A CO_2-Catalyzed Transamidation Reaction

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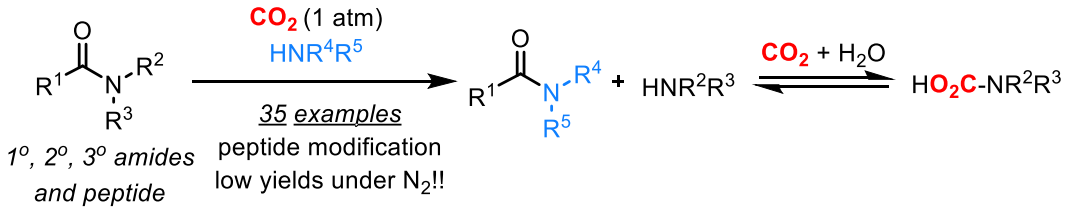


Abstract: Amide bond formation reactions are often mediated by reactive substrates in the presence of over-stoichiometric activating reagents and/or catalysts. Here we report a CO_2-promoted transamidation reaction without additive metal catalysts or coupling reagents. The reaction forms byproducts, ammonia, primary and secondary amines, which can form adducts with CO_2, thereby shifting the equilibrium in the desired direction. A comparison of Hammett studies under CO_2 and N_2 atmospheres suggests that the reaction transition state can be stabilized by electrophilic CO_2. Selective modification of peptides was demonstrated, showing that CO_2 can be utilized to control the nature of the electrophilicity and nucleophilicity of reaction partners under practical reaction conditions.

Amides are fundamental building blocks of biological polymers and small bioactive organic molecules. There is, therefore, a significant interest in amide synthesis processes beyond conventional peptide coupling reactions.[1] Recent developments in amide bond formation reactions have shown novel catalytic protocols and atom-economic activating reagents for carboxylic acid substrates.[1d] Transamidation reactions[1b]—starting from carboxylic amides and amine reactants—possess, in principle, a thermodynamic disadvantage, because of the stability of the amide bonds in the starting materials and the reverse reaction, an aspect that limits their utility and potential applications (Figure 1A). However, studies from Garg,[2] Gellman, Stahl, and co-workers[3] revealed that Lewis acidic transition metals (i.e., Ni, Al^{III}, Zr^{IV}) were efficient catalysts for amide activation. Maulide and co-workers[4] have also demonstrated new modes of activation for amide functional groups, with triflic anhydride rendering diverse synthetic procedures, highlighting the utility of the amide bond activation. Direct aminolysis is feasible when activated carboxylic acid derivatives are employed; for example, with carboxylic esters and activated amides in the presence of transition metal catalysts and strong bases.[5] Enzymes can also catalytically mediate aminolysis to form peptide bonds by using acyl phosphates and thioesters, taking advantage of activated carbonyl intermediates.[6]

