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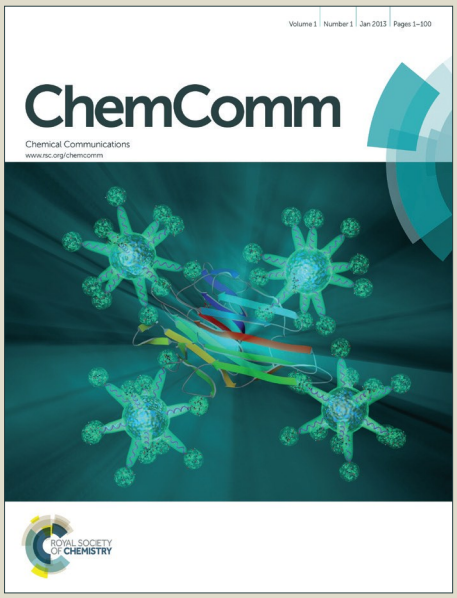

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Thiazolium Carbene Catalysts for the Fixation of CO_2 onto Amines

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The catalytic N-formylation and N-methylation of amines using CO_2 as the carbon source represents a facile and sustainable approach for the synthesis of pharmaceuticals and natural products. Herein, we describe highly effective and inexpensive thiazolium carbene-based catalysts derived from vitamin B1 for the N-formylation and N-methylation of amines, using polymethylhydrosiloxane (PMHS) as a reducing agent, which operate under ambient conditions.

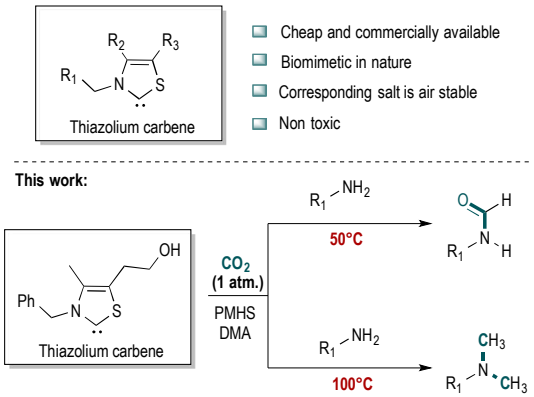
Continued emissions of carbon dioxide has led to increased CO_2 levels in the atmosphere that is impacting on climate.[1] Various approaches to reduce CO_2 levels in the atmosphere, such as capture of CO_2 and injection deep into the earth, a practice known as carbon capture and storage (CCS),[2] are under intensive investigation. To increase the viability of such processes, CO_2, often regarded as a waste, can be considered as an increasingly abundant chemical feedstock,[3] and can be employed to generate value-added products. This approach is referred to as CCUS (carbon capture, use and storage).

The activation of CO_2 is highly challenging due to its high thermodynamic stability and kinetic inertness.[4] One approach is to use energy-rich substrates such as epoxides and aziridines to overcome this high activation barrier to generate heterocycles.[5] Strong (energy rich) nucleophiles such as Grignard reagents, organolithium agents, organoboranes and organozinc compounds have also been used to form new C-C bonds with CO_2. Often these procedures require high pressures and harsh reaction conditions, which limit practical applications of these methods in industry. Therefore, mild reaction conditions are desirable, preferably taking place at atmospheric pressure and at ambient temperatures.

Recently, N-heterocyclic carbenes (NHCs) were shown to activate CO_2 under mild reaction conditions.[6] Based on this discovery we investigated their applications for the synthesis of various N-methylated amines using Ph_2SiH_2 as a hydrogen source.[7]

In addition to the N-methylation of amines, N-formylation via CO_2 fixation is also an attractive reaction as N-formylated compounds are key chemical intermediates and for the synthesis of drugs, agrochemicals, dyes and fragrances.[8] Formyl groups may also be transformed into other functional groups, as in the Vilsmeier reaction,[9] allylation reactions,[10] etc. Their typical synthesis includes the use of chloral, formic acid, formaldehyde or formate,[11] and generating them from carbon dioxide would be advantageous.

Scheme 1: Thiazolium carbene catalysts employed in the selective N-formylation or N-methylation of amines using CO_2.



