system enabling the addition of a defined pressure of CO$_2$ at a given temperature.

Figure 2: Reductive functionalization of CO$_2$. Synthesis of compounds **1** and **2**.

Figure 3: Carbene-mediated C-C bond formation. Synthesis of compounds **3** and **4**.

Figure 4: ^1H NMR analyses of compound 1-4, recorded at room temperature in THF-d^8. (a) In situ generated compound **1**, (b) in situ generated compound **2**, c) isolated compound **3**, d) in situ generated compound **4** from CO$_2$, e) isolated compound **4** from D,L-Glyceraldehyde.

Figure 5: Representative characterization of compound 4 isolated from D,L-Glyceraldehyde. $^{13}C\{^1H\}$ NMR analysis recorded at room temperature in THF-d^8; inlet: zoom of the C1-C3 area.

DISCUSSION:

Herein, we present the one-pot two-step versatile transformations of CO$_2$ into complex products. The first step of the method concerns the selective 4 e$^-$ reduction of CO$_2$ with a hydroborane reductant. This step is critical because selectivity toward the 4 e$^-$ reduction is challenging. Very few systems have been reported that describe the selective generation of bis(boryl)acetal[23-25]. In our case, an iron hydride complex catalyzes this selective 4 e$^-$ reduction of CO$_2$ with 9-BBN, affording compound **1**, under mild conditions (25 °C) and with very short reaction time (45 min) (**Figure 2**)[18]. Our study shows that the reaction conditions are very important. In our hand, each attempt to change the concentration, solvent, CO$_2$ pressure and temperature led to the decrease of the yield in compound **1**. A longer reaction time is also detrimental because it leads to over-reduction to the methanol level or evolution of the bis(boryl)acetal into several oligomeric compounds. From our experience, it is necessary to verify the outcome of this reduction step by in situ ^1H NMR characterization. The reproducibility of the method needs to be probed over several runs.

The in situ condensation reaction of the intermediate **1** with a bulky aniline gives rise to the corresponding imine **2** (**Figure 2**). This is a straightforward method and compound **2** is readily formed in a high yield (83%). This reaction can also be used to probe the efficiency of the reduction step. This method is the only method enabling the synthesis of imine function from CO_2. Moreover, intermediate **1** was proved to be a versatile source of methylene in various condensation reactions leading to the formation of C-N, C-O, C-C and C=C bonds[18]. This method thus offers a straightforward way of using CO_2 as a surrogate of formaldehyde in condensation reactions[26].

Intermediate **1** reacts with Ender's carbene to afford compounds **3** or **4**, depending on the reaction conditions (**Figure 3**)[20]. With the support of in-depth experimental and theoretical study, we were able to explain the observed reactivity. In this case, compound **1** does not react as formaldehyde since boryl moieties remain in compounds **3** and **4**. This feature arises from the formation of an unprecedented O-Borylated Breslow intermediate (**Figure 3**)[27-32]. This intermediate is not observed experimentally but may act as a bifunctional Lewis acid/Lewis base activator toward CO_2 to afford compound **3** or leads to the homocoupling of two more carbon centers to afford compound **4**. In both products, chiral centers are generated and in the case of compound **4**, the two chiral centers, C2 and C3, are obtained in a diastereoselective manner, thanks to the presence of the bridging boryl fragment.

The advances presented herein were possible thanks to the one-pot two-step method employed and to the high and versatile reactivity of intermediate **1** generated from the selective $4e^-$ reduction of CO_2. Following a similar method to further improve the scope and the complexity of the synthesized molecules, on-going works are dedicated i) to tune the properties of bis(boryl)acetal in using other hydroborane reductants and ii) to probe different coupling conditions in using other organo-catalysts.

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DISCLOSURES:

The authors have nothing to disclose.

