

# Soft Approaches to CO<sub>2</sub> Activation

Shoubhik Das, Felix D. Bobbink, Aswin Gopakumar, and Paul J. Dyson\*

**Abstract:** The utilization of CO<sub>2</sub> as a C1 synthon is becoming increasingly important as a feedstock derived from carbon capture and storage technologies. Herein, we describe some of our recent research on carbon dioxide valorization, notably, using organocatalysts to convert CO<sub>2</sub> into carboxylic acid, ester, formyl and methyl groups on various organic molecules. We describe these studies within the broader context of CO<sub>2</sub> capture and valorization and suggest approaches for future research.

**Keywords:** Catalysis · CO<sub>2</sub> activation · Green chemistry · Sustainable chemistry

Valorization of CO<sub>2</sub> is currently receiving increasing attention as it is non-toxic, cheap and is becoming increasingly abundant in the atmosphere,<sup>[1]</sup> which has a direct impact on climate change.<sup>[2]</sup> However, the activation of CO<sub>2</sub> is challenging, as CO<sub>2</sub> is highly inert due to the carbon being in the highest oxidized form, which leads to high thermodynamic and kinetic stability.<sup>[3]</sup> Energy-rich substrates such as epoxides<sup>[4]</sup> and aziridines<sup>[5]</sup> can overcome this high activation barrier under harsh reaction conditions (Scheme 1). In addition, strong nucleophiles such as Grignard reagents,<sup>[6]</sup> organolithium,<sup>[7]</sup> organoboron<sup>[8]</sup> and organozinc<sup>[9]</sup> reagents have been also used to form new C–C bonds encompassing CO<sub>2</sub> (Scheme 1). The reduction of CO<sub>2</sub> to simple compounds such as formic acid and methanol with homogeneous transition metal catalysts has also been a field of intensive research.<sup>[10]</sup>

It should be noted that these procedures, although employing energetic reagents, often require high pressures of CO<sub>2</sub> and harsh reaction conditions, which tends to hinder the development of these methodologies

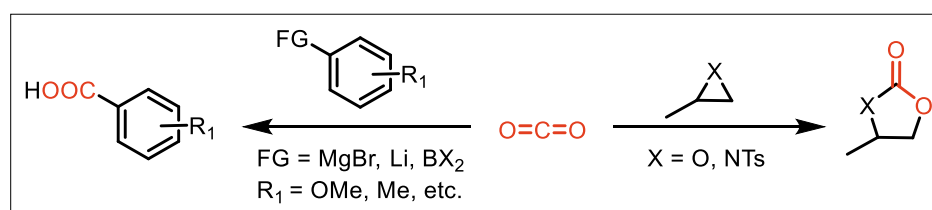
on an industrial scale. Despite these difficulties some processes are being commercialized, for example, Bayer recently announced that it will produce polyols incorporating 20% CO<sub>2</sub> in an installation with a 5,000 metric ton capacity (Scheme 2).<sup>[11]</sup> However, to reach more widespread applications, on a scale that would have a sizeable impact on carbon capture and sequestration technologies,<sup>[12]</sup> reaction conditions preferably need to be mild, *i.e.* at atmospheric pressure, and take place at moderate temperatures. For this purpose finding new catalysts is highly important.

Organocatalysts such as *N*-heterocyclic carbenes (NHCs) are able to activate CO<sub>2</sub> at atmospheric pressure, potentially allowing the harsh reaction conditions usually required for CO<sub>2</sub> activation to be overcome.<sup>[14]</sup> In general, organocatalysts are less expensive than metal-based catalysts, are readily accessible and, consequently, represent an interesting avenue for further investigations.<sup>[15]</sup> Moreover, these small organic molecules are typically non-toxic and environmentally friendly. Based on these above-mentioned properties, com-

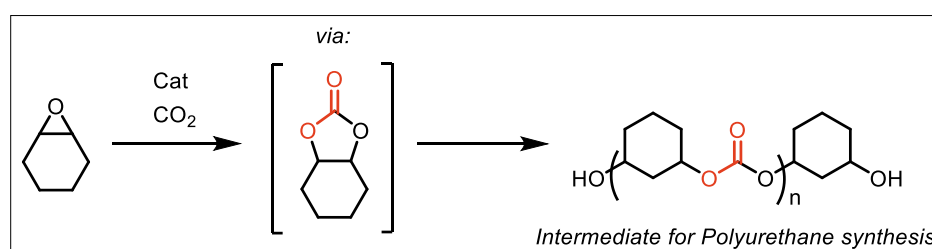
bined with our on-going research activities on imidazolium salts,<sup>[16]</sup> we decided to evaluate the ability of carbene catalysts to fix CO<sub>2</sub> onto organic molecules such as amines and alkynes to provide easy access to a range of valuable molecules, *e.g.* *N*-methylated amines, *N*-formylated amines, alkynyl carboxylic acids or esters, *etc.*