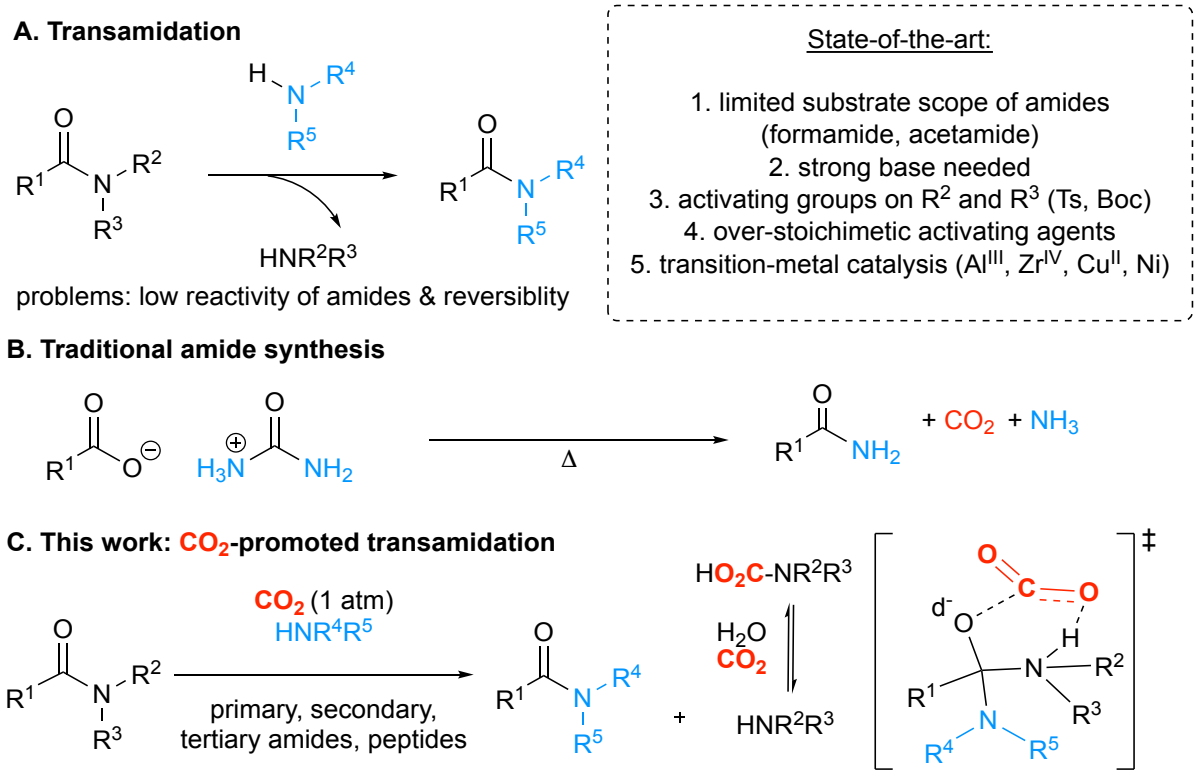
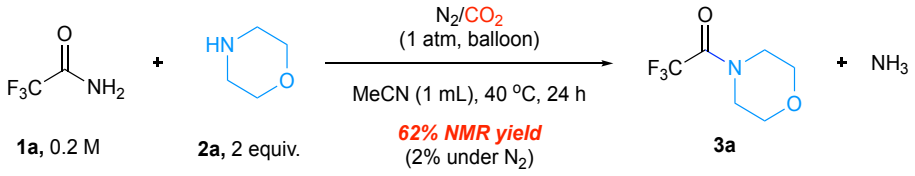


Figure 1. (A) State-of-the-art transamidation; (B) representative traditional amide bond synthetic procedure using urea as an ammonia surrogate; and (C) CO_2-mediated transamidation reaction.

Traditional amide synthesis requires carboxylate salts of ammonia or urea ($RCO_2{\bullet}NH_4$ or $RCO_2{\bullet}NH_3CONH_2$; Figure 1B) at high reaction temperatures for the dehydrative addition/elimination reaction.[7] This reaction generates CO_2 and ammonia as byproducts; an additional equilibrium between CO_2 and ammonia is expected, but remains unnoticed. Recently, we demonstrated catalytic applications of CO_2[8] in which CO_2 acts as a Lewis and Brønsted acid catalyst in a 1,4- and 1,2-cyanide addition reactions.[9] Expanding this concept, we proceeded to addition/elimination reactions, particularly in carbonyl compounds; for example, we addressed the intrinsic stability of amide bonds—and, therefore, slow transamidation reactions—by employing CO_2-catalysis. We postulated that the electrophilic CO_2 can activate carbonyl groups of amides, while sequestrating the ammonia byproduct by forming ammonium (bi)carbonate (Figure 1C). In this context, the CO_2-mediated transamidation reaction will be governed by the $pK_{a\text{-}H}$ of the corresponding conjugate acids of amine nucleophiles (blue amines in Figure 1) and leaving group amines.[11] However, rationalization of the thermodynamic and kinetic parameters of two amine groups under CO_2 atmosphere can be complicated;[12] we therefore decided to empirically test

the idea with various amide donors and amine nucleophiles. In addition, a successful implementation of amide bond activation using CO_2 will be beneficial to mediate functionalization and selective degradation of peptides, enzymes and other biological and artificial polymers (plastic) based on carboxylic acids and amide functional groups.

