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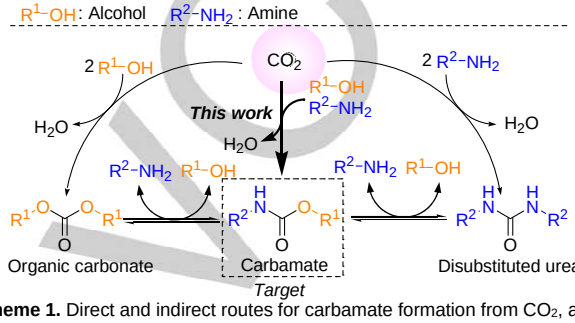
Direct catalytic synthesis of *N*-arylcarbamates from CO_2, anilines and alcohols

Masazumi Tamura,*[a][b] Ayaka Miura,[a] Masayoshi Honda,[a] Yu Gu,[a] Yoshinao Nakagawa,[a] and Keiichi Tomishige*[a]

Dedication ((optional))

Abstract: We achieved direct catalytic synthesis of carbamates from CO_2, amines and methanol by controlling both the reaction equilibrium and reactivities of the three components. Combination of CeO_2 and 2-cyanopyridine was an effective catalyst, providing various carbamates including *N*-arylcarbamates in high selectivities.

Transformation of CO_2 to valuable chemicals can contribute not only to CO_2 fixation but also to effective CO_2 utilization as a C1 resource. Carbamates attract much attention because of their many applications to pharmaceuticals, agrochemicals, protecting groups and polyurethanes.[1] Carbamates are traditionally produced by using toxic and hazardous reagents such as phosgene or CO[2], and environmentally-friendly alternative catalytic methods have been intensively investigated: aminolysis of organic carbonates[3], alcoholysis of ureas[4], coupling reaction of dimethyl carbonate (DMC) and *N,N'*-substituted urea[5] and so on. Recently, carbamate syntheses with CO_2 as a carbonyl source have been demonstrated using reactive reagents such as *N*-tosylhydrazones[6], alkylhalides[7], metal alkoxides[8] and silicate esters[9]. Compared with these approaches, carbamate synthesis from CO_2, amines and alcohols will be ideal (Scheme 1) because the by-product is theoretically only water and all substrates are easily available.[10] *N*-Arylcarbamates are the most useful among various carbamates[11], however there are no effective catalyst systems for the arylcarbamate synthesis from CO_2, arylamines and alcohols (yield≤10%, Table S1) owing to the inert character of CO_2, equilibrium limitation and side reactions as well as the low reactivity (low basicity and nucleophilicity) of arylamines.[6] The prospective byproducts are organic carbonates from CO_2 and alcohols, and *N,N'*-disubstituted ureas from CO_2 and amines (Scheme 1). Therefore, development of catalyst systems which can sophisticatedly control the reactivities of the three components and overcome the equilibrium limitation is desirable. Recently, we found that combination of CeO_2 and 2-cyanopyridine was an effective catalyst system for the synthesis of dimethyl carbonate (DMC) from CO_2 + CH_3OH[12] and cyclic carbonates[13] and polycarbonates[14] from CO_2 + diols. Urakawa and co-workers also applied the combination catalyst system to the DMC synthesis at high CO_2 pressure.[15] The severe equilibrium was



Scheme 1. Direct and indirect routes for carbamate formation from CO_2, amine and alcohol.

overcome by removal of H_2O from the reaction media through the nitrile hydration over CeO_2. In addition, 2-cyanopyridine can be recovered by dehydration of the produced 2-picolinamide over alkali metal-supported SiO_2 catalysts.[12a,d] We envisioned that the combination catalyst was applicable to the one-pot carbamate synthesis from CO_2, amines and alcohols.