Amine derivatives are important intermediates in the chemical and pharmaceutical industries, the functionality being found in agrochemicals, dyes and flavors, fragrances and medicines.<sup>[17]</sup> We found that NHCs can methylate different aromatic, heteroaromatic and aliphatic amines using CO<sub>2</sub> as the carbon source with diphenylsilane as the reductant under ambient conditions and in high yield.<sup>[18]</sup> Aromatic, heteroaromatic and aliphatic amines react smoothly leading to excellent yields (Scheme 3). Cantat and coworkers have also shown that amines can be methylated using hydroboranes and a proazaphosphatane as organocatalyst.<sup>[19]</sup>

Both electron-donating and -withdrawing substituents on the aromatic ring at the *para* position react well whereas amines

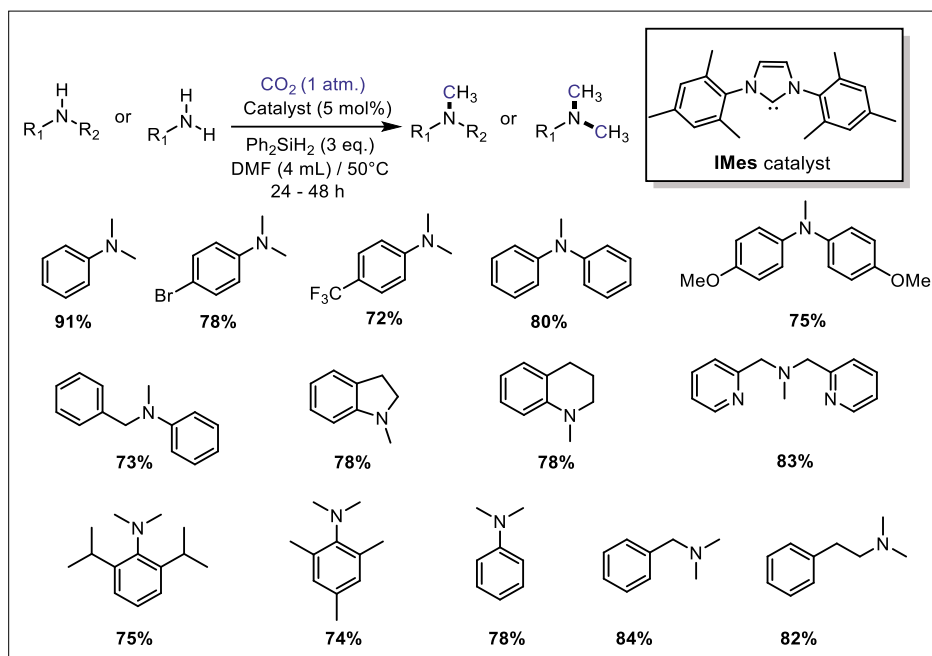


Scheme 1. Examples of reactions using CO<sub>2</sub> as a reagent with highly reactive substrates.



Scheme 2. An example of the synthesis of polycarbonate polyols using CO<sub>2</sub> as a C1 source.<sup>[13]</sup>

\*Correspondence: Prof. Dr. P. J. Dyson  
Institut des Sciences et Ingénierie Chimiques  
Ecole Polytechnique Fédérale de Lausanne (EPFL)  
CH-1015 Lausanne, Switzerland  
E-mail: paul.dyson@epfl.ch

Scheme 3. Different methylated-amines prepared using CO<sub>2</sub> and the **IMes** NHC catalyst.

with electron-withdrawing groups are less reactive and require prolonged reaction times. Steric hindrance on both sides of the amine has minimal effect on the yield of the reaction. Various symmetric and non-symmetric amines were also reacted under the optimized reaction conditions (5 mol% **IMes**, 1 atm. CO<sub>2</sub>, 3 equiv. Ph<sub>2</sub>SiH<sub>2</sub>, DMF, 50 °C) and the procedure worked well with these substrates. The carbene catalyst **IMes** is also tolerant to heteroaromatic amines such as picoline, indoline and 1,2,3,4-tetrahydroquinoline. Additionally, primary amines react in a similar fashion to secondary amines, selectively forming dimethylated products. We also evaluated the use of **IMes** in the *N*-methylation of complex molecules such as nortriptyline, cinacalcet, duloxetine and sertraline obtaining pure products in good yields without degradation or separation problems (Fig. 1).