In a seminal paper ruthenium-based catalysts were used to prepare N-formylated amines using carbon dioxide and hydrogen the reducing agent.[12] Subsequent papers describe the use of palladium-

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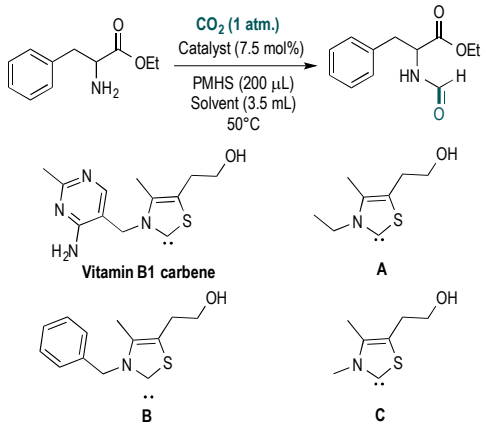
and copper-based heterogeneous catalysts for this reaction.[13,14] Due to the relatively harsh reaction conditions of these reactions employing H_2, other reducing agents such as hydrosilanes have broad appeal,[15] especially as they are stable, easy to handle and commercially available.[16] Inspired by the role of vitamin B1 in CO_2 fixation in animal tissues to synthesize oxaloacetate from pyruvate, we decided to evaluate thiazolium carbenes (**Scheme 1**) as alternatives to NHC catalysts.[17] Compared to typical NHC catalysts, thiazolium carbenes are inexpensive and non-toxic. Additionally, the corresponding salt is air stable and can be stored without the need to exclude moisture and oxygen.[18] Carbene catalysts employ silanes as reductants which can also help to control chemoselectivity.[19] Polymethylhydrosiloxane (PMHS) is stable, inexpensive and easily removed after reaction and, therefore, was selected for this study.

Table 1: Optimization of reaction conditions for the N-formylation of ethylphenylalaninate employed as model substrate.[a]



Entry	Catalyst	Silane	Solvent	Yield (%)[b]
1	**Vit. B1**	PMHS[c]	DMA[d]	58
2	**A**	PMHS	DMA	63
3	**B**	PMHS	DMA	95
4	**C**	PMHS	DMA	43
5	**B**	PMHS	DMF[e]	77
6	**B**	PMHS	Acetonitrile	0
7	**B**	PMHS	Toluene	0
8	**B**	PMHS	THF	0

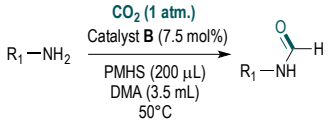
[a] Reaction conditions: substrate (0.5 mmol), catalyst (7.5 mol%), silane (200 μL), solvent (3.5 mL), CO_2 (1 atm.), 50°C, 15 h. [b] Yield determined by GC using n-decane as an internal standard. [c] PMHS = polymethylhydrosiloxane. [d] DMA = N,N-dimethylacetamide. [e] DMF = N,N-dimethylformamide

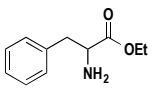
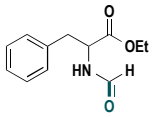
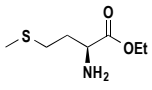
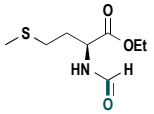
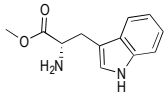
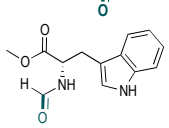
Several thiazolium carbenes were investigated for the N-formylation of ethylphenylalaninate, used as a model substrate to identify and optimize the reaction and key reaction parameters (**Table 1**). In the presence of 7.5 mol % of **B** (**Table 1**) the corresponding ethyl formylphenylalaninate was obtained in 95% yield. The other catalysts evaluated are active, but gave lower yields of the product. The solvent used is critical, high yields were obtained in DMA and DMF in which the solubility of CO_2 is high. No activity was observed in toluene, THF and acetonitrile, possibly due to the instability of the catalyst in these solvents.

Based on the optimized reaction conditions the scope of the thiazolium carbene catalyzed N-formylation reaction was explored using catalyst **B** (**Table 2**). Aromatic, alicyclic and aliphatic amines afforded yields of up to 90%. Different amino acids such as methionine and tryptophan ethyl ester (substrates **1a-3a**) reacted smoothly under the optimized reaction conditions. Moreover, *para*-bromo-substituted amines gave the corresponding products in 80% yield (e.g. substrate **9a**) and reductive dehalogenation was not observed. Notably, the reaction may also be performed on a multigram scale without the formation of N-methylated products.

The formyl group is used as an amino-protecting reagent in peptide synthesis,[20] subsequently being converted into isocyano acids. Formylation of peptides is achieved using formic anhydride, ammonium formate or related reagents.[21] These methods have several limitations such as the thermal instability of peptides at elevated temperatures resulting in decomposition and the formation of by-products. We evaluated the N-formylation of dipeptides using catalyst **B** (10 mol%) and full conversion of the starting material was obtained (see supporting information). N-methylation of the amide bonds or other by-products were not observed. We also conducted a competition reaction in which N-methylbenzyl amine and benzyl amine were reacted in the same pot under the optimized conditions. The secondary amine was found to react faster (ca. 2-3 times) than the primary amine and, hence, selectivity for a substrate containing both primary and secondary amines is expected to be low.