At first, we applied the catalyst of CeO_2 and 2-cyanopyridine to methyl *N*-phenylcarbamate (MPC) formation from CO_2, aniline and CH_3OH as a model reaction (Figure 1 and Table S2). Fortunately, the reaction with CeO_2 and 2-cyanopyridine proceeded smoothly to reach >99% conversion at 8 h. The selectivity to diphenyl urea (DPU) was very high (~80%) at 0 h and it decreased with reaction time, in contrast, the MPC selectivity increased to reach 98% at 6 h. These results indicate that DPU is the intermediate. The maximum MPC yield was 97% at 8 h, which is much higher than the reported ones (Table S1). On the other hand, only CeO_2 provided almost no conversion (<1%, Table S3), and only 2-cyanopyridine hardly provided the carbamate, and *N*-phenyl-pyridine-2-carboxamidine (amidine) was mainly produced from 2-cyanopyridine and aniline (Table S4). These results indicate that combination of CeO_2 and 2-cyanpyridine is essential for the reaction. From the time-course, MPC will be formed by two consecutive reactions (Scheme 2): (I) DPU formation from CO_2 and aniline, and (II) MPC formation from DPU and methoxy source. To clarify the advantage of the present reaction system, the consecutive reactions were conducted step by step (Figure S1). At the first step, DPU formation from aniline and CO_2 was performed using CeO_2 and 2-cyanopyridine. The reaction proceeded smoothly at the initial stage and leveled off at about 80% conversion. After the 8 h reaction time, the autoclave reactor was cooled to room temperature, and then methanol was added to the reaction mixture and heated to 423 K. At the second step, the conversion gradually increased, however stopped at about 90%. The DPU selectivity decreased and MPC selectivity increased to reach 91% yield at 4 h of the second step (total 13 h), which is lower than that of the present reaction system (97% at 8 h). These results demonstrate that direct synthesis of MPC

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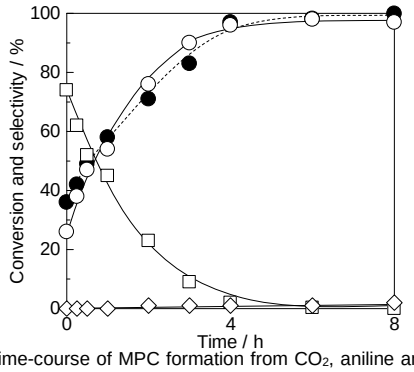
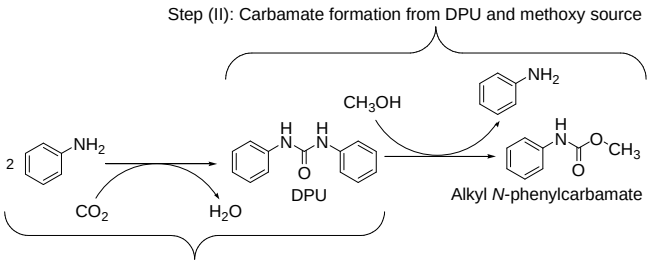


Figure 1. Time-course of MPC formation from CO_2, aniline and CH_3OH using CeO_2 and 2-cyanopyridine (●: conversion; ○: selectivity to MPC; □: selectivity to DPU; ◇: selectivity to amidine). Reaction conditions: CeO_2 0.17 g, aniline 5.0 mmol, 2-cyanopyridine 75 mmol, CH_3OH 75 mmol, CO_2 5 MPa (at r.t.), 423 K.



Scheme 2 Formation of MPC from CO_2, aniline and CH_3OH

from CO_2, aniline and methanol using CeO_2 and 2-cyanopyridine is preferable reaction system.

The performance with combination of various metal oxides and 2-cyanopyridine was compared (Figure 2 and Table S5). CeO_2 provided much higher total selectivity to MPC and DPU with comparatively high conversion than other metal oxides. On the other hand, other metal oxides provided mainly amidine. These results indicate that CeO_2 is the only effective metal oxide in

