# Transition metal-free synthesis of carbamates using $CO_2$ as the carbon source

MINIREVIEW

# Synthesis of Carbamates Using $CO_2$ as the Carbon Source

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***Abstract:*** *Utilization of carbon dioxide as a C1 synthon for the synthesis of valuable chemicals are highly attractive. However, activation of $CO_2$ is highly challenging due to the thermodynamic stability and kinetic inertness. Keeping this in mind, several new strategies have been discovered recently for the generation of new C-heteroatom bonds. Among these, formation of C-N bonds is highly attractive, especially, when carbamate can be synthesized directly from $CO_2$. This minireview focuses on green, and transition metal-free approaches for the fixation of $CO_2$ to generate carbamates for the production of fine chemicals and pharmaceuticals. Last ten years, several reports have been published and transition metal-free approaches gained increasing attention. Traditional reviews focus rarely on the transition metal-free approaches and even less often perform direct comparison between those and their correlations. This review tries to close this discrepancy.*

## 1. Introduction

Carbamates are highly important for the synthesis of pharmaceuticals, agrochemicals as well as have been used as synthetic intermediates in the organic synthesis.[1] Additionally, carbamates are well known for the protection of amino acids to bring chemical stability in the peptide.[2] The main reason for this chemical stability is to gain the conformational stability due to the delocalisation of non-nonbonding electrons on nitrogen atom into the carboxyl moiety.[3] Expediently, hydrogen bonding through the carboxyl group and the backbone NH also enhances this stability. This high chemical stability offers enormous opportunities for the improvement in pharmacokinetic properties.[4] For this reason, this functional group often can be found in anticancer, antibacterial, antifungal, antimalarial, antiviral, anti-HIV drugs or active pharmaceutical ingredients (API) (**Figure 1**). Thus, there is strong interest for the synthesis of carbamates in a sustainable way.[5]

Synthesis of carbamates can be achieved by reacting with amines using various C1 sources such as chloroformates or dialkyl carbonates etc.[6] Parallel to these, toxic carbon monoxide can be also considered as a C1 source for the synthesis of carbamates.[7] However, high pressure is required to achieve high conversion. Additionally, carbamates can be synthesized by reacting alcohols with isocyanate or isocyanides.[8] It is clear that traditional synthesis of carbamates requires specialized reagents and/or operational complexity to achieve high yield of the product formation.

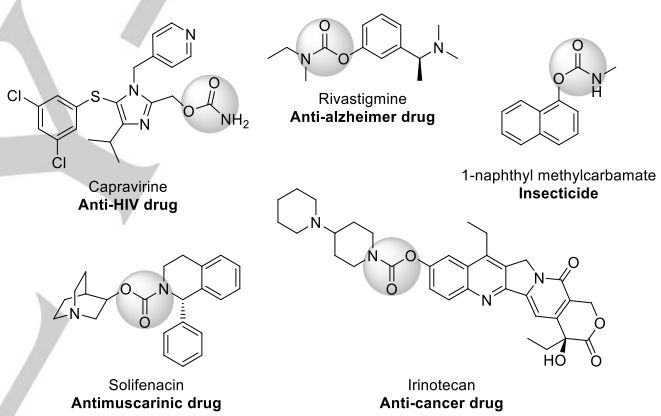



**Figure 1:** Carbamate containing pharmaceutical drugs

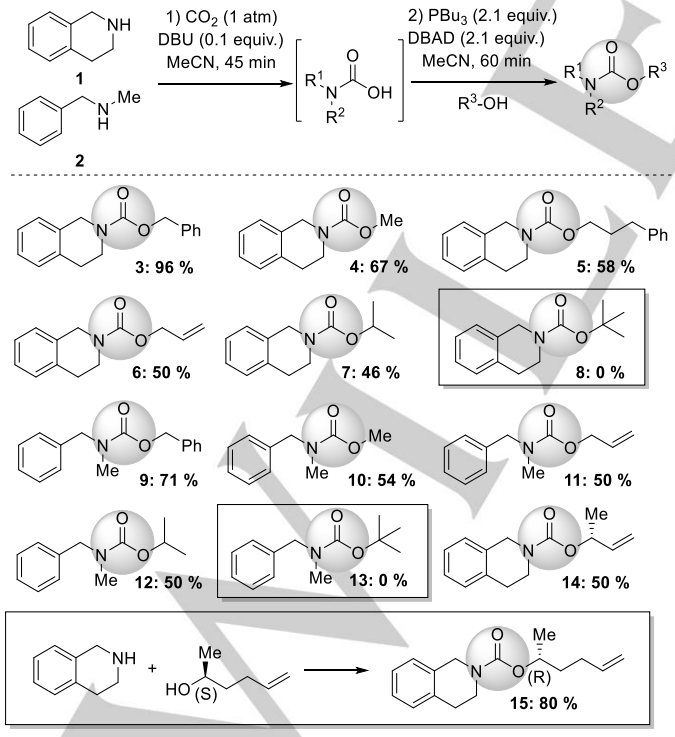
Compared to all these methods, using $CO_2$ as C1 source for the synthesis of carbamates is the most appealing one as $CO_2$ is well known of being abundant, nontoxic, nonflammable and renewable.[9] However, the main drawback of utilizing $CO_2$ is its high thermodynamic stability and kinetic inertness.[10] Nevertheless, addition of catalysts or suitable reagents can lower the kinetic barrier and can promote $CO_2$-medaited organic synthesis.[11] In fact, various C-C bonds and C-heteroatom bonds have been achieved using $CO_2$ as the carbon source.[12] Inspired by these, organic chemists have applied this knowledge to generate carbamates via the formation of C-N bonds.[13] In fact, amines are widely available and therefore, fixation of $CO_2$ onto amines to achieve carbamates should provide a straightforward and sustainable strategy.[14]

Different homogeneous and heterogeneous metal catalysts based on Ru, Sn, Al and Au are well-known for the conversion of amines to carbamates using $CO_2$ as the carbon source.[15] Additionally, macrocyclic polyether and potassium superoxide also have been used to improve the reaction conditions.[16] Except these, various inorganic and organic base catalyzed

or mediated transition metal-free systems have been developed recently.[17] In recent years, many reviews have been written on carbon dioxide fixation, as also on the advances of the carbamate synthesis including the use of $CO_2$ as a synthon.[18] Each of the reviews focuses on different key features, but none of them was focused on the recent advances in transition metal-free carbamate synthesis. In general, transition metal-free systems are cheaper in price and mostly preferable for the synthesis of pharmaceutical drugs in the industries.[19] Based on all these, we will summarize here the recent protocols (last 10 years) for the syntheses of carbamates using transition metal-free systems.

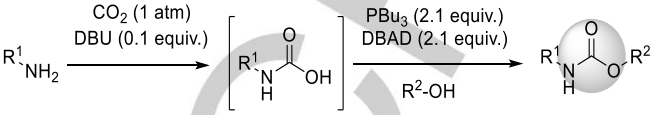
## 2. Synthesis of Acyclic Carbamates

In 2010, the research group of Dinsmore showed that $CO_2$ can be used to react with amines to form urea and carbamates under metal free and mild reaction conditions by utilizing 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU).[20] By this, they established an efficient library synthesis technique without the presence of transition metal to gain access to carbamates. During their investigation they utilized 24 different amines for the generation of the carbamic intermediates, which they could dehydrate under Mitsunobu conditions to transform them further to carbamates. They chose two different amines for the further reaction with different alcohols to obtain different carbamates. They showed various alcohols combined with the two chosen amines with good to excellent yields (**Scheme 1**, entries: **3**-**7**, **9**-**12**).