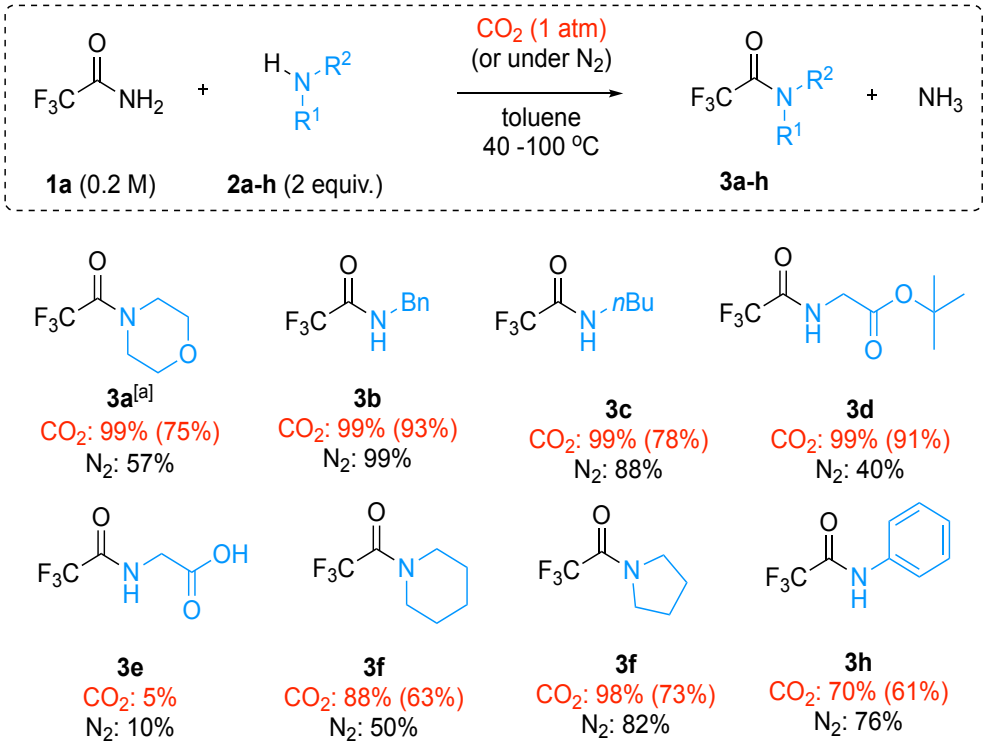
First, we probed the feasibility of CO_2-mediated transamidation reactions with an activated amide donor to provide electron-poor amide products, which can undergo severe backward aminolysis with ammonia (Scheme 1). Under mild reaction conditions (40 °C, 1 atm CO_2), the reaction afforded high selectivity towards trifluoroacetamide of morpholine (**3a**), whereas we detected only trace amounts of the product under an inert nitrogen atmosphere. This confirmed the positive effect of CO_2 in transamidation, with the competing reaction pathway—a reverse reaction with ammonia—presumably suppressed by the action of CO_2, thus expanding the transamidation scope beyond DMF (dimethylformamide) and acetamide as amide donors.[10, 11]



Scheme 1. CO_2-promoted transamidation reaction with trifluoroacetamide and morpholine under CO_2 and N_2.

Considering the interest of trifluoroacetyl groups in synthesis,[13] we quickly investigated the utility of trifluoroacetylation reactions using CO_2 via transamidation with amide donor **1a**. The preparation of trifluoroacetamide often requires reactive trifluoroacetic anhydride or chloride as substrates. Under practical reaction conditions, various amines (**2b-j**)—primary amine (**2b**), aniline (**2h**), and amino acid derivatives **2d** and **2e**—were smoothly converted to the desired products starting from stable trifluoroacetamide, **1a** (Figure 2). The substrate scope was tested keeping in mind that the current methodology can be applied in peptide modification, offering selective amide cleavage and/or formation reactions. For example, when *t*-Butyl-protected glycine (**2d**) was employed, a high yield of trifluoroacetamide product **3d** was obtained (99% ^{19}F NMR yield, 91% isolated yield), showing a significant difference under nitrogen atmosphere (N_2: 40% NMR yield). Glycine (**2e**) presented poor reactivity in the transamidation process (5-10% yield of **3e**), partly because of its poor solubility in toluene. The addition of water resulted in the hydrolysis of the amide donor, trifluoroacetamide, despite the increased solubility of glycine. It is noteworthy here that the hydrolysis can be suppressed in the presence of CO_2. (See Table S3). Therefore, the optimized reaction conditions result in practical procedures without strictly anhydrous reaction media. Secondary amines (**2a**, **2f**, **2g**) could also form new amide bonds with significant differences between reactions with and without CO_2, even at large scale (up to 20 mmol, **3a**, 75% isolated yield). This indicates that the

transamidation reactions can be productive considering the pre-equilibrium of CO_2 and the amine nucleophiles, which can be detrimental for addition reactions (see Table



S2).