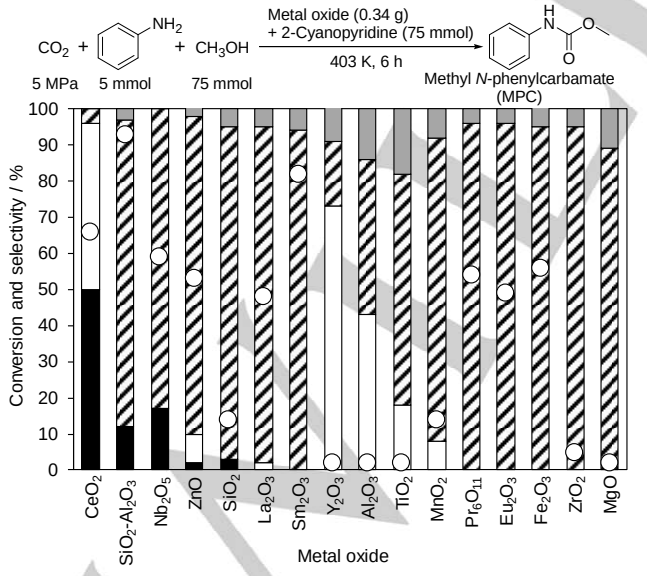


Figure 2. Screening of metal oxides with 2-cyanopyridine in MPC formation from CO_2, aniline and methanol. ○: aniline conversion. The bars represent selectivity. black: MPC, white: DPU, stripe: amidine, gray: others. Others include *N*-methylaniline, *N,N*-dimethylaniline and methyl *N*-phenyl-pyridine-2-carboximidate.

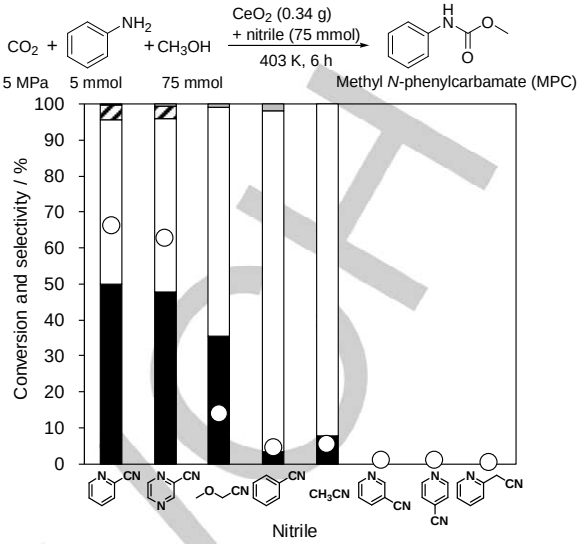


Figure 3. Screening of nitriles with CeO_2 in MPC formation from CO_2, aniline and methanol. ○: aniline conversion. The bars represent selectivity. black: MPC, white: DPU, stripe: amidine, gray: others. Others include *N*-methylaniline, *N,N*-dimethylaniline and methyl *N*-phenyl-pyridine-2-carboximidate.

combination with 2-cyanopyridine. Effect of nitriles was also investigated using CeO_2 (Figure 3 and Table S6). 2-Cyanopyridine, cyanopyrazine and methoxyacetonitrile showed high conversion of aniline and selectivity to MPC and DPU, and among these nitriles, 2-cyanopyridine showed higher conversion and selectivity. Therefore, it was confirmed that combination of CeO_2 and 2-cyanopyridine was the most effective for the reaction.

The effect of 2-cyanopyridine amount was investigated by changing 2-cyanopyridine amount from 5 to 75 mmol (Table S7). In the case of 5 mmol aniline as a substrate, 5 mmol 2-cyanopyridine is essential for removal of the H_2O produced by the reaction. When 50 mmol 2-cyanopyridine was used, the conversion of aniline was similar to that in the case of 75 mmol 2-cyanopyridine. However, the conversion decreased with decreasing the 2-cyanopyridine amount from 50 mmol to 5 mmol, because 2-cyanopyridine was exhausted by hydration with the H_2O produced from DMC formation. Therefore, an excess amount of 2-cyanopyridine is essential for the reaction system.

The scope of amines was studied using CeO_2 and 2-cyanopyridine (Scheme 3(A) and Table S8). Various *p*-substituted aniline derivatives with electron-withdrawing groups such as F, Cl, Br, and I or electron-donating groups such as methoxy, methyl, and ethyl reacted to afford the corresponding carbamates in high conversions and selectivities. *o*- or *m*-Toluidines were also converted to the carbamates. Furfurylamine and 2-(aminomethyl)thiophene, amines with a five-membered ring, morpholine and *N*-methylpentylamine, secondary amines, and *tert*-butylamine were also converted to the corresponding carbamates in high conversions and selectivities. Note that 2,4-diaminotoluene was converted to the dicarbamate in moderate selectivity (54%), which is an important intermediate for the synthesis of toluene-2,4-diisocyanate (2,4-TDI), a main raw material for polyurethane[16]. Next, the scope of alcohols was also investigated (Scheme 3(B) and Table S9). Linear and branched alcohols reacted to provide the carbamates effectively. Benzyl alcohol was also transformed to the corresponding carbamate, which is an important scaffold for prodrugs such as

