CO_2 as a starting material in the catalytic synthesis of carbonates and carbamates

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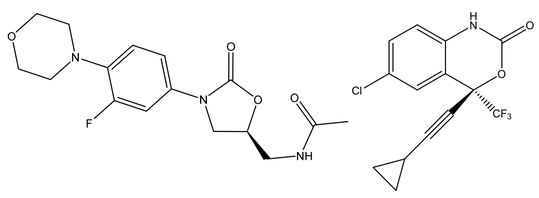
1. Introduction

CO_2 is a cheap, environmentally friendly C1 reagent whose utilization in organic synthesis has been explored in recent decades. One possible use of CO_2 is the synthesis of carbonates and carbamates from unsaturated alcohols and amines, as some recent reviews have demonstrated [1,2].

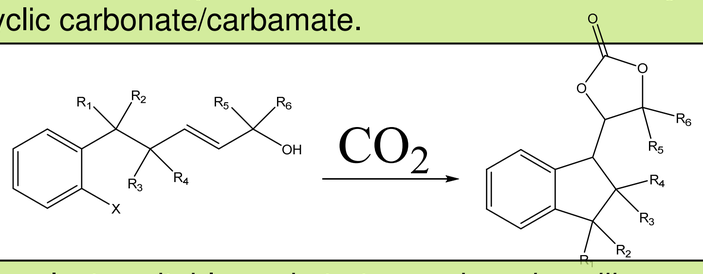
Cyclic carbonates and **carbamates** are very useful compounds, particularly in drug discovery. Drugs that include a cyclic carbamate motif include Linezolid and Efiravenz. The quest to find an environmentally friendly catalyst that can catalyze the conversion of CO_2 into cyclic carbonates and carbamates is ongoing.



Scheme 1 Significant cyclic carbamate drugs – Linezolid (left) and Efavirenz (right)

2. The aims of the project

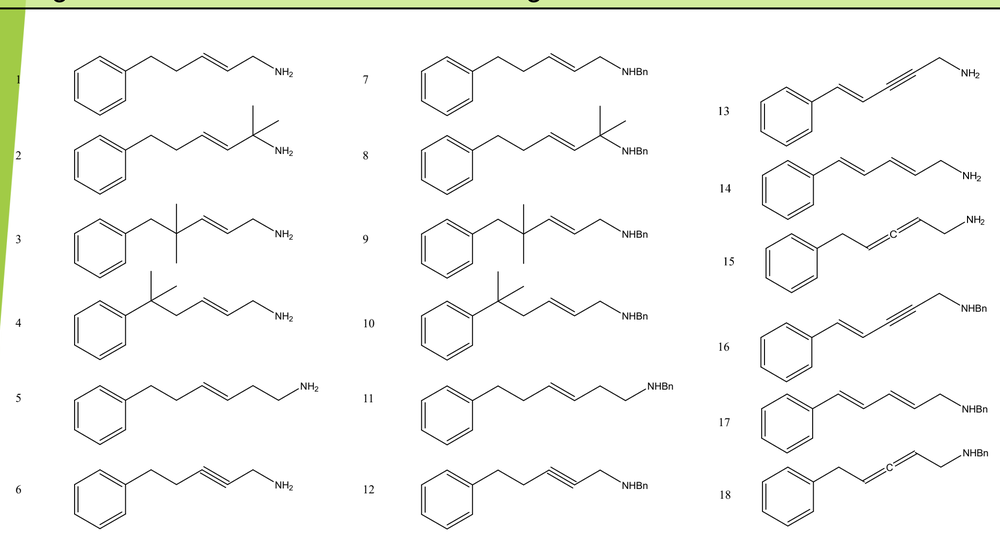
The primary aim of our project is to develop a method of forming a complex bicyclic carbonate and carbamate motif using CO_2 as a reagent. Our reaction is a two-step process: the first cyclization creates the indane ring and the second produces the cyclic carbonate/carbamate.



We aimed to select suitable substrates using *in silico* methods and to experimentally optimize reaction conditions and catalyst properties. After the reaction conditions are optimized, we aim to investigate the mechanism of the reaction in silico and experimentally, using NMR methods. If successful, a series of compounds with this motif will be tested for anti-bacterial activity.