The functional group tolerance of a reaction potentially enhances the overall sustainability of the route in the synthesis of complex structures, since protecting and deprotecting steps are not necessarily required, leading to a high atom economy. The selectivity of the carbene catalyst was evaluated using some particularly challenging substrates with different functional groups attached to different parts of the amine. Remarkably, it was found that nitrile, nitro, double and triple carbon-carbon bonds, ether, and ester substituted amines were well tolerated, providing the corresponding *N*-methylated amines in good to excellent yield. Moreover, methylation took place chemoselectively even in the presence of a ketone group, which could have been reduced by the silane.<sup>[20]</sup> To demonstrate the chemoselective poten-

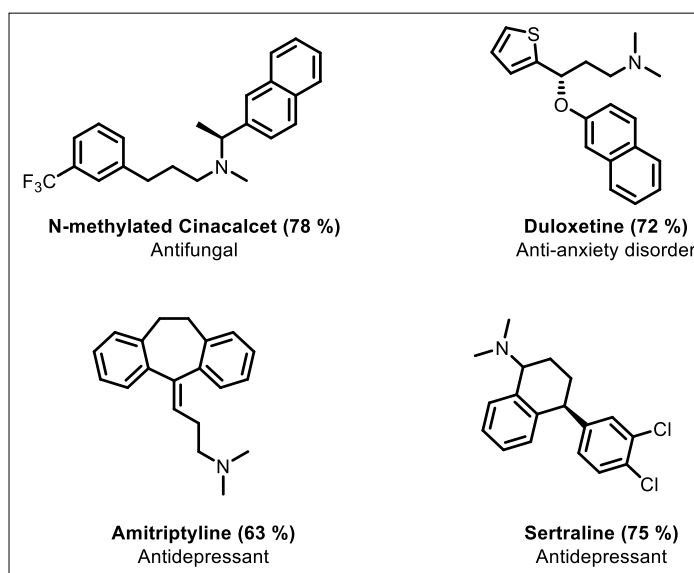
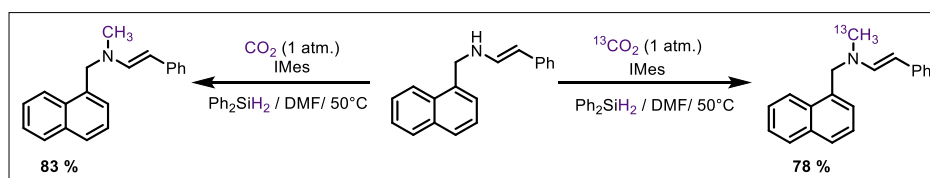
tial of the reaction it was used to prepare naftifine, an antifungal drug for the topical treatment of fungal infections in a two-step catalytic procedure (Scheme 4). The NHC catalyst was also used to prepare <sup>13</sup>C-labelled naftifine using <sup>13</sup>CO<sub>2</sub> in 78% yield.

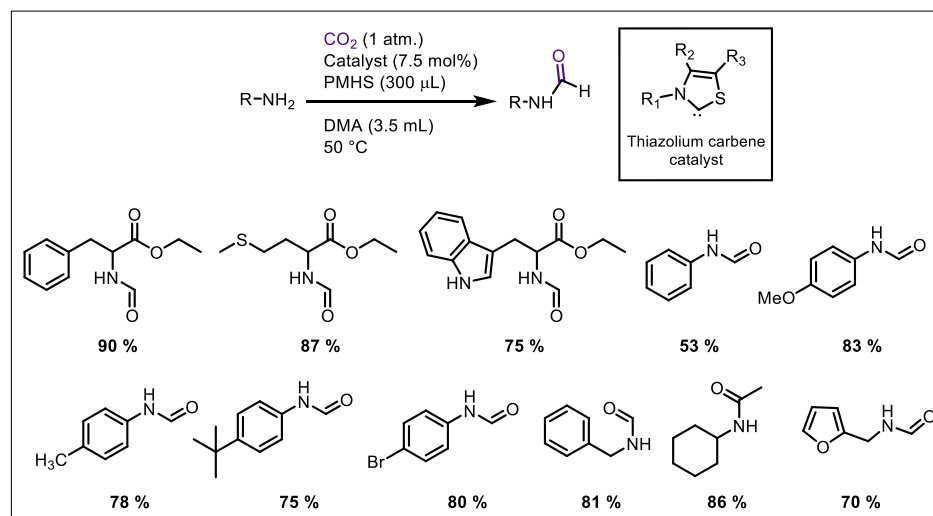
During the *N*-methylation reaction, the corresponding *N*-formyl compound was observed as an isolatable intermediate. Therefore, tuning the catalyst and catalytic conditions to recover *N*-formylated prod-