Figure 2. Substrate scope of the CO_2-mediated transamidation reaction with trifluoroacetamide and various amine donors. Reaction conditions: Amide (0.6 mmol), amine (2 equiv., 1.2 mmol), toluene (3 mL), N_2/CO_2 balloon. Yields were determined by ^{19}F NMR spectroscopy, and values in parenthesis were determined after isolation of the final amide products.

Recognizing that trifluoroacetamide amide donor is an electronically biased substrate, we further attempted to utilize various secondary and tertiary amides to explore the scope of the transamidation process with CO_2. The electronic effect was proven to be important for primary amide donors: α-nitrile substituted acetamide (**1b**) showed high reactivity under CO_2, affording the desired products (**3ba**, **3bc**, **3bd** and **3bg**, up to 78% isolated yield), while negligible conversion was detected under N_2 (2–17% conversion). Primary amides including acetamide (**1e**) and its derivatives were transformed to the desired transamidation products with high selectivity under the optimized reaction conditions (**3eb** and **3ec**, 50% conversion under CO_2; 2% under N_2). Benzoylamide showed poor reactivity towards *n*-butylamine (under CO_2/N_2, 0%) and pyrrolidine (under CO_2: 7%; under N_2: 0%), indicating that amide-bond cleavage is a substrate-controlled process depending on the thermodynamic stability of the amide bonds. When cyclic imide (**1f**) was employed as a substrate, no transamidation reaction but the ring-opening products were observed (See supporting information).

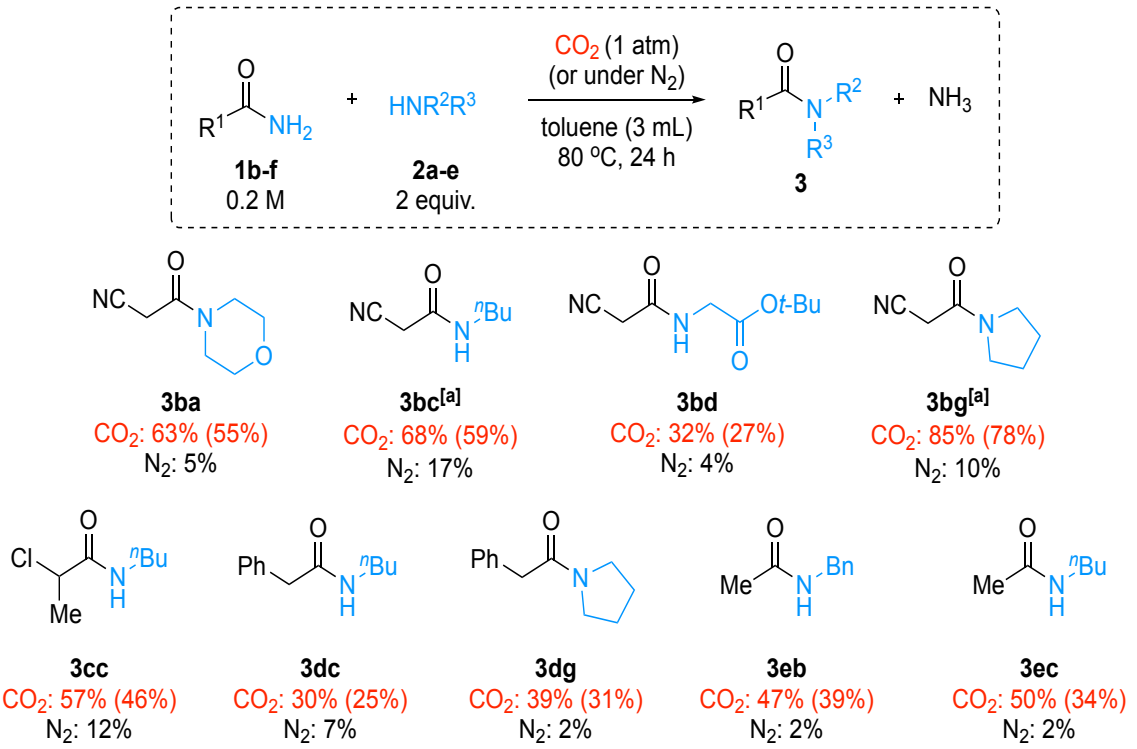


Figure 3. Reaction scope with primary amides (**1b-f**) and amine donors. Reaction conditions: Amide (0.6 mmol), amine (2 equiv., 1.2 mmol), toluene (3 mL), N_2/CO_2 balloon. Yields were determined by ^1H NMR spectroscopy with an internal standard (1,3,5-trimethoxylbenzene), and values in parenthesis were determined after isolation of final amide products. [a]Reactions were performed at 60 °C.