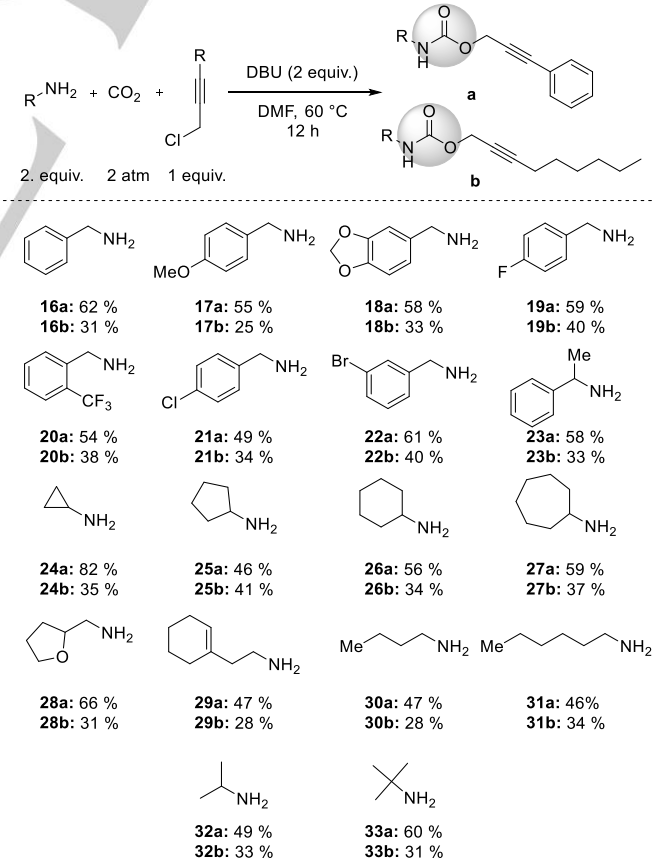

**Scheme 1.** Substrate scope for the generation of carbamates utilizing different alcohols.

However, sterically hindered *tert*-butanol showed a limitation to this synthetic strategy (entries **8** and **13**). During their initial testing of different amines, *tert*-butylamine also showed comparable lower activity. Attempts to bypass the low activity at elevated temperatures could not improve the results. Surprisingly, use of chiral alcohols (entries **14** and **15**) showed an inversion of the stereochemical information.



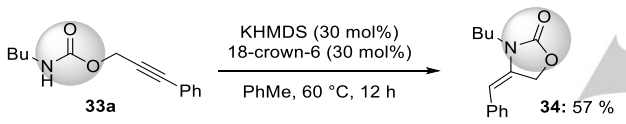

**Scheme 2.** Proposed mechanism for the library synthesis protocol of Dinsmore *et al.*

During the investigations, they were able to prove the formation of isocyanate intermediate and a suitable mechanism based on this intermediate (**Scheme 2**). Based on trapping and competition experiments, combined with the observed inversion of the stereocenter they derived a plausible mechanism for the reaction. The starting amine reacted with the carbon dioxide atmosphere under the support of DBU to form a carboxylic acid intermediated which was then treated with the Mitsunobu conditions, by $PBu_3$ and DBAD. The applied reaction conditions enabled an $S_N2$ displacement with the activated alcohol to yield the desired carbamate.




**Scheme 3.** Substrate scope for the synthesis of carbamates developed by Zhang et al.

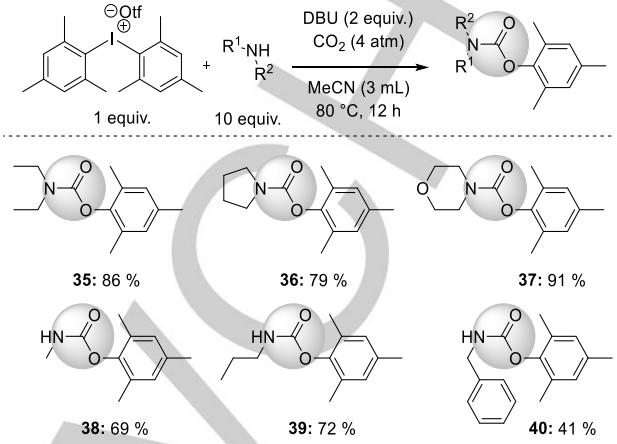
In 2015, Zhang *et. al.* took up the interest in this field and showed further DBU mediated carboxylative couplings of primary amines, carbon dioxide and propargyl chlorides.[21] They performed their entire substrates scope with two different propargyl chlorides which were labeled **a** and **b** for their respective products and yields (**Scheme 3**). Consistently, the yield of the utilized propargyl chloride **b** showed decreased reactivity for the formation of the product, demonstrating a structural dependence in this reaction. For the investigations of different amines in this reaction, several aromatic primary amines were examined (**Scheme 3**, entries: **16**-**27**). Interestingly, electron withdrawing and electron donating groups did not change the yield of the reaction (**Scheme 3**, entries: **17a and 18a**). A wide selection of different nonaromatic primary amines was also examined under their reaction conditions and up to 82% yield of the corresponding carbamate was observed (**Scheme 3**, entries: **24**-**28**). Additionally, several aliphatic amines showed reactivity under their reaction conditions and up to 60% yield was obtained (**Scheme 3**, entries: **28**-**33**). The size of the utilized amine showed in some cases a significant role to achieve the highest yields (entries: **24a**, **28a**, **33a**), but was not present for the smallest amine (**32a**).



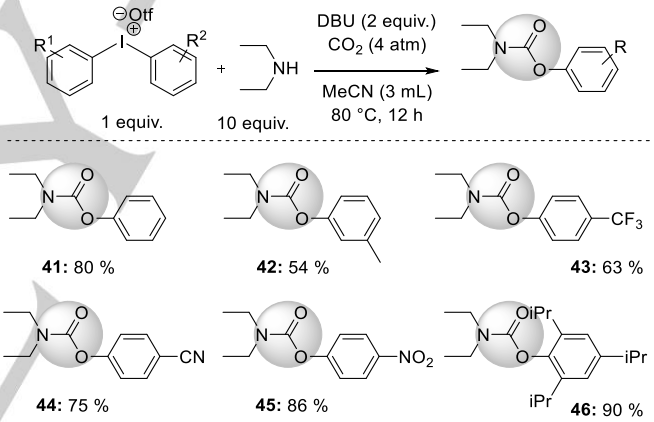

**Scheme 4.** KHMDS mediated 5-exo-dig cyclisation reaction

Nevertheless, the incorporation of the C-C-triple bond provided rich possibilities for further cyclisation. They chose to demonstrate the 5-exo-dig cyclisation in the presence of semi-stoichiometric amount of KHMDS (**Scheme 4**). Besides, the extension of carbamate synthesis through propargyl chlorides and their further cyclisation, no further mechanistic information was provided.