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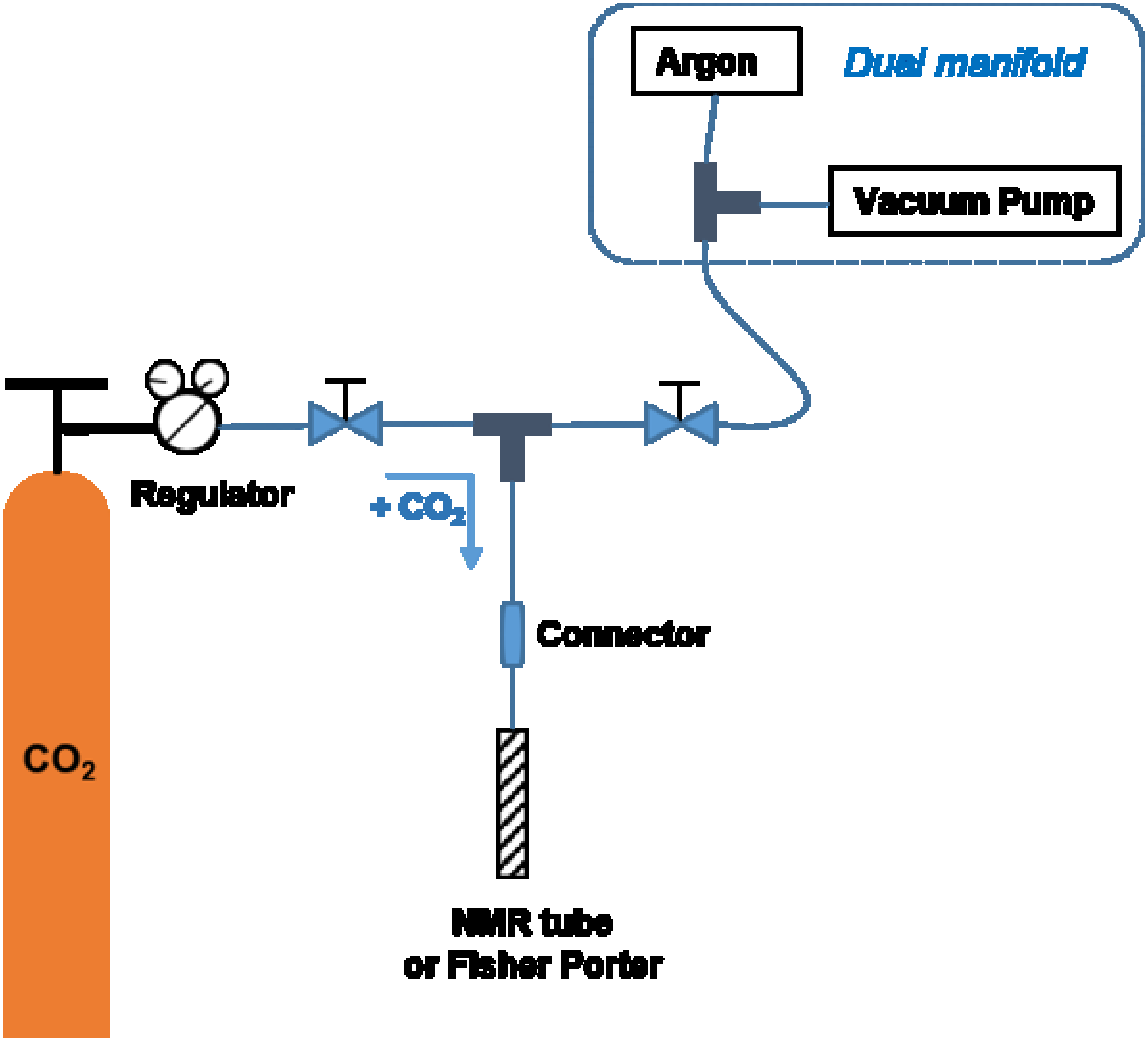
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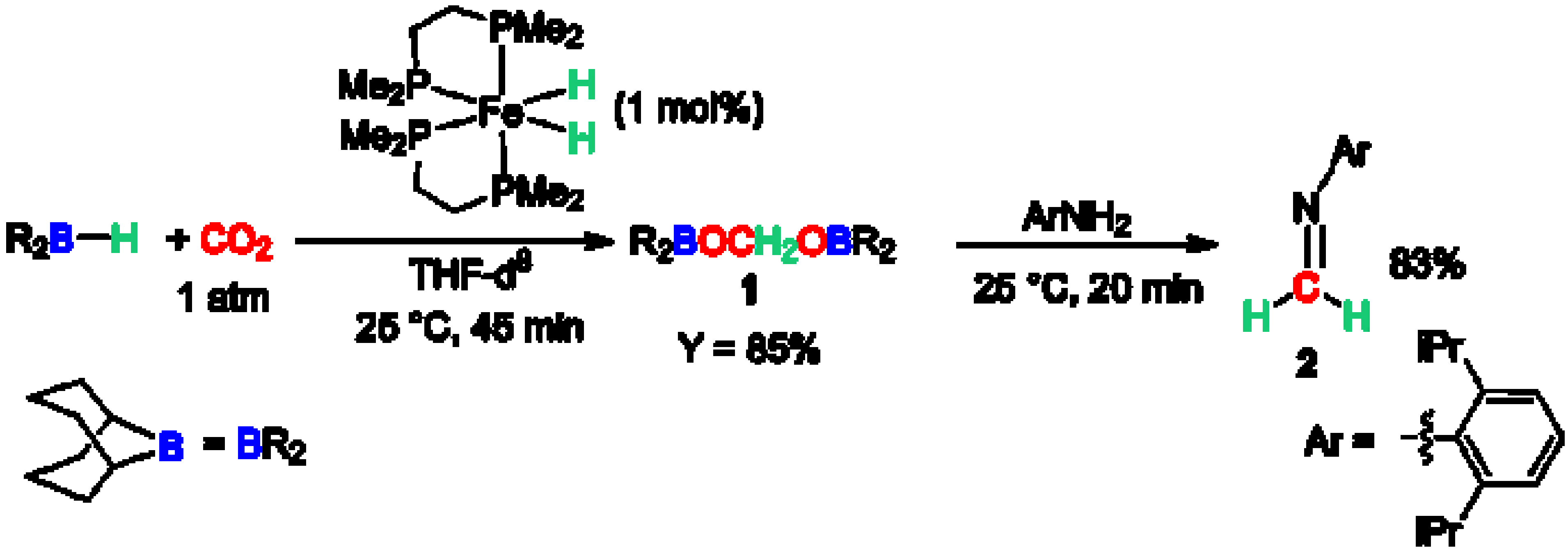