To further probe the scope of the CO_2-mediated transamidation reactions, we evaluated tertiary and secondary amides with the model amine nucleophile (**2c**), as summarized in Figure 4. We found out that Weinreb amides are particularly responsive towards CO_2-mediated transamidation reactions as a leaving group, presumably because of their electron-rich nature.[14] For example, Weinreb amide **1j** and acetamide **1k** showed distinct reactivity under CO_2 and N_2: **1j** showed quantitative conversion to the desired *n*-butyl amide product (**3ec**) in 90% yield, while displaying no conversion in the absence of CO_2. Moreover, amide donor **1j** was quantitatively transformed to the desired product *under catalytic conditions*: 20 mol% of CO_2 was sufficient to obtain >90% conversion (77% isolated yield). The dimethyl amide substrate (**1k**), however, exhibited no conversion under CO_2 and N_2, confirming the importance of the leaving group for the transamidation reaction. The presence of 2-pyridyl groups on amide donors (**1l** and **1m**) afforded insignificant CO_2 effects, although a CO_2-pyridine interaction was expected, which might increase the leaving group ability.[15] Electron-deficient secondary amide **1n** showed an inferior reactivity, confirming that electron-rich amides are more reactive. The substrate scope was

further expanded with aromatic substrates with Weinreb amide (**1o**-**1u**); all the tested substrates showed positive effects of CO_2 for transamidation reactions. The formation of the amide products was monitored by ^1H NMR, and all products were isolated after column chromatography. The substrate scope was further evaluated—using various amine donors including amino acid derivatives and diamines affording high yields of transamidation products—by varying the reaction temperature from room temperature to 120 °C. (up to 90% isolated yield, Figure 5). A highly reactive substrate such as trifluoroacetamide with 2-pyridine (**1v**) showed high conversion under CO_2 and N_2, while a less reactive benzamide substrate (**1m**) required high temperature to enable the transformation, therefore increasing the rate of thermal background reaction. We found that various Weinreb amides were adequate substrates for CO_2-mediated transamidation, and afforded high selectivity only under CO_2. For example, amide donor **1q** and *t*Bu-protected glycine (**2d**) afforded the transamidation product in 61% yield under CO_2, while only a 6% conversion was detected under N_2, highlighting the application potential in amide functionalization and exchange reactions in peptides and other biologically relevant molecules.