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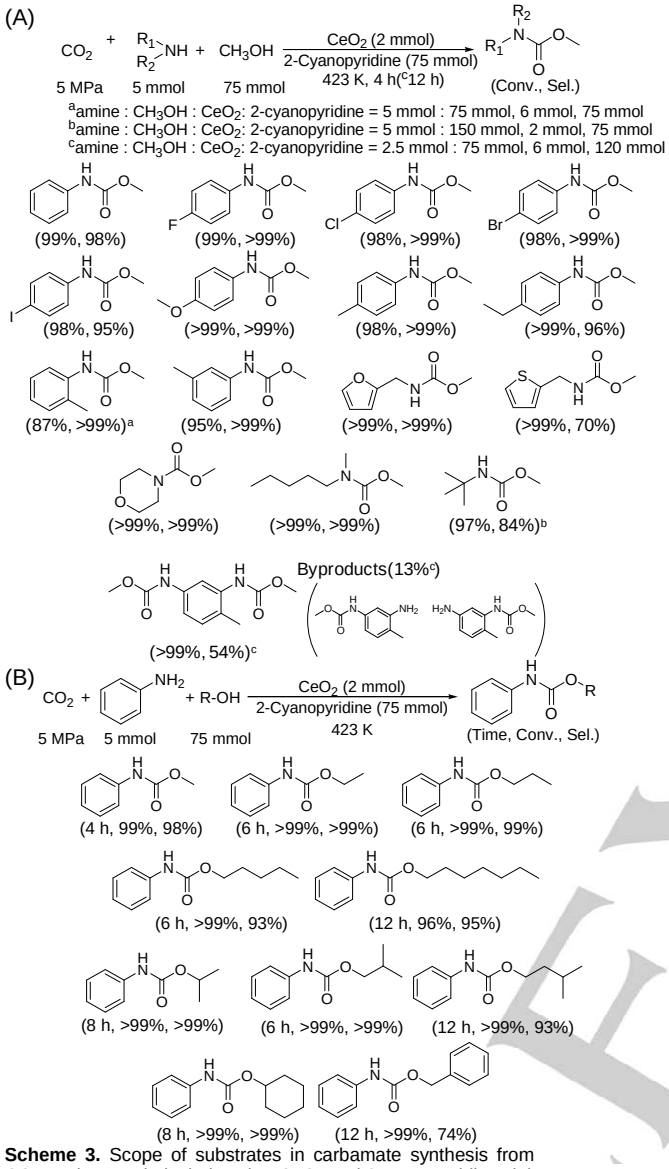


Scheme 3. Scope of substrates in carbamate synthesis from CO_2, amines and alcohols using CeO_2 and 2-cyanopyridine. (A) Scope of amines. (B) Scope of alcohols.

PEG-daunorubicin conjugates for anti-cancer drugs[17].

To confirm the methoxy source at the step (II) in Scheme 2, reactions of DPU with CH_3OH or DMC were investigated in the presence of CO_2 (Figure S2 and Table S10), because DMC was actually formed from CO_2 and methanol in the present reaction. The DPU conversion with methanol was much higher than that with DMC, and the formed MPC amount with methanol was about 4-fold larger than that with DMC, indicating that the reaction of DPU with CH_3OH is the main route. Next, to clarify the catalyst system in each step, various catalysts (CeO_2+2-cyanopyridine, only CeO_2, and only 2-cyanopyridine) were applied to the DPU formation from aniline and CO_2, and MPC formation from DPU and CH_3OH in the presence of CO_2. In DPU formation (Figure 4(a) and Table S11), CeO_2+2-cyanopyridine provided DPU selectively, in contrast, only CeO_2 and only 2-cyanopyridine showed almost no formation of DPU, indicating that both CeO_2 and 2-cyanopyridine are essential for DPU formation. In MPC formation (Figure 4(b) and Table S12), only CeO_2 showed almost no activity. Surprisingly, only 2-cyanopyridine showed high activity for the reaction. The conversion with CeO_2+2-cyanopyridine was about twice higher than that with only 2-cyanopyridine. 2-Cyanopyridine promotes MPC formation and combination of CeO_2 with 2-cyanopyridine further promotes the reaction.