In 2015, the interest further increased in carbamate targeted $CO_2$-fixations and the research groups of Zhang and Jiang extended the methodology to gain access to O-mesityl carbamates.[22] They showed DBU assisted synthesis with a variety of different amines (**Scheme 5**) and diaryliodonium salts (**Scheme 6**), gave access to O-mesityl carbamates. Several different secondary (**Scheme 5**, **35**-**37**) and primary amines (**38**-**40**) were examined and performed with good to excellent yields. Changing the focus to investigate different diaryliodonium salts showed that the counter anion was essential for the reaction, triflate as a counter anion was well tolerated, as a change to tetrafluoroborate, bromide and tosylate inhibited the reaction completely. Applying different derivatives of the diaryliodonium salts performed well. They also used different nonsymmetric diaryliodonium salts and compared the effects of the different substitutions between each other. Their substrate scope included electron withdrawing, -donating and neutral substrates (**Scheme 6**, **41**-**46**). Summarizing their findings, showed that electron withdrawing groups resulted in the product formation and an increase of the reaction yield, with gradual decrease in reactivity by increasing electron donating character.



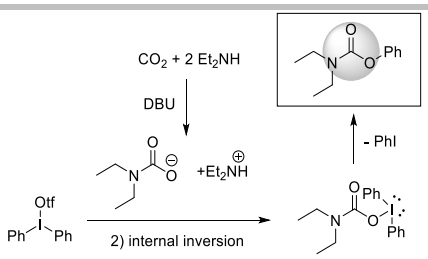

**Scheme 5.** Selection of the amine-based substrate scope for the synthesis of O-mesityl carbamates.




**Scheme 6.** Selection of the diaryliodonium salts for the substrate scope.

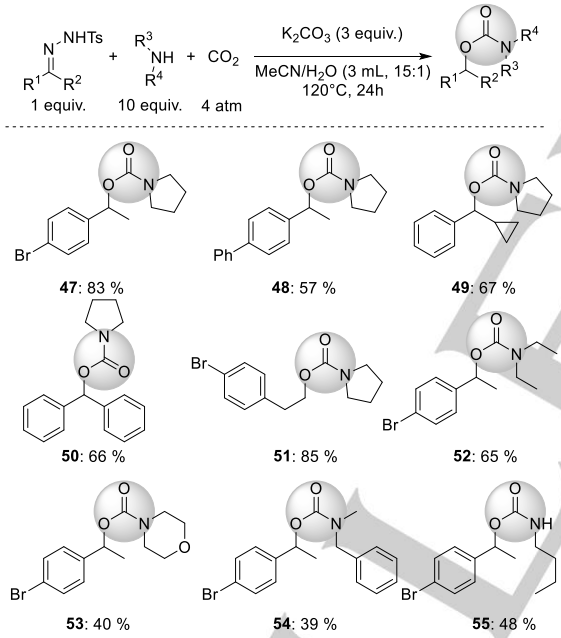
Most of their products achieved good to excellent yields and based on their properties, different reactivities could be observed, giving the possibility of predicting possible further combination. By their investigation of the different amines, counter anions, symmetrical and nonsymmetrical diaryliodonium salts, the results of untested combinations could be estimated.

Based on their extensive substrate scope of over 25 distinctive combinations and literature research, they proposed a plausible mechanism. They utilized the same mechanistic pathway already described by Dinsmore *et al.* and expanded it by literature known steps for their diaryliodonium salts addition (**Scheme 7**). The amine and the $CO_2$ were activated together by the base and afterwards reacted with the diaryliodonium salts. After internal inversion of the salt adduct, the intermediate possessed a suitable PhI leaving group and formed a stable product.



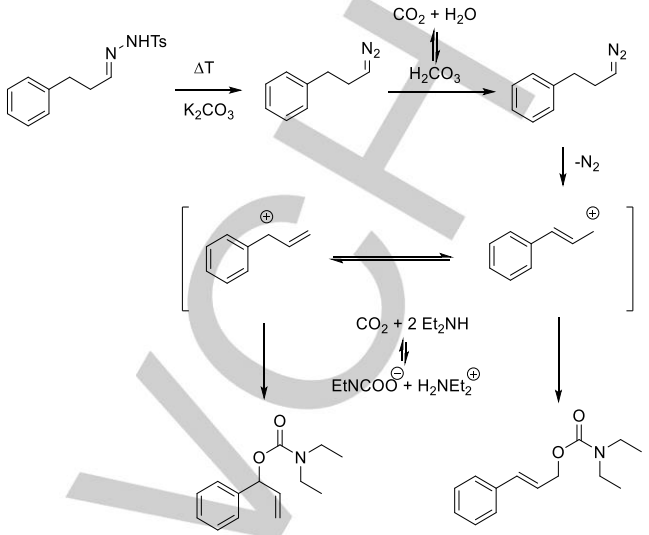

**Scheme 7.** Mechanism for the synthesis of O-mesityl carbamates.

In 2015, Xiong *et al*. showed a base-promoted coupling of carbon dioxide, amines and *N*-tosylhydrazones.[23] Thereby, they used the decomposition of *N*-tosylhydrazones to initiate the incorporation of carbon dioxide for the formation of carbamates promoted by potassium carbonate as a base. They could demonstrate a substrate scope of 22 different tosylhydrazones with a broad variety of structural motives. On the side of amines, they utilized several different amines including on example of primary amine, but had to report that aniline as a used amine source was not able to yield the desired product entirely (**Scheme 8**).




**Scheme 8.** Selection of the substrate scope including different hydrazones and amines as starting materials.

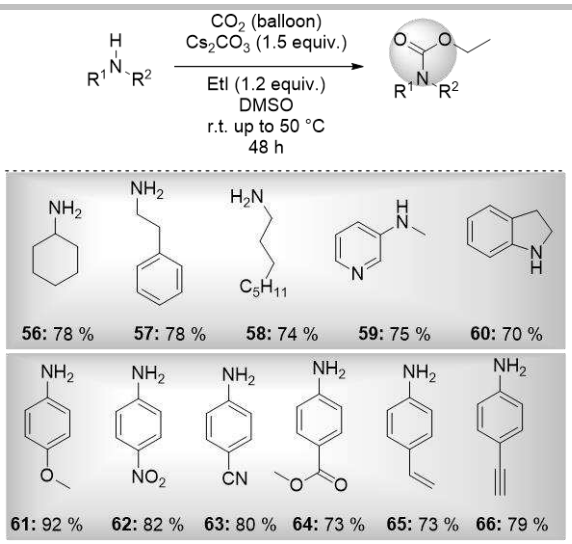
After establishing a broad substrate scope with moderate to excellent yields, they demonstrated that it was possible in a one pot manner to synthesize the hydrazone *in situ* and perform the reaction directly starting from a non hydrazone. Further they attempted to investigate the underlying mechanism by labelling experiment of the different reaction partners and postulated a possible reaction mechanism, which was not clearly describing the use of the base. They assumed that through the base, the decomposing of the *N*-tosylhydrazone was promoted to form the diazo compound. This was deprotonated by carbonic acid, which was formed from the present water and the carbon dioxide. The formed carbocation then further reacted with a preformed carbamate anion, which was formed from the amine and the carbon dioxide (**Scheme 9**).