Figure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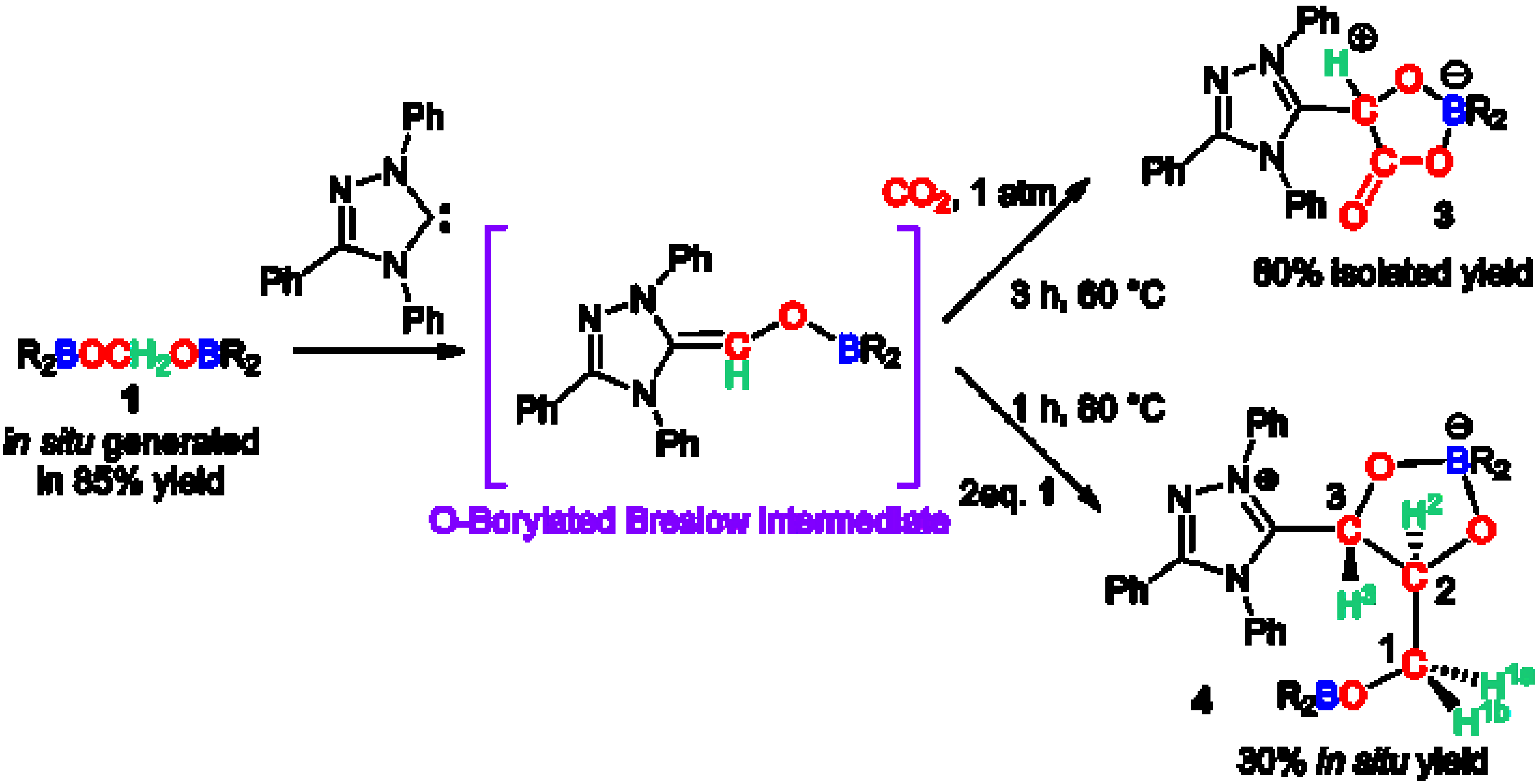
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