The role of 2-cyanopyridine is important in DPU formation from CO_2 and aniline (Step (I)), because this step is the rate-determining one. The equilibrium yield is below 1% as shown in Figure 1(b). The reaction rate of hydration of 2-cyanopyridine was measured with various H_2O amount in the presence of CO_2 and aniline (Figure 5(a)), providing linear relationship between log(reaction rate) and log(H_2O amount). The reaction rate at almost zero amount of H_2O was calculated by extrapolation of the relationship to be 360 mmol•h^{-1}•g^{-1}, which is about 5-fold higher than that of the carbamate synthesis (76 mmol•h^{-1}•g^{-1}). This result is in good agreement with the fact that the produced amount of 2-picolinamide was almost equal to the sum of MPC, DPU, and DMC amount in the MPC synthesis (Table S2) because these products were accompanied by the equimolar amount of water. Therefore, water was efficiently removed by hydration of 2-cyanopyridine over CeO_2, enabling the smooth reaction by shifting the equilibrium to the product side. Moreover, the reaction rates over CeO_2 and CeO_2+2-cyanopyridine were estimated under the conditions where the conversion is below the equilibrium to be 4.4 and 76 mmol•h^{-1}•g^{-1}, respectively, (Figure 5(b)), indicating that addition of 2-cyanopyridine increased the reaction rate of CeO_2 by a factor of about 17, and the combination of CeO_2 and 2-cyanopyridine catalyzed DPU formation.

The reaction route of MPC formation from CO_2, aniline, and CH_3OH using CeO_2+2-cyanopyridine catalyst system was proposed in Scheme 4. First, DPU and H_2O are formed from CO_2 and aniline by CeO_2+2-cyanopyridine. Second, alkolysis of DPU with CH_3OH provided MPC and aniline, which is also catalyzed by

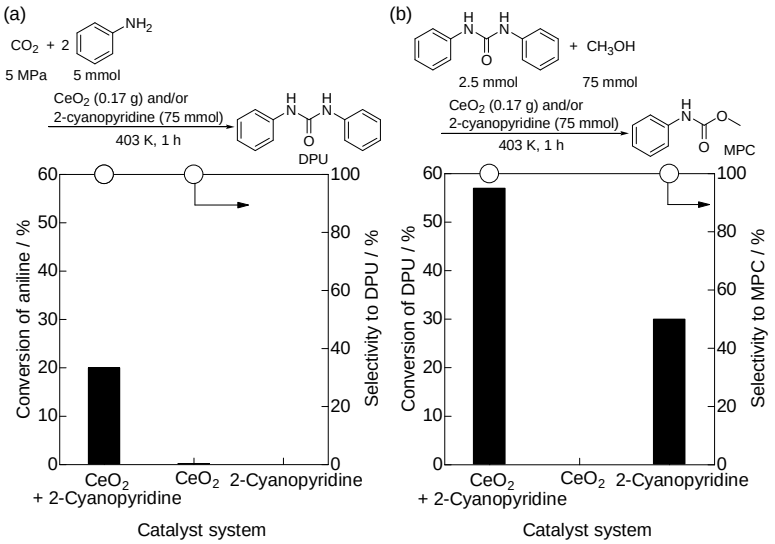


Figure 4. Comparison of catalysts. (a) reaction of aniline with CO_2. (b) reaction of DPU with CH_3OH in the presence of CO_2.