uct as a major (only) product is of value as *N*-formylated compounds are also versatile compounds employed as intermediates in organic synthesis and the formyl group is also present in pharmaceuticals.<sup>[21]</sup> Formyl groups are often used as protecting groups in organic synthesis and, in particular, *N*-formylated amino acid esters and peptides have been used widely in peptide synthesis as well as for precursors of isocyanides that find use in multicomponent reactions.<sup>[22]</sup>

We discovered a thiazolium carbene, closely related to vitamin B1, which is a potent *N*-formylation catalyst that operates under CO<sub>2</sub> at atmospheric pressure.<sup>[23]</sup> The catalyst is selective for different primary amines and amino acid esters. Aromatic, heteroaromatic, alicyclic and aliphatic amines afforded yields of up to 90% (Scheme 5).

Different amino acids such as methionine and tryptophan ethyl ester react smoothly under the optimized reaction conditions (7.5 mol% thiazolium carbene catalyst, 1 atm. CO<sub>2</sub>, PMHS, DMA, 50 °C). Moreover, *para*-bromo-substituted amines afford the corresponding products in 80% yield without any signs of reductive dehalogenation taking place. The catalyst is also tolerant to heteroaromatic amines such as furan derivatives. We also performed the reaction on a multigram scale without the *N*-methylated products being observed. Interestingly, *N*-methylated products can be obtained with the thiazolium carbene catalyst at higher temperatures, *i.e.* 100 °C (Scheme 6). As mentioned above, the

Fig. 1. Drug molecules prepared using the **IMes** catalyst.Scheme 4. Application of the **IMes** catalyst for the synthesis of complex structures.



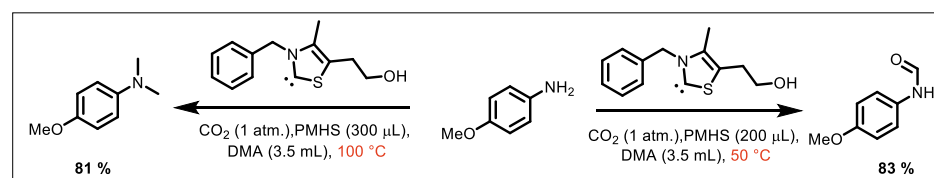
Scheme 5. Use of a thiazolium carbene catalyst for the *N*-formylation of amines using CO<sub>2</sub> as a carbon source: PMHS = Polymethylhydrosiloxane.

catalyst is closely related to vitamin B1, which in nature is used to decarboxylate pyruvate, a metabolite obtained from glycolysis.<sup>[24]</sup>

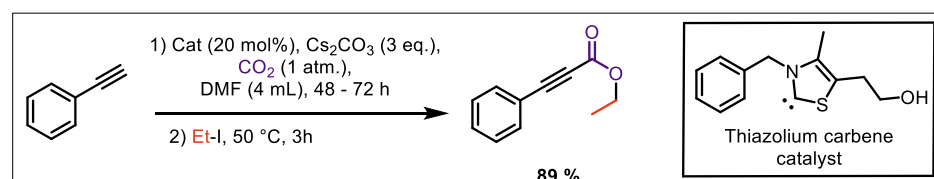
We have extended the concept of fixing CO<sub>2</sub> via organocatalysts towards terminal alkynes.<sup>[25]</sup> In terminal alkynes the proton is suitably acidic so the addition of a base leads to the formation of the corresponding acetylide anion. Acetylide anions are strong nucleophiles that can spontaneously attack a weak electrophile such as CO<sub>2</sub> to generate alkynyl carboxylic acids. Alkynes functionalized with carboxylic acids are widely found in medicinally relevant compounds and they also find uses as synthons in organic synthesis. While several metal-based catalysts have been reported for this reaction, we found that the thiazolium carbene compound catalyzes the carboxylation reaction to give the corresponding alkynyl carboxylic acids or esters, depending on the conditions, in excellent yield (Scheme 7). This protocol opens up access to a pool of highly functionalized propiolic acids from CO<sub>2</sub>.