3. Substrate selection *in silico*

In the first step, alkyl groups were introduced into various positions along the carbon chain. The thermodynamics of the isodesmic reaction [3] was modelled using B2PLYP/B3LYP. The results are given in Table 1.



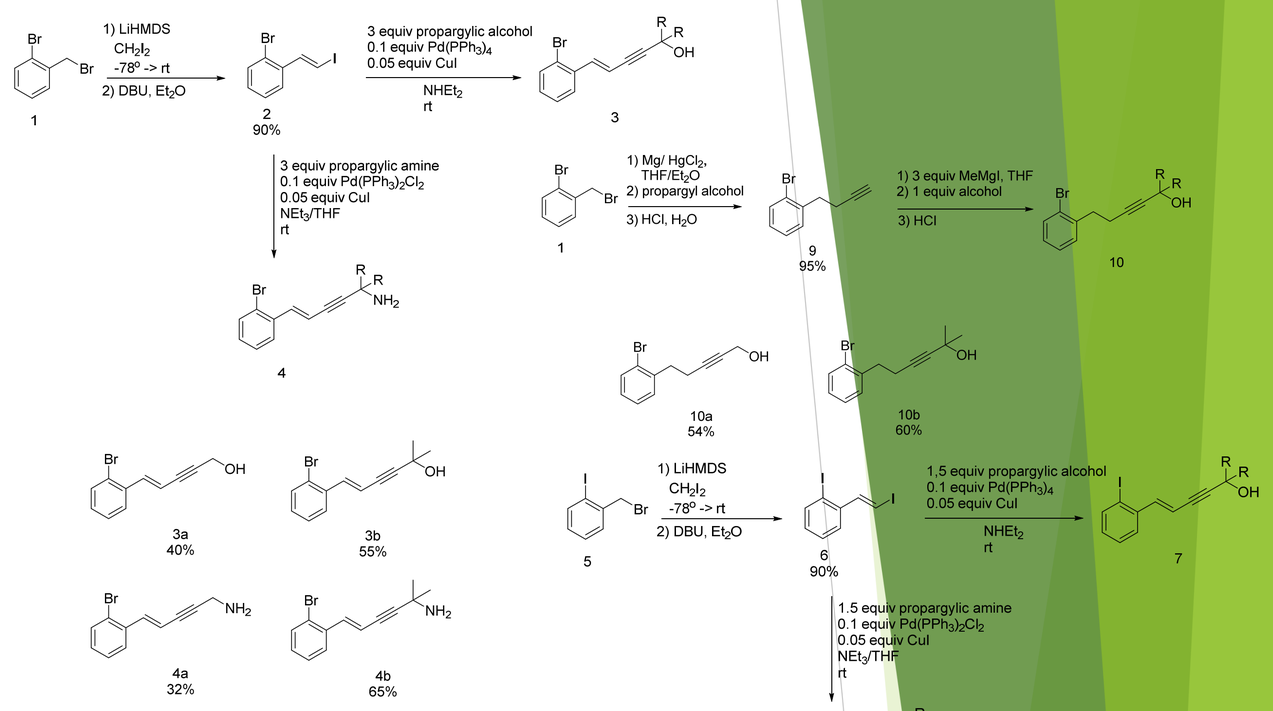
Substrate	ΔG(kJ/mol)	Substrate	ΔG(kJ/mol)	Substrate	ΔG(kJ/mol)
1	150.34	**7**	158.42	13	**-44.86**
2	163.73	**8**	155.67	14	25.61
3	153.22	**9**	153.43	15	**-63.11**
4	**144.23**	**10**	**139.34**	16	**-41.33**
5	162.98	**11**	164.33	17	22.75
6	**12.43**	**12**	**11.98**	**18**	**-61.48**

Substrates containing two methyl groups next to the benzene ring experience slightly higher reaction favorability and substrates containing a triple bond instead of a double bond are much better at capturing CO_2. In order to achieve even higher CO_2 capture capacity, we tried to model substrates with a conjugated double-triple bond system. Clearly, the allene and alkenyne substrates are the best substrates for CO_2 in this type of reaction (allene due to substrate instability and alkenyne due to product stability).