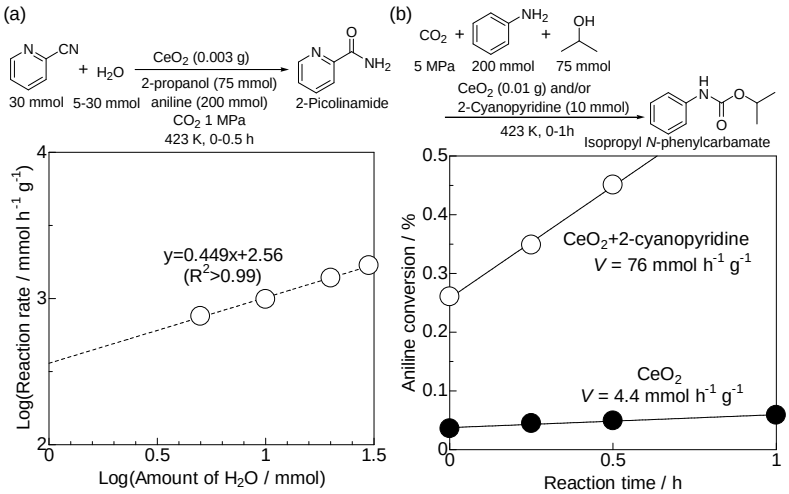
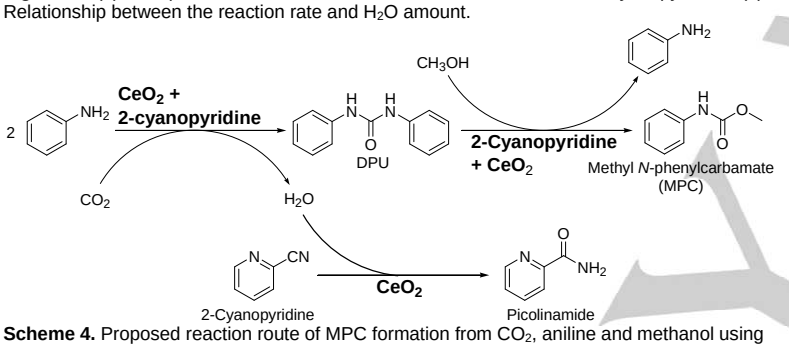


Figure 5. (a) Comparison of reaction rates over CeO_2 and CeO_2+2-cyanopyridine. (b) Relationship between the reaction rate and H_2O amount.



Scheme 4. Proposed reaction route of MPC formation from CO_2, aniline and methanol using CeO_2 and 2-cyanopyridine.

combination of CeO_2 and 2-cyanopyridine. CeO_2-catalyzed hydration of 2-cyanopyrdine effectively proceeded under the same reaction conditions, which can remove the produced H_2O from the reaction media to shift the equilibrium of DPU formation to the product side. The MPC formation from DPU and methanol also plays a role in shifting the equilibrium by decreasing the DPU amount in the reaction media. In addition, smooth MPC formation also enabled high selectivity by maintaining the low concentration of DPU and amidine.

A new one-pot selective synthesis of carbamates from CO_2, amines and alcohols was demonstrated by using the combination catalyst of CeO_2 and 2-cyanopyridine. This method enables sequential formation of C-N and C-O bonds by the drastic shift of the reaction equilibrium in *N,N'*-substituted urea formation and remarkable catalytic function of CeO_2 and 2-cyanopyridine in exchange-reaction of C-N and C-O bonds, providing various carbamates including *N*-arylcarbamates in high selectivities.

Acknowledgements

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Keywords: carbon dioxide • carbamate • ceria •heterogeneous catalyst • arylamine

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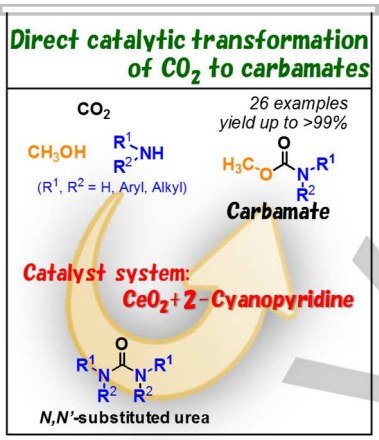
One-pot selective syntheses of carbamates directly from CO_2, alcohols and amines was substantiated by using the combination catalyst of CeO_2 and 2-cyanopyridine. The catalyst was applicable to various alcohols and amines including arylamines, providing the corresponding carbamates, particularly *N*-arylcarbamates, in high selectivities.



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