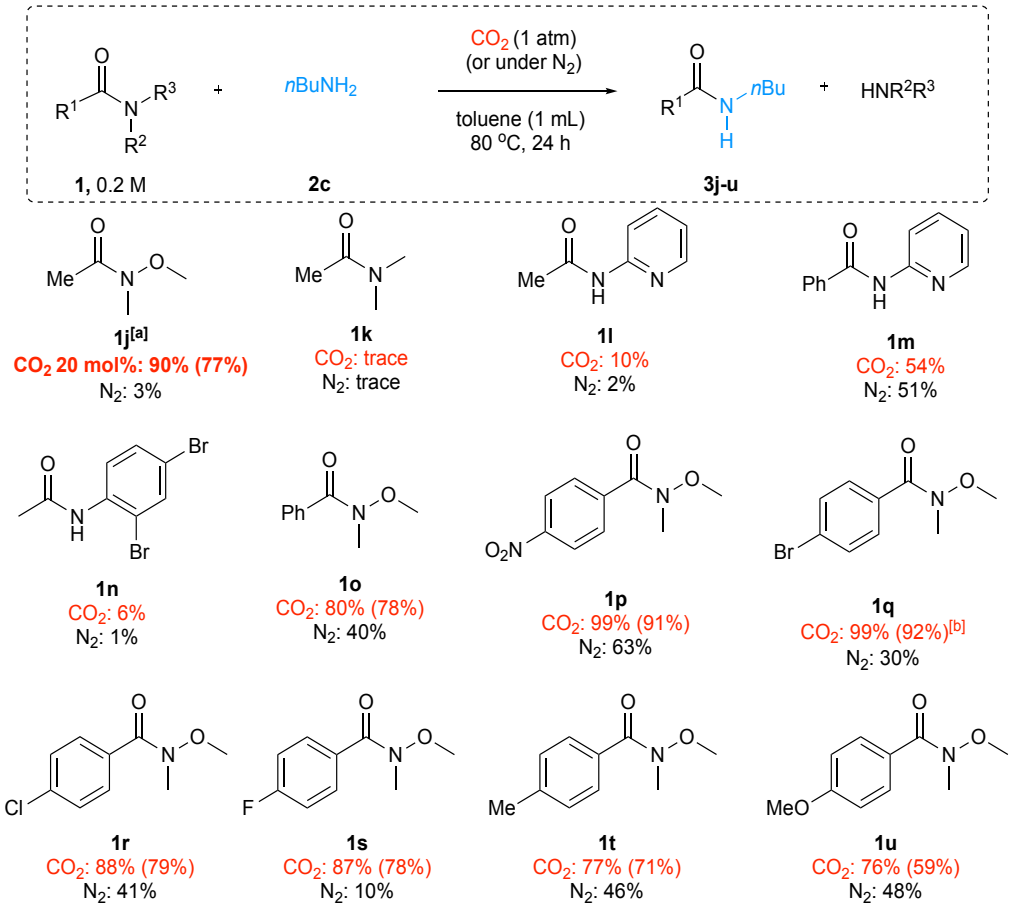
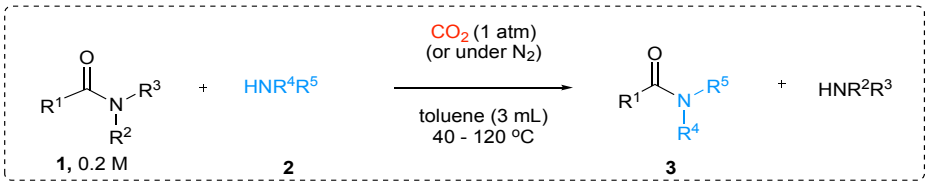


Figure 4. Transamidation reactions with secondary/tertiary amides donors and *n*-butylamine. (Values in parenthesis are isolated yields after column chromatography). Reaction conditions: amide (0.2 mmol) and amine (2 equiv., 0.4 mmol) were dissolved in dry toluene (1 mL) under N_2 or CO_2 atmosphere (1 atm), 80 °C, 24 h. After toluene

was removed, the reaction mixture was subjected to silica gel column chromatography. [a] 10 mmol scale. [b] 4.1 mmol scales, purified without column.



Amide	Amines	Product	Conversion, % (isolated yield, %)
1v	**2a**	**3va**	CO_2: 97% (90%) N_2: 94% r.t., 24 h
1m	**2g**	**3mg**	CO_2: 99% (87%) N_2: 93% 100 °C, 24 h
1j	**2a**	**3ja**	CO_2: 68% (59%) N_2: 0% 80 °C, 48 h
1j	**2d**	**3jd**	CO_2: 96% (86%) N_2: 88% 100 °C, 24 h
1o	**2g**	**3og**	CO_2: 96% (84%) N_2: 1% 80 °C, 24 h
1o	**2d**	**3od**	CO_2: 93% (74%) N_2: 59% 120 °C, 24 h
1q	**2d**	**3qd**	CO_2: 86% (61%) N_2: 6% 60 °C, 39 h
1q	**2b**	**3qb**	CO_2: 80% (72%) N_2: 7% 60 °C, 40 h
1q	**2f**	**3qf**	CO_2: 68% (65%) N_2: 20% 100 °C, 24 h

Figure 5. Transamidation reactions with secondary, tertiary amides (**1**) and various amine nucleophiles (**2**). Reaction conditions: amide (0.6 mmol) and amine (2 equiv.,

1.2. mmol) were dissolved in dry toluene (3 mL) under a N_2/CO_2 atmosphere (1 atm). (Values in parenthesis are isolated yields after column chromatography)