**Scheme 9.** Proposed mechanism of the reaction involving *N*-tosylhydrazones.

In 2016, our research group further expanded the number of useable bases for this kind of chemistry and provided several applications of the protocol.[24] During the optimizations, it was observed that DBU could be replaced by several other bases in DMSO. $Cs_2CO_3$ achieved the best results among other cost-effective bases like DBN, $Na_2CO_3$ and $K_2CO_3$. Our investigations included several different amines for the carbamate synthesis and functional group tolerances (**Scheme 8**), as also the use of different halogen alkyl as the coupling partners. Additionally, we were able to utilize aryl amines with excellent yields, which were rarely performing in the previous transition metal free reports. Furthermore, we achieved the synthetic protocol under the atmospheric pressure utilizing $CO_2$ in a balloon. For the substrate scope based on different primary (**Scheme 10**, entries: **56**-**59**) and secondary amines (entries: **60**-**61**) were shown among further. For the study of functional group tolerance, a broad variety of different substituted anilines were chosen and examined for the respective yields (**Scheme 10**, **61**-**66**). The tolerance studies revealed that the reaction was highly selective in the presence of carbonyl-, ester-, aldehyde-, amide-, triple-bond-, double-bond-, nitro-, nitrile-, chloride- and bromide-substituted amines.

Based on these studies, we utilized the carbamate synthesis in formation of different pharmaceuticals beginning from bulk chemicals. For this application, we selected complex molecules such as nortriptyline (**Fig. 2**, entry: **67**) cinacalcet (entry: **68**) and methodology also provided the corresponding carbamates in an excellent yield. Furthermore, synthesis of the URB 602 analog (**Figure 2**, entry: **69**) revealed the possibility to use this method for the library synthesis of a variety of different analog.




**Scheme 10.** Selection of the utilized amines and their respective carbamate yields.

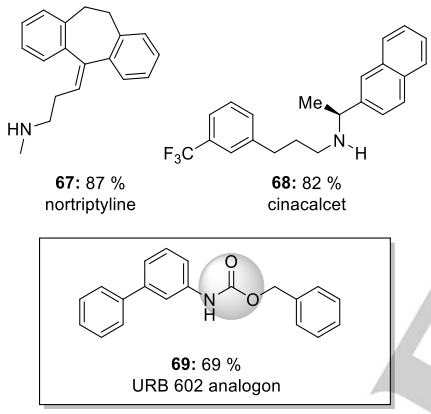
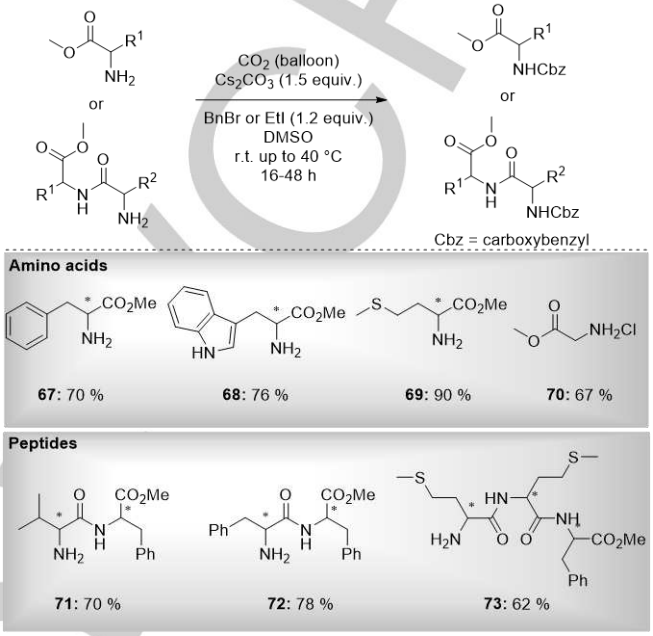


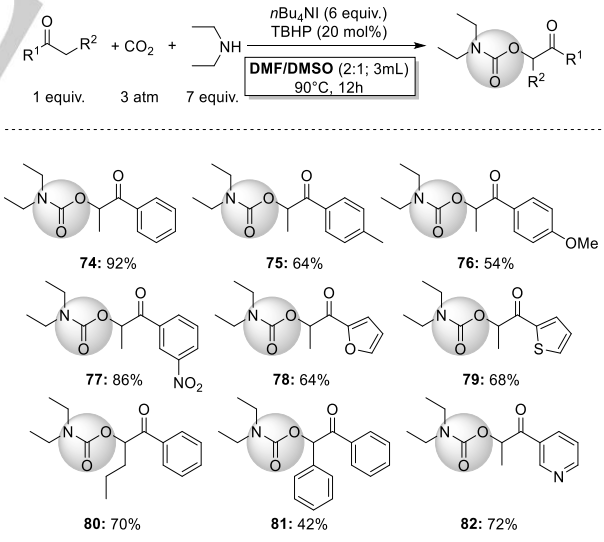

**Figure 2.** Late stage carbamate formation and synthesis of URB 602 analog.

The investigations how the methodology could be utilized further was extended by further utilizing different alkyl bromides. We expanded this protocol to be applied for the peptide chemistry as well (**Scheme 11**, entries: **67**-**74**). The methodology could be used for introducing protecting groups by replacing traditional protecting reagents. In fact, with the use of this reaction system, $CO_2$ can be utilized as a sustainable C1-source for the synthesis of natural products and pharmaceuticals under mild reaction conditions.

In 2017, the group of Jiang collaborated with the Qu and Yuan groups to report a *n*Bu$_4$NI-catalysed oxidative cross coupling reactions to form O-*β*-oxoalkyl carbamates by utilizing aryl ketones as the starting material. [24´5] This was adding a new synthetic strategy to the spectrum of metal-free carbamate synthesis. After optimizations, they could show that *n*Bu$_4$NI as a catalyst and TBHP as an oxidant can provide excellent yields in the solvent mixtures of DMF and DMSO. This observation showed high possibilities for further studies, to study different effects of solvent mixtures in this reaction. Their substrate scope was intensively investigated with respect to the different ketones and amines (**Scheme 12-13**). For the ketones, different substituent patterns were used (**Scheme 12**, entries: **74**-**77**), and different heterocycles (entries: **78**-**79**, **82**). Further substitutions in the α-position of the ketone were also successful (entries: **80**-**81**).