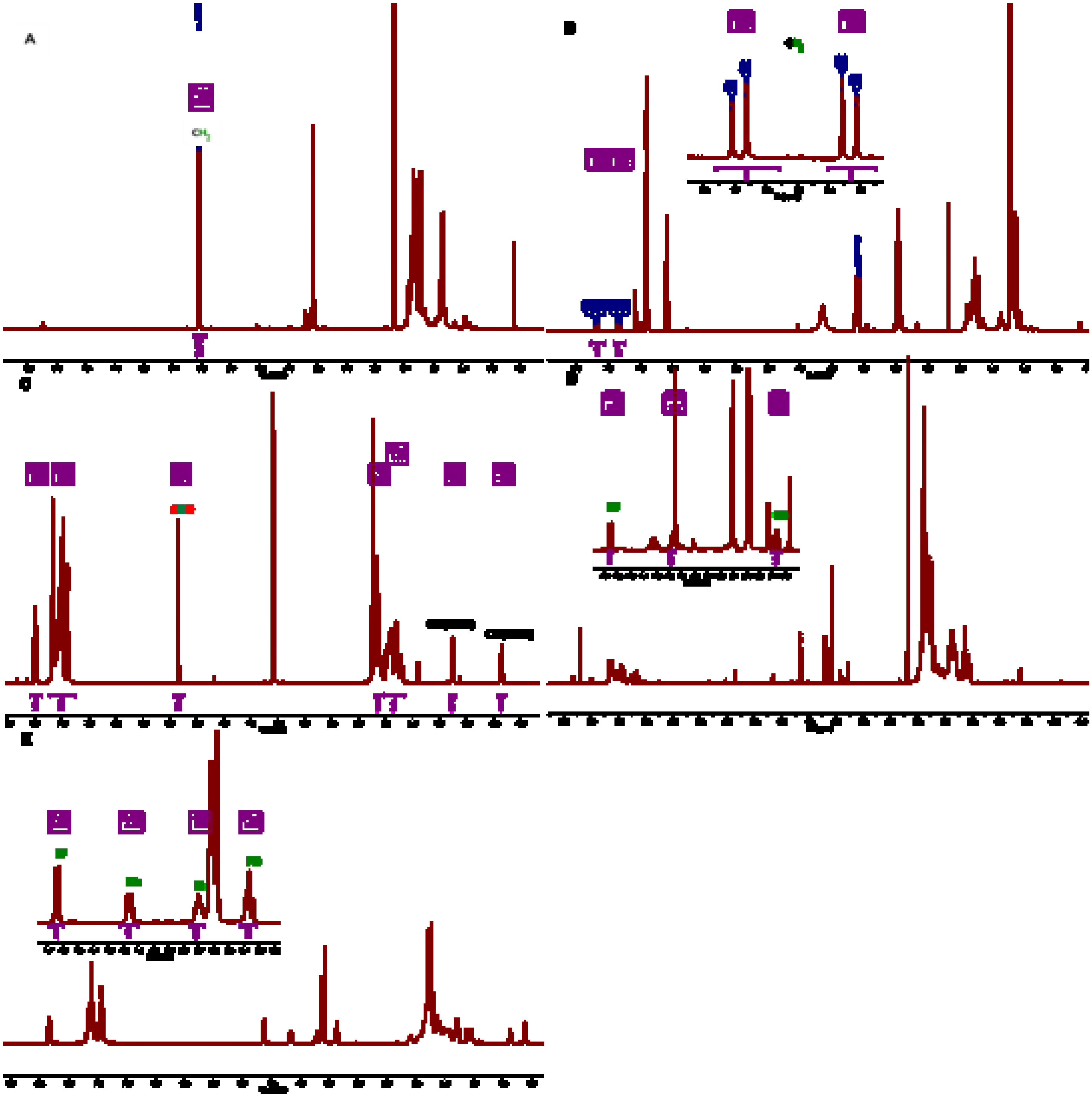
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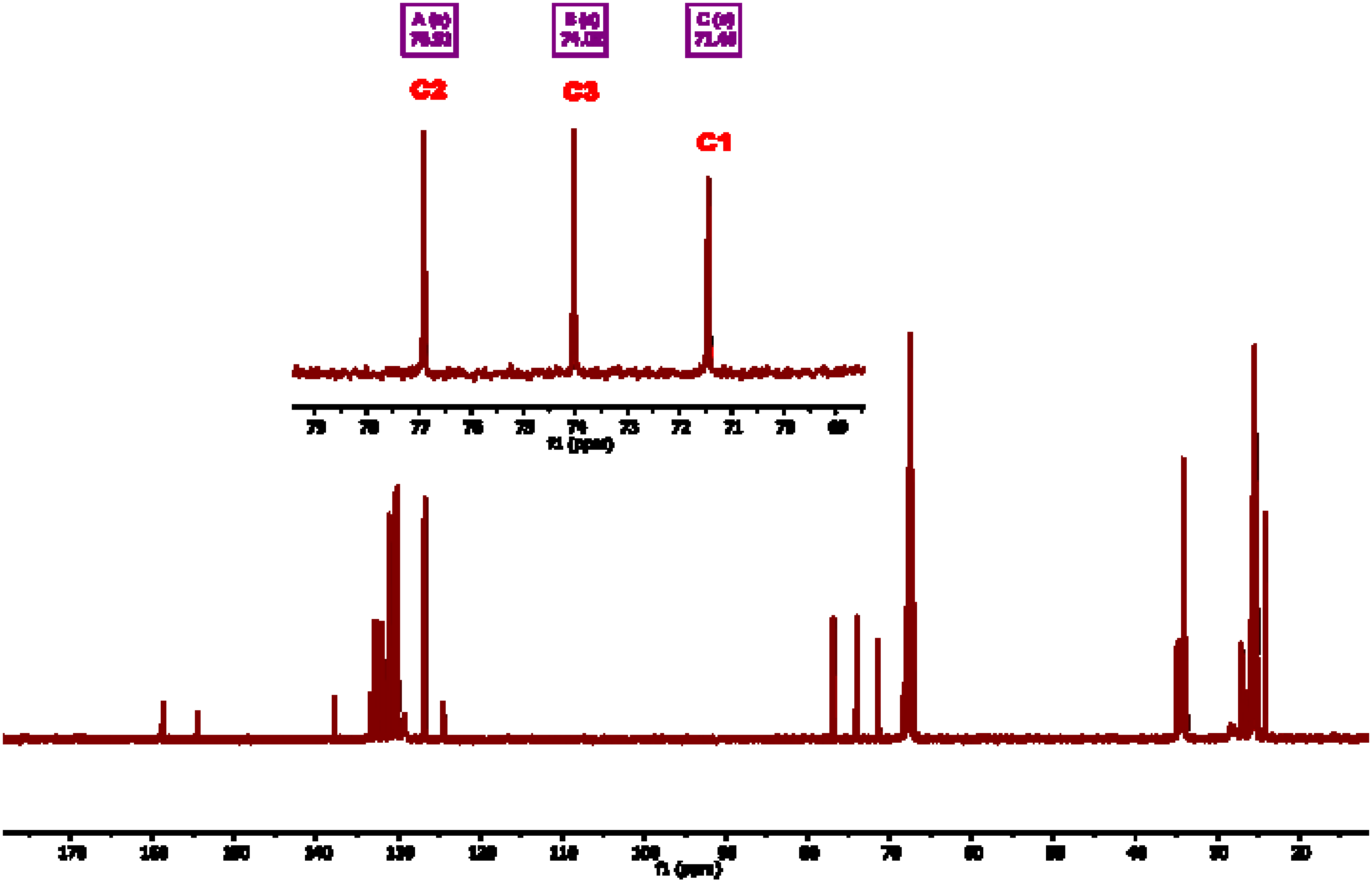
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Title of Article: Versatile CO_2 transformations into complex products: a one-pot two-step strategy

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