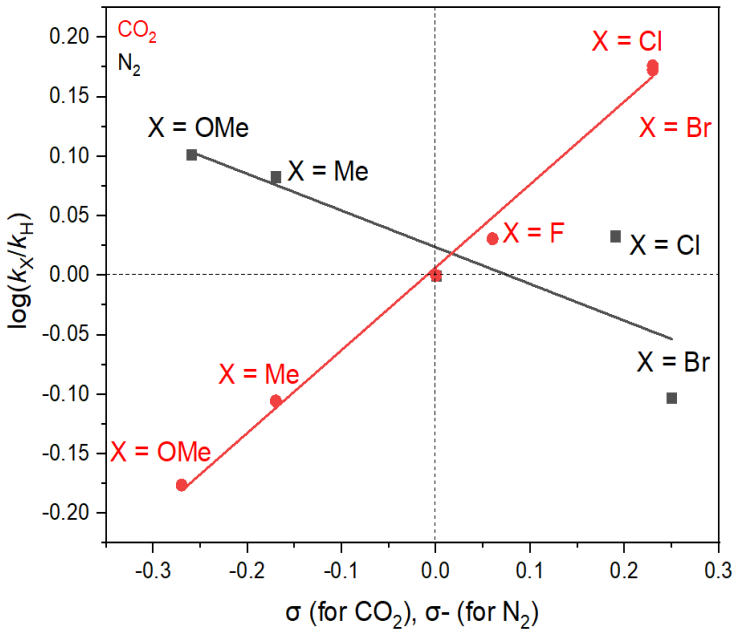


Figure 6. Hammett plots of transamidation reactions of Weinreb amides (under CO_2: red, under N_2: black).

Taking advantage of the prepared Weinreb amides, we conducted Hammett studies under CO_2 and N_2 atmospheres, to investigate the reaction mechanism. Figure 6 shows two Hammett plots (red: under CO_2, black: under N_2); the positive slope (ρ = 0.70 ± 0.025) for CO_2 indicates that the reaction rate accelerated with electron-withdrawing groups, whereas a negative slope (ρ = −0.31 ± 0.114) was observed under a nitrogen atmosphere. This stark difference may result from the influence of CO_2 and solubilized CO_2 derivatives (carbonic acid and carbamic acid) on the reaction transition state. The anionic active complex of the tetrahedral intermediate can be stabilized under our reaction conditions, demonstrating an early transition state (Figure 7, with CO_2). The new C-$N_{nucleophile}$ bond formation can be a rate-limiting step in the presence of CO_2. On the other hand, in the absence of CO_2, the C−$N_{leaving\ group}$ bond cleavage step is the rate limiting step, because of the reversible nucleophilic addition step (Figure 7), although the equilibria between CO_2 and nucleophilic amines are supposed to be detrimental (see Table S2). The observed positive CO_2 effect shows the role of CO_2 as a molecular catalyst to decrease the activation barrier of the process.