In addition to our studies on homogeneous organocatalysts we have been studying dispersed transition metals nanoparticles that catalyse selective *N*-formylation and *N*-methylation reactions (Fig. 2). In general, homogeneous catalysts usually give better selectivities than their heterogeneous counterparts as they tend to operate under milder conditions.<sup>[26]</sup> Nevertheless, we discovered a viable palladium nanoparticle catalyst (palladium is known to efficiently activate/store hydrogen),<sup>[27]</sup> for these reactions using diphenylsilane as the hydrogen source. A wide variety of palladium nanoparticles were prepared and compared to classical heterogeneous systems such as Pd/Al<sub>2</sub>O<sub>3</sub>, CuAlO<sub>x</sub> and Pd/CuZrO<sub>2</sub> and Pt-MoO<sub>x</sub>/TiO<sub>2</sub>.<sup>[28]</sup> These reported heterogeneous catalysts employ

hydrogen, but operate under harsh reaction conditions and require prolonged reaction times to achieve high yields. In contrast, our hydrosilylation approach functions under ambient pressures at relatively low



Scheme 6. Temperature controlled reaction of amines with the thiazolium carbene catalyst related to vitamin B1.



Scheme 7. Reaction of terminal alkynes to afford esters using the thiazolium carbene catalyst and CO<sub>2</sub> as the source of the carboxylate moiety.

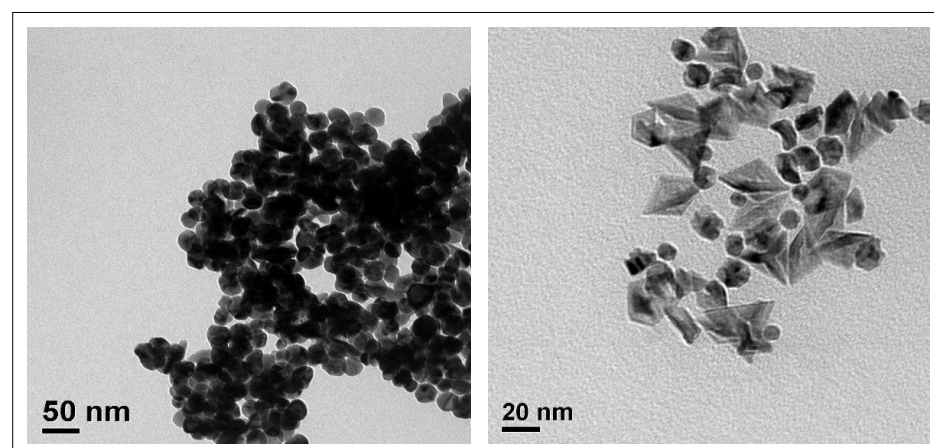


Fig. 2. TEM images of unsupported palladium nanoparticles prepared using (left) ascorbic acid and (right) formaldehyde as the reducing agent. Both types of nanoparticles catalyse the *N*-methylation reaction.

temperatures (50–80 °C). Such conditions also enable a sinter-free environment to the unsupported palladium nanoparticles, which can be detrimental to recycling experiments.

The selectivity towards *N*-formylated or *N*-methylated products depends on the nature of the palladium nanoparticles. From the results obtained so far, there is not an obvious correlation between the particle size and the selectivity, but catalysts such as palladium on activated carbon (commercial grade, Pd content 10 wt%), did not promote either reaction.

In summary, despite the rise in strategies for avoiding CO<sub>2</sub> production, gigatons of CO<sub>2</sub> are produced each year to fulfil the world's energy and chemical demands. And although there is a considerable mismatch in the amount of CO<sub>2</sub> produced and the amount that would be consumed for chemical applications, the long-term goal to produce fuels such as methane, methanol and hydrocarbons from CO<sub>2</sub> using renewable energy could one day end dependence on fossil fuels. Hence, using CO<sub>2</sub> as a C1 carbon source warrants inten-

sive study and all types of catalysts, *i.e.* homogeneous, heterogeneous, organo and enzymatic.

In the examples provided herein, a relatively small fraction of the product is derived from CO<sub>2</sub> and, for a greater impact, the majority of the carbon atoms in any organic product should be derived from CO<sub>2</sub>. Progress in this direction should be feasible by combining the selective catalysts described here with a process that generates base chemicals from CO<sub>2</sub>. A CO<sub>2</sub> refinery powered by renewable energy could ultimately produce not only fuels, but also sophisticated organic structures that meet the needs of a modern society.

Received: August 19, 2015

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