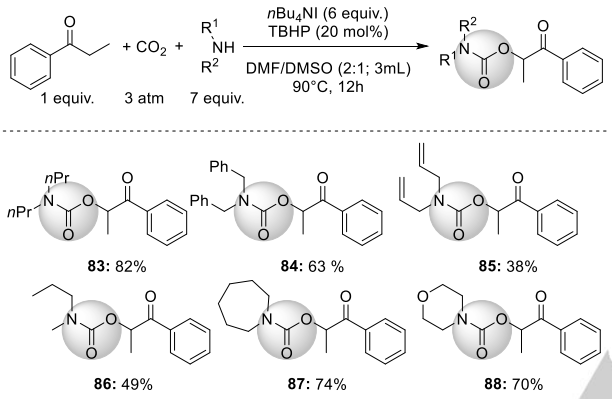

**Scheme 11.** $CO_2$ as a protecting reagent in peptide chemistry.



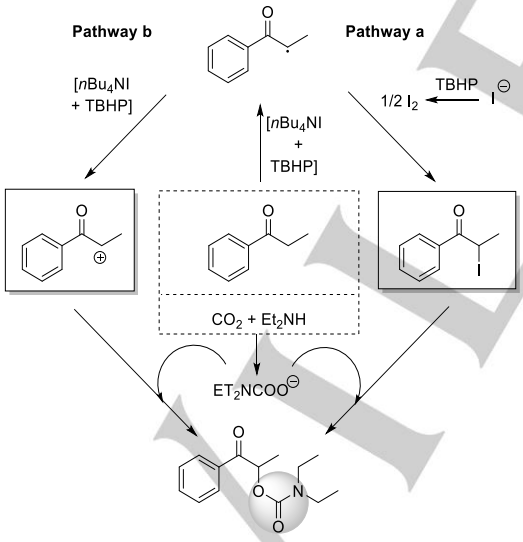

**Scheme 12.** Substrate scope for the *n*Bu$_4$NI-catalysed oxidative coupling reactions based on different aryl ketones.

Investigation of different amines for their methodology showed that symmetrical (**Scheme 13**, entries: **83**-**86**) and non-symmetrical (entry: **86**) secondary amines could be utilized under their reaction conditions. Additionally, cyclic secondary amines also reacted excellently (entries: **87**-**88**). However, aniline and primary aryl amines were not reactive under the

given reaction conditions. Based on the substrate scope and further mechanistic experiments, they could provide two plausible pathways for this reaction (**Scheme 14**). In both of the cases, the ketone was activated by the catalyst in a radical fashion via abstracting a proton. **Pathway a** included a reaction with *in situ* generated iodine to form a iodosubstitutes intermediate, which underwent a nucleophilic attack with the carbamate anion, which was formed from the amine and the atmospheric carbon dioxide. **Pathway b** included alternatively the oxidation of the radical intermediate to form the cation intermediate, which further reacted with the carbamate anion. Both pathways shared the formation of carbamate anion and only differed in the activation of the ketone.

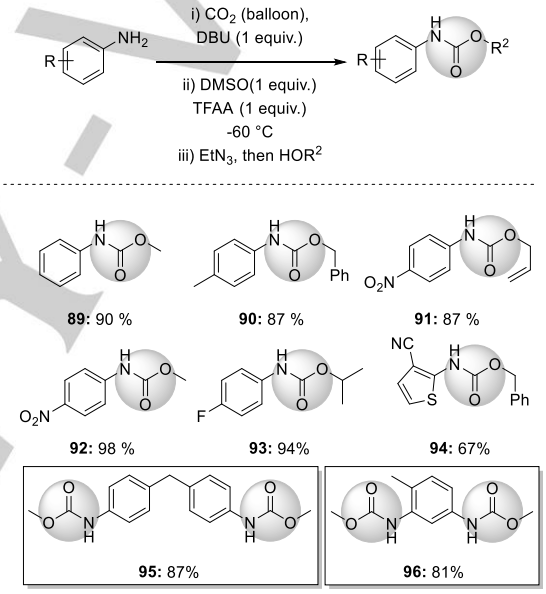



**Scheme 13.** Substrate scope for the *n*Bu4NI-catalysed oxidative coupling based on different amines.




**Scheme 14.** Proposed mechanistic pathways for *n*Bu4NI-catalysed oxidative coupling reaction.

In 2017, the group of Rousseaux continued the work of the Dinsmore group to find an efficient protocol for the synthesis of nonsymmetrical urea and carbamates based on primary substituted anilines.[26] They reported a three step one pot synthesis at low temperatures of -60°C, with 15 diverse nonsymmetric urea and 8 carbamates (**Scheme 15**, entries: **89**-**96**), of which 2 were double amines (entries: **95** and **96**) formed double carbamates without the polymerization. Given by the low temperature of the reaction, practical application for synthetic proposes beyond laboratory have to be investigated due to the very fast reaction speed compared to most of the other methodologies. Through IR spectroscopy they have proven that their key intermediate and the involvement of the DMSO in the reaction and this is why the presence of DMSO was essential in this reaction. These results provided the possibility to lower the need of toxic reagents, which were needed for typical Mitsunobu protocol. These results provided valuable insights in this type of reactions and especially new point of view about the effect of DMSO for the synthesis of carbamates. In fact, very similar findings were observed by Das *et al.* and Jiang *et al.* when both of them reported efficient benefits of using DMSO.

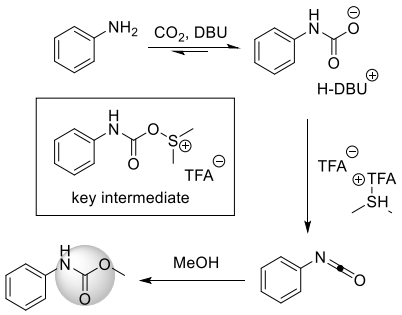



**Scheme 15.** Carbamates substrate scope using activated dimethyl sulfonium reagents.

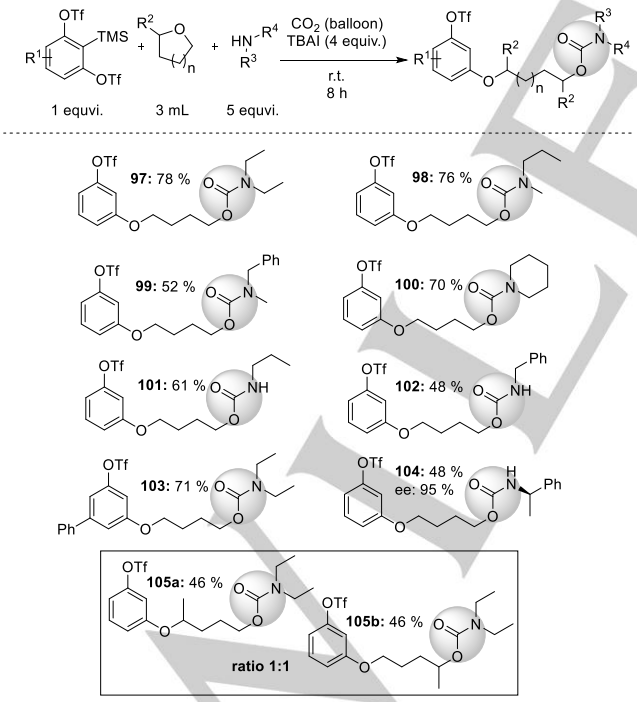
Based on their results they were able to postulate a reasonable mechanism based on Dinsmore *et al.* and further literature known interactions (**Scheme 16**). The amine was activated *via* base assisted $CO_2$ incorporation forming a carbamic acid salt with the protonated base together. This salt was able to interact with the TFA activated DMSO to form an effective isocyanate, which underwent further reaction with added alcohol to yield desired carbamate. The activated intermediate between the TFA activated DMSO and the carbamic acid intermediate was proven IR-spectroscopy.