Table 2: Catalytic N-formylation of amines using CO_2 as carbon source.[a]



Entry	Substrate (a)	Product (b)	Yield[b] (%)
1			90
2			87
3			75

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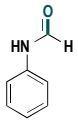
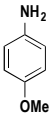
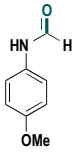
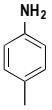
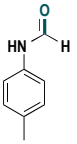
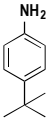
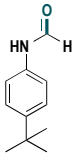
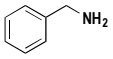
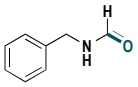
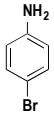
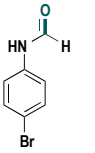
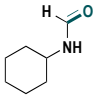
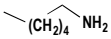
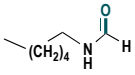
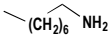
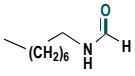
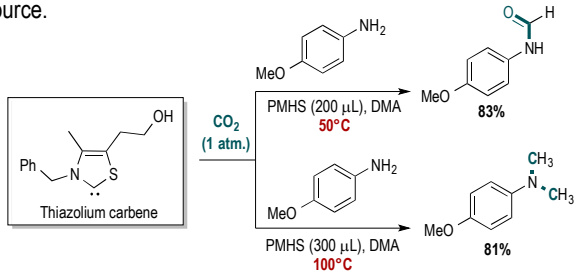
4			53[c]
5			83
6			78
7			75
8			81
9			80
10			86
11			73
12			75

[a] Reaction conditions: substrate (0.5 mmol), catalyst **B** (7.5 mol%), PMHS (200 μL), solvent (3.5 mL), CO_2 (1 atm.), 50°C, 15-24 h. [b] Isolated yield. [c] Yield determined by GC using n-decane as an internal standard for substrate **4a.**

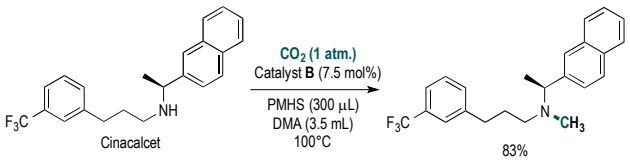
Scheme 2: Catalytic N-methylation of amines using CO_2 as a carbon source.



The thiazolium carbene catalyst may also be used for N-methylation reaction using CO_2 combined with PMHS under slightly more forcing conditions. Numerous reports describe methylation using CO_2 and hydrogen or silanes as the reducing agent.[22,23] In the presence of catalyst **B**, 4-methoxyaniline was converted to the corresponding N,N-dimethylated aniline at 100°C in 81% yield (**Scheme 2**).

N-methylation of amines has been shown to enhance the biological activity of certain drug molecules.[24] For example, inserting one or more methyl groups into a bioactive molecule can enhance lipophilicity and thereby facilitate transport through cell membranes. We successfully applied catalyst **B** to the N-methylation of cinacalcet (**Scheme 3)**. The N-methylated products were purified in a facile fashion.

Scheme 3: Catalytic *N*-methylation of cinacalcet using CO_2 as a carbon source.



Conclusions

In summary, we have demonstrated that a bioinspired thiazolium carbene compound is an efficient catalyst for fixing CO_2 onto different amines in the presence of PMHS. The lead catalyst is cheap and non-toxic. The reaction product, i.e. N-formylation versus N-methylation, may be tuned by simply changing the reaction temperature. The catalyst shows a broad substrate scope and thereby providing high application in CO_2 fixation reactions.

Experimental Section

Full details are provided in the SI. General procedure for the N-formylation reaction: The thiazolium salt (0.15 mmol) and sodium hydride (0.15 mmol) were dissolved in DMA (2 mL) in a 10 mL Schlenk flask and stirred for 30 min to generate the carbene (0.075 mmol/mL solution). The solution was then stored under nitrogen without stirring, until the inorganic salts settled at the bottom of the flask. 1 mL of the carbene solution was transferred into a dry three neck flask (after three vacuum and CO_2–purge cycles), already charged with the amine (0.5 mmol) and connected to a CO_2 balloon. Next, DMA (2.5 mL) and PMHS (200-300 μL) were introduced and the reaction was monitored by TLC and GC-MS. Upon completion, the reaction mixture was filtered through celite and washed with ethyl acetate and an aqueous work up was performed, the solution dried with anhydrous sodium sulfate, and the product purified using column chromatography using ethyl acetate/pentane and 1% triethyl amine. All yields are isolated yields unless otherwise stated.

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