4. Methodology - experimental

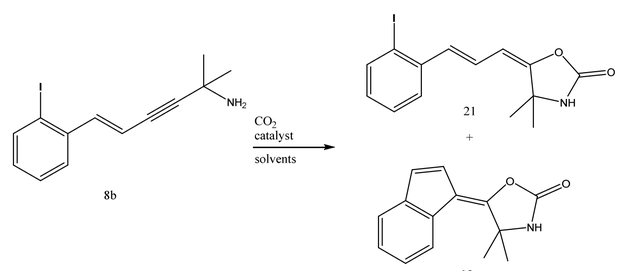
The loading of the reactor (mini-autoclave) with a palladium catalyst, co-catalyst, solvent and reagent takes place inside a glove box (Mbraun). The pressure of CO_2 within the autoclave can rise to 6 bar and the palladium catalysts used include $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$ and $Pd(dppf)Cl_2$ (2,5-10 mol%) and the co-catalyst NaO^tBu (1-3 eq). Solvents include DMF, THF and DMSO.

5. Substrate synthesis



6. Attempts to synthesize carbonates and carbamates by CO_2 capture

The CO_2 capture reactions are conducted under a range of conditions, where both the substrates and reaction conditions are screened.



	Katalizator	Mol% katalizatora	Otapalo	Temperatura (°C)	Tlak CO_2 (bar)	Iskorištenje (21)
1	$Pd_2(dba)_3$	10%	DMF	40	4	/
2	$Pd_2(dba)_3$	10%	DMF	60	4	/
3	$Pd_2(dba)_3$	10%	DMF	100	4	/
4	$Pd(dppf)Cl_2$	5%	DMF	40	4	/
5	$Pd(dppf)Cl_2$	5%	DMSO	40	4	5%
6	$Pd(dppf)Cl_2$	10%	DMSO	40	4	13%
7	$Pd(dppf)Cl_2$	5%	DMSO	40	1	3%
8	$Pd(dppf)Cl_2$	5%	DMSO	60	1	/

DMF and DMSO generally make the best solvents. As for catalysts, electron-rich palladium catalysts such as Pd(0) catalysts and $Pd(dppf)Cl_2$ seem to perform the best. Likewise, increasing the temperature gives better results. However, only the monocyclised product has been isolated so far. Further optimisation is required to produce bicyclic products.

A new approach examines the possibility that oxidation of Pd(0) breaks the catalytic cycle. In these studies, a stoichiometric amount of copper(I) iodide is added to the reaction mixture in order to reduce the palladium. Mechanistic studies (NMR, computational are underway to determine which step in the reaction is being inhibited..

	Katalizator	Mol% katalizatora	Otapalo	Temperatura (°C)	Tlak CO_2 (bar)	Iskorištenje (24)
1	$Pd(dppf)Cl_2$	5%	DMF	40	4	/
2	$Pd(dppf)Cl_2$	5%	DMSO	40	4	4%
3	$Pd(dppf)Cl_2$	10%	DMSO	40	4	20%
4	$Pd(dppf)Cl_2$	5%	DMSO	40	1	2%
5	$Pd(dppf)Cl_2$	5%	DMSO	60	4	/
6	$Pd(dppf)Cl_2$	2.5%	DMSO	40	4	4%
7	$Pd(dppf)Cl_2$	10%	DMSO	25	1	5%
8	$PdCl_2$ + 10% DavePhos	5%	DMSO	40	4	13%

7. References

[1] Lopes, E. J., Ribeiro, A. P., & Martins, L. M. (2020). New Trends in the Conversion of CO2 to Cyclic Carbonates. *Catalysts, 10*(5), 479. doi:10.3390/catal10050479

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[3] Ponomarev, D. A., & Takhistov, V. V. (1997). What are Isodesmic Reactions? *Journal of Chemical Education, 74*(2), 201. doi:10.1021/ed074p201

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