In 2018, the groups of Jiang and Qi reported further on their research showing a four-component reaction between amines, carbon dioxide, cyclic ethers and 3-triflyloxybenzynes.[27] The new methodology improved in complexity by introducing a fourth reaction partner and lowering the E-factor of the reaction by applying more equimolar conditions of the reactants, as also lowering the reaction temperature and

reaction time. This development showed high advancement compared to previous research of those groups. All three non-carbon dioxide reactants have been exchanged in the substrate scope (**Scheme 17**). Different amines showed as previous possibilities for the use of primary and secondary amines (entries: **97**-**102**) with the remaining limitation that aniline could not be utilized. Different 3-triflyloxybenzynes could also be utilized (entries: **103**-**104**). The cyclic ether functioned as a solvent as also as a reagent at the same time in this methodology and could be exchanged for other cyclic ethers (entry: **105**). In case of 2-methyl-tetrahydrofuran two different products were possible and were obtained with equal distribution.

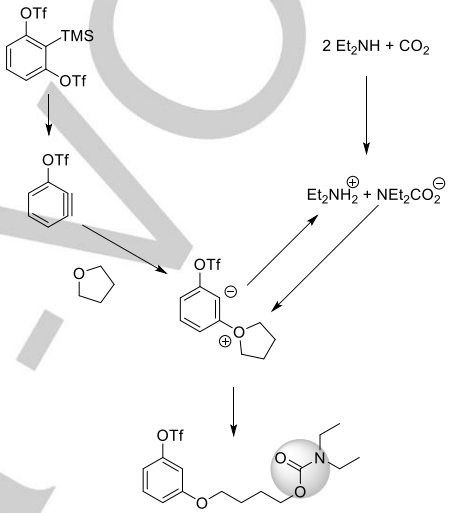



**Scheme 16.** Reaction mechanism based on the IR data and the key intermediate.




**Scheme 17.** Synthesis of carbamates using four component reaction strategy.

Based on the previous reports and additional labelling experiments utilizing deuterated reagents, a plausible mechanism was proposed (**Scheme 18**). Firstly, 3-triflyloxybenzyne was formed *in situ* from 2-(trimethylsilyl)-1,3-phenylene bis (trifluoromethanesulfonate). This reactive intermediate underwent nucleophilic attack with the cyclic ether to form a zwitterionic intermediate. At the same time, the amine and carbon dioxide were activated by the base to form the well-known activated adduct of both. After the protonation of the zwitterionic species, both intermediates react and after the ring opening the final product is received.

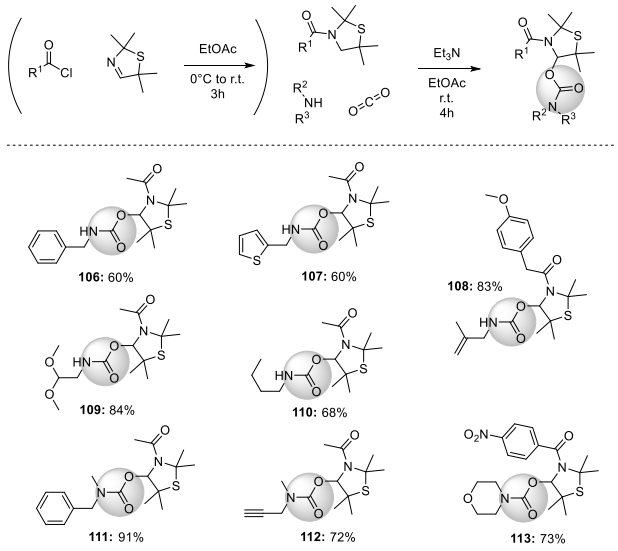



**Scheme 18.** Proposed mechanism for the four-component coupling reaction.

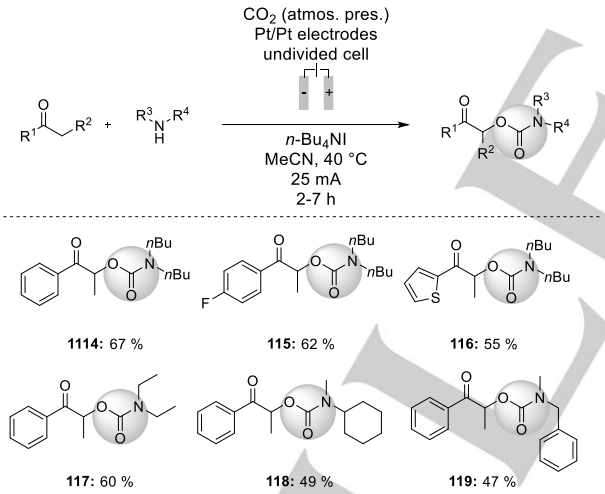
In the same year, Martens *et al.* showed a catalyst free reaction of carbon dioxide and *N*-acyliminium ions under ambient conditions to form complex thia- and oxazolidinyl carbamates.[28] They utilized carbon dioxide under balloon pressure in a four-component reaction strategy utilizing acetyl chloride as the substrate. The reaction had to be performed in two steps and needed cooling by ice bath. Advantageously, there was the possibility to utilize aniline and other primary amines in their synthetic strategy. The work up procedure was reported to be simple and efficient. Their substrates scope showed 27 different carbamates including the possibility of targeted dimerization. A selection of their substrate scope has been shown in **Scheme 19**.

In 2019, the groups of Zha and Wang published electrocatalytic version for the synthesis of carbamate derivatives.[29] Utilizing the two platin electrodes and currents of only 25 mA in an undivided, the reaction could perform in MeCN. This methodology revealed that the $CO_2$ pressure and the reaction temperature could be lowered significantly without losing efficiency. During their optimizations, they could reproduce the observation, that the iodine in *n*-$Bu_4NI$ was essential for the reaction and changing to other halogens yielded no product. Interestingly, KI could also be deployed as an alternative. Considering the substrates scope, they were able to reproduce the yields and functional group tolerance of the previous reports with shorter reaction time and in higher

atom efficiency (**Scheme 20**). Because, different optimization amines were chosen, the efficiency of both protocols cannot be compared with each other. Based on the close proximity of both reports they postulated that the path a as their proposed mechanism. However, primary amines and anilines still could not be used for this synthetic protocol.