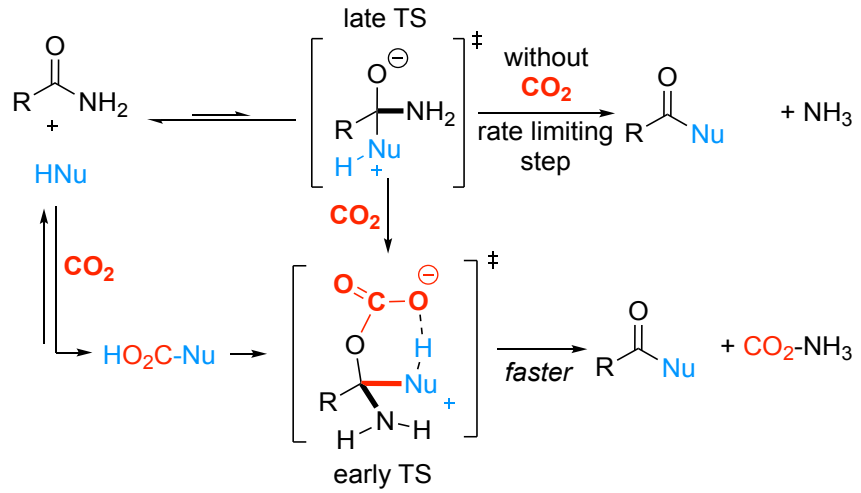
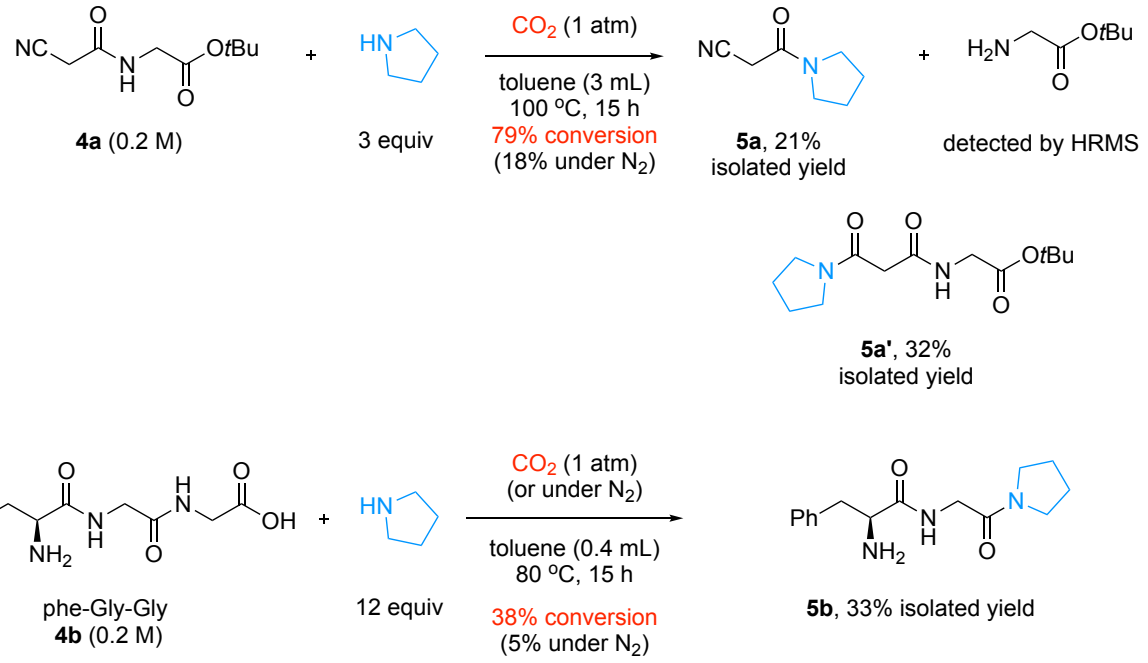


Figure 7. A plausible reaction mechanism for the CO_2-promoted transamidation reaction.



Scheme 2. Peptide cleavage reactions of di- and tripeptides under CO_2 atmosphere, compared with reactions under N_2 atmosphere.

Based on our experiments, we concluded that our transamidation reaction conditions can be applied to substrates with multiple amide functional groups, such as peptides. Gratifyingly, the modification of di- and tri-peptides was achieved under a CO_2 atmosphere, while showing low conversion under N_2 (Scheme 2). An electronically biased amide (**4a**) was subjected to transamidation reaction conditions with pyrrolidine, and showed 79% conversion under CO_2 and 21% isolated yield of the desired product, **5a** (18% conversion under N_2; see Figure S7 for more details). A hydrolysis product on alkylnitrile was obtained in 32% yield, and the structure was attributed to the

pyrrolidine adduct (**5a'**) uncovering a new role of CO_2 in nitrile transformation in the absence of strong bases and acids or transition-metal catalysts.[16] It is noteworthy here that the side product, glycine *t*-butyl ester leaving group, was observed by HRMS from the reaction mixture. Further attempts with the tripeptide (Phe-Gly-Gly, **4b**) confirmed the selective formation of dipeptidoamide **5b** in 33% isolated yield (see SI Section 6). Under otherwise identical conditions, only 5% conversion of the starting material (**4b**) was detected under an N_2 atmosphere, showing the significant role of CO_2 in the peptide cleavage process.

In conclusion, we developed a CO_2-promoted transamidation reaction with various amide donors and amine nucleophiles, including peptides and amino acid derivatives. The reaction exhibits an intrinsically high reaction barrier. However, it can be controlled by using CO_2, which can stabilize anionic active complexes and sequestrate leaving group amines. Further investigations are ongoing in our laboratory to perform CO_2-accelerated organic reactions and various mechanistic studies to reveal the true role of CO_2 as a molecular catalyst.

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Keywords: amides • transamidation • carbon dioxide • peptides • CO_2 catalysis

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