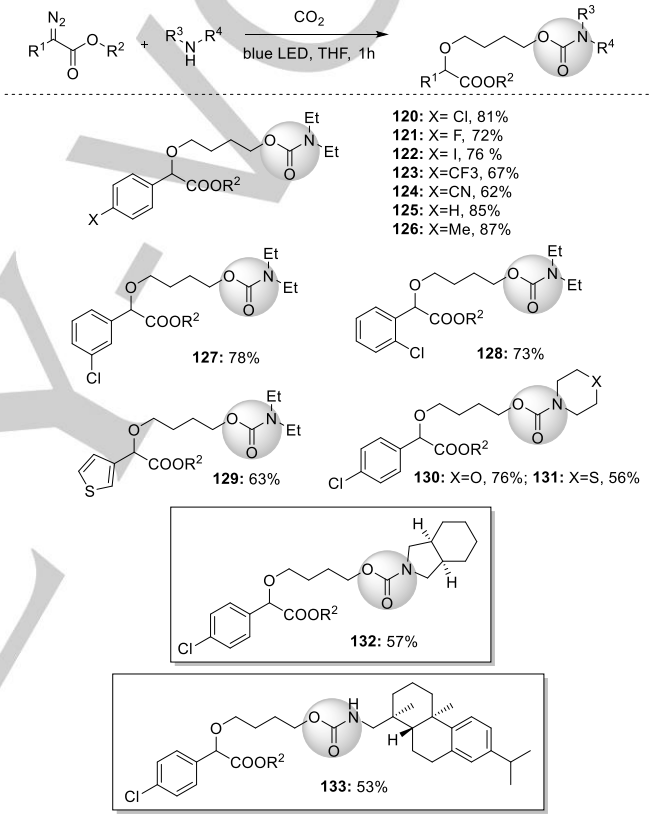



**Scheme 19.** Selected substrates for the four-component coupling reactions.




**Scheme 20.** Selective substrates scope for the electrochemical $CO_2$ fixation.

In 2020, the group of Jiang reported visible light-promoted synthesis of organic carbamates in a 4- and 3-component reaction of aryl diazoesters, amines and carbon dioxide without the necessity of a catalyst, nor additive. [30] Additionally, the reaction resulted in good to moderate yields in relatively fast reaction times of 1 hour. Utilizing tetrahydrofuran (THF) as a solvent they were able to access a wide array of different carbamates similar to their work in 2018, with an additional increase in substrate scope. Utilizing visible light as the primary source for the reaction showed that as an additional benefit no base was needed for this type of methodology, increasing the E-factor of the reaction further. During the investigation of the substrate scope, they showed fast conversions and good to excellent yields for a total of 15 different aryl diazoesters and 12 different amines (**Scheme 21)**. They showed different substitution patterns in *para* (entries: **120**-**126**), *meta* (entry: **127**) and *ortho* (entry: **128**) position, with a wide functional group tolerance including, halides, trifluoromethyl, nitrile, methyl, *tert*-butyl, methoxy groups, and different other aromatic systems. Additionally, primary and secondary amines including more complex structures for possible drug synthesis were also successful (entries: **132** and **133**)

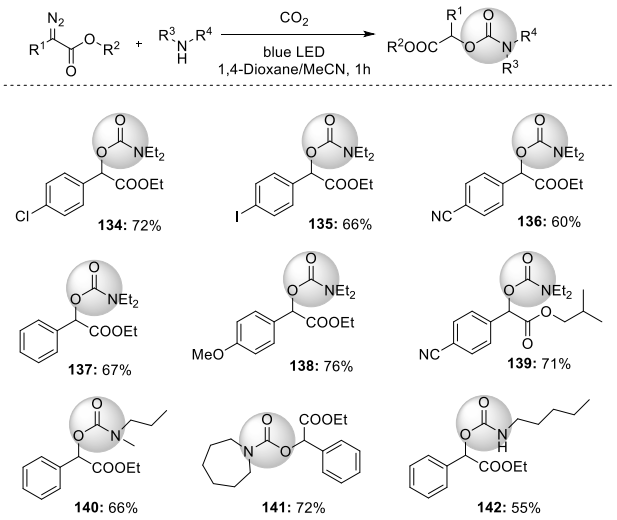



**Scheme 21.** Selection of the substrate scope of the photochemical $CO_2$ fixation.

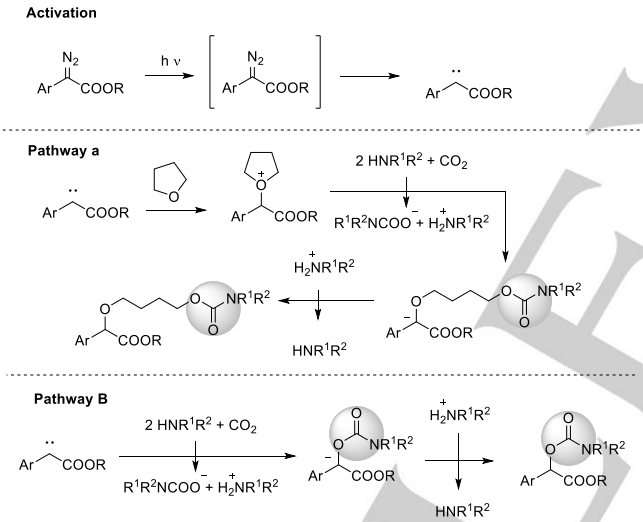
Changing the utilized solvent from THF to a mixture of dioxane and acetonitrile enabled a second pathway, which yielded alternative carbamates for their reported photochemistry. Also, for this case they investigated different aryl diazoesters and amines which showed similar behavior. No additional attempts for more complex structures were performed for this pathway (**Scheme 22**).

Based on the new concept of photochemical transformation, the group further performed mechanistic investigations in great detail to evaluate the underlying mechanism. UV-vis absorption spectra, labeling experiments as also quenching experiments were recorded to show that the reaction was not concluded via a radical pathway, but the aryl diazoester was activated by the visible light. They performed the

investigations for both reaction pathways and could propose a plausible mechanism (**Scheme 23**).




**Scheme 22.** Selection of the substrate scope of the photochemical $CO_2$ fixation.

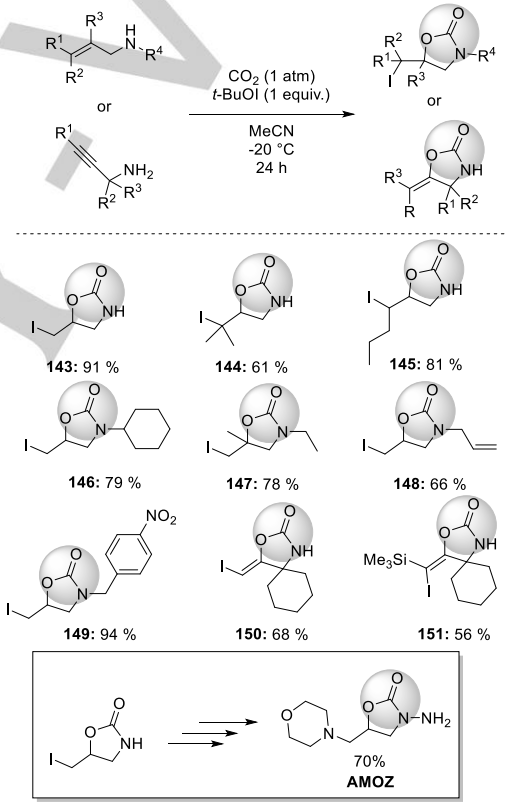



**Scheme 23** Mechanism for the photochemical synthesis of carbamate using $CO_2$ as the carbon source.

In both of the cases, substrate was activated by the visible light. In **pathway a,** for the 4-component reaction, the tetrahydrofuran attacked at the alpha position of the aryl and formed a cationic oxonium ylide. This underwent ring opening during the reaction to the carbamic anion of the amine and carbon dioxide. The cationic species of the activation was afterwards deprotonated to yield the desired carbamate product. In case of **pathway b,** for the reaction in 1,4-dioxane and acetonitrile, the interaction with the THF was skipped and resulted in a simpler carbamate end product.

## 3. Synthesis of cyclic carbamates **via** $CO_2$-fixation

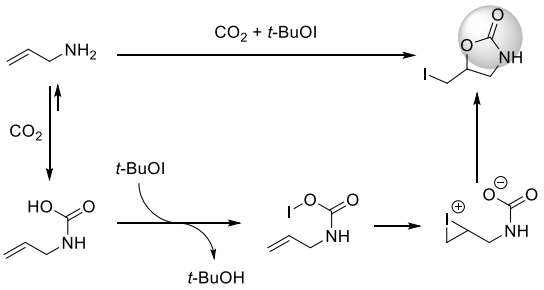
In 2012, Takeda *et al.* reported a reaction of unsaturated amines with *t*-BuOI and carbon dioxide to form the cyclic carbamates.[31] This system provided good substrates scope with a number of primary and secondary amines as well as very good functional group tolerance. Among several complex scaffolds, they utilized their protocol for the synthesis of **AMOZ** (3-amino-5-morpholi-nomethyl-2-oxyzolidinone), which is a crucial intermediate for the synthesis of several drugs such as the antiparasite drug moxnidazole and the antibacterial drug furaltadone (**Scheme 24**). The synthesis was performed additionally in gram scale to show its excellent scalability.




**Scheme 24.** Selection of substrate scope of the cyclisation reaction for CCSU based $CO_2$-fixation.

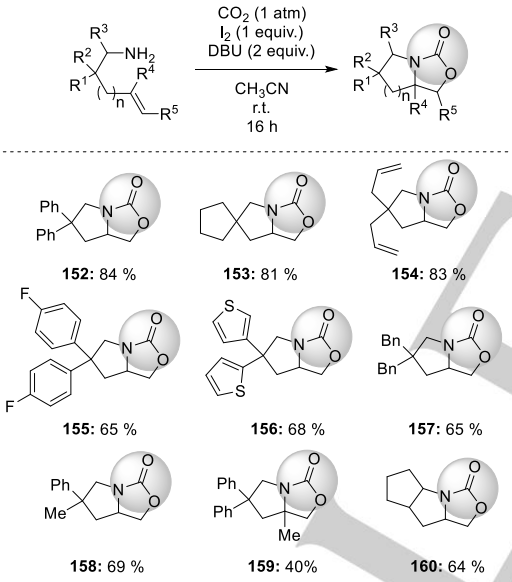
For the substrate scope investigation, they studied two different starting materials, containing a double bond and triple bond. They tested derivatives with substitution at all possible positions (**Scheme 24,** entries: **143**-**151**). Based on the NMR experiments and FT-IR monitoring, they were able to postulate a reasonable mechanism (**Scheme 25**). First, the amine and the carbon dioxide formed an adduct based on an equilibrium. With a strong distribution on the product side to have sufficient activation to the carbamic acid. The resulting carbamic acid could have a proto-iodine exchange forming an iodinated species. This performed an intramolecular

rearrangement followed by cyclisation to form the final cyclic carbamate.



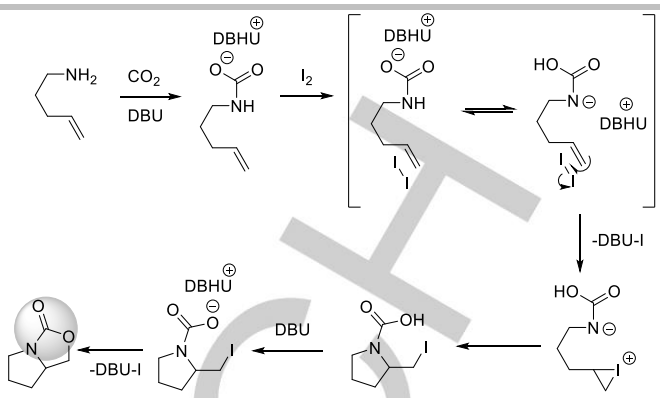

**Scheme 25.** Proposed mechanism of Takeda *et al*.

In 2017, the groups Xi and Chen further showed that the fixation of carbon dioxide could be mediated by $I_2$ and DBU to form the cyclic carbamates. [32] Benefit of their synthetic protocol was that several different solvents can be utilized for this reaction without changing yields significantly (**Scheme 26**).




**Scheme 26.** Selection of the substrate scope performed by XI *et al.*

Based on their results and control experiments, they were able to postulate the reaction mechanism (**Scheme 27**). Due to the presence of DBU, amine and the carbon dioxide formed together a carbamic salt, which was confirmed by NMR and ESI. They assumed that the formation of the salt interacted with iodine to form an intermediate. After abstraction of DBU-I species, the formed intermediate performed a cyclisation reaction and the second iodo-group was abstracted in a second cyclisation.




**Scheme 27.** Proposed reaction mechanism of the oxidative bicyclization.

# 4. Conclusion

In summary, several interesting methodologies have been developed recently based on the transition metal-free procedures. Many of those have close relation between each other and by comparing those in close proximity show new insights about the metal-free synthesis of carbamates. These insights provide reason for possible reinvestigation of the previously reported methodologies. The recently reported methodologies show comparable yields, reaction speeds and selectivity compared with traditional metal-based catalysis and can give access to environmentally friendlier alternatives, especially for the pharmaceuticals and specialized find chemicals. The reports on the valorization of cyclic carbamates is still limited, due to many reports just focusing on cyclic carbamates as sole carbon dioxide capture strategies, instead of utilization of carbon dioxide as a viable C1-building block. Efforts should also be paid for the development of heterogenous metal-free systems so that all the added reagents can be recycled to lower the price of the reaction system and that should make this transformation very attractive to the industries.[33]

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**Keywords:** Carbon dioxide utilisation • Carbamates • Transition Metal-free • Green Chemistry • Pharmaceuticals

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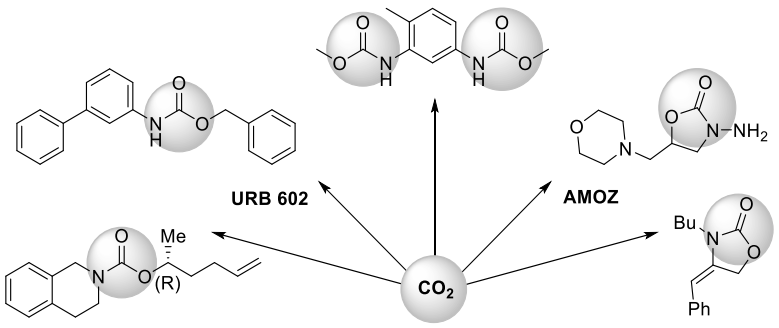


Transition Metal-Free Approaches for the Synthesis of Carbamate Using $CO_2$ as a $C_1$ Synthon

**Carbamates from $CO_2$:** Green and transition metal-free approaches for the generation of carbamates with the direct utilization of carbon dioxide ($CO_2$) as a C1 Synthon. This review focuses on the benefits of the recent advances of transition metal-free methodologies and the mechanistic insights in the pursuit of carbamate synthesis for fine chemicals and pharmaceuticals as final $CO_2$ fixation strategies.