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Oxovanadium(V)-Catalyzed Synthesis of Unsymmetrical Ureas by Activation of Carbon Dioxide under Ambient Pressure

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ABSTRACT: A sustainable approach for the catalytic synthesis of unsymmetrical ureas from disilylamines through catalytic activation of carbon dioxide as a C1 building block under ambient pressure was performed by using a commercially available easy-to-handle NH_4VO_3 . This catalytic system displayed a wide range of substrate applicability without the use of any dehydrating reagents or bases. Gram-scale catalytic reaction was successfully performed to validate the scalability of this catalytic synthesis of unsymmetrical ureas under ambient carbon dioxide pressure.

INTRODUCTION

Ureas are regarded as the most prominent carbonyl compounds that widely used in pesticides, herbicides, and raw material of resins.¹ In particular, ureas used in pharmaceuticals and agrochemicals often have unsymmetrical structures such as Daimuron, Linuron, and Thidiazuron (Figure 1). Numerous efforts have been devoted to the synthesis of unsymmetrical ureas.² Conventionally, unsymmetrical ureas have been synthesized using toxic compounds such as phosgene and carbon monoxide, or condensing reagents such as carbonyl diimidazole as a carbon source.³ Therefore, the development of more environment-friendly alternatives is much sought in today. Recently, as an alternative, the use of carbon dioxide as a carbon source, being abundant on the earth and non-toxicity, has been drawing considerable attention. This strategy is more powerful approach from points of view of utilizing carbon dioxide as a renewable resource and reducing fossil fuels consumption. However, the previous synthetic approach using carbon dioxide for ureas requires harsh reaction conditions such as high reaction temperature and high pressure of carbon dioxide.⁴ Also, in the case of the one-pot, one-step synthesis of unsymmetrical ureas from amine and carbon dioxide, the selective synthesis of unsymmetrical ureas is difficult because symmetrical ureas are simultaneously produced as by-products (Scheme 1a).^{4b,5} Mitsunobu type reactions are often employed for the synthesis of unsymmetrical ureas, wherein stoichiometric amount of tributylphosphine oxide is produced as a by-product (Scheme 1b).⁶ Recently, Rousseaux and co-workers have reported the synthesis of unsymmetrical ureas via the formation of isocyanates using dimethylsulfonium reagents, but this reaction required multiple steps (Scheme 1c).⁷

We have previously succeeded in synthesizing symmetrical ureas from primary amines and carbon dioxide under ambient pressure using a commercially available $\text{VO}(\text{O}^i\text{Pr})_3$ catalyst.⁸

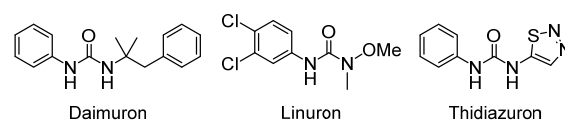
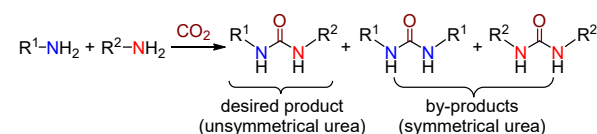


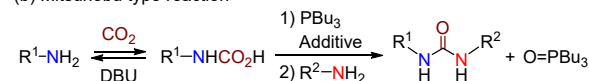
Figure 1. Unsymmetrical ureas used in pharmaceuticals and agrochemicals.

Scheme 1. Synthesis of Unsymmetrical Ureas

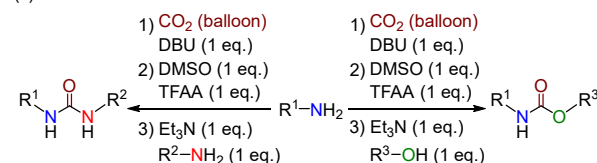
(a) Synthesis of unsymmetrical ureas from amines and carbon dioxide



(b) Mitsunobu type reaction



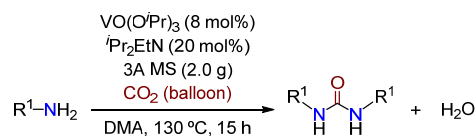
(c) Rousseaux's work



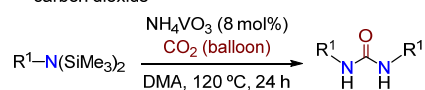
However, it was necessary to use an air-sensitive $\text{VO}(\text{O}^i\text{Pr})_3$ catalyst, 3A MS as a dehydrating reagent, and *N,N*-diisopropylethylamine as a base in this catalytic system (Scheme 2a). Recently, we have reported an efficient catalytic synthesis of symmetrical ureas from disilylamines and carbon

Scheme 2. Oxovanadium(V)-Catalyzed Synthesis of Ureas Using Carbon Dioxide under Ambient Pressure

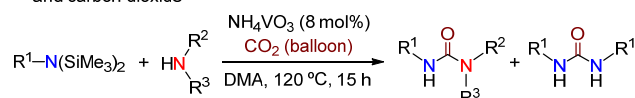
(a) **Previous work:** synthesis of symmetrical ureas from amines and carbon dioxide



(b) **Previous work:** synthesis of symmetrical ureas from disilylamine and carbon dioxide



(c) **This work:** synthesis of unsymmetrical ureas from disilylamines, amines, and carbon dioxide



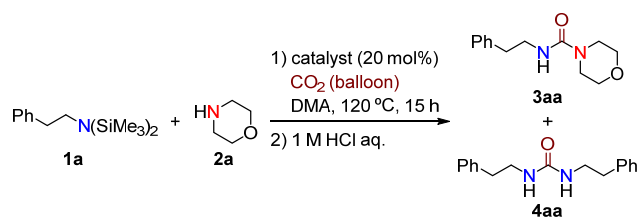
dioxide under ambient pressure using a commercially available easy-to-handle NH_4VO_3 catalyst (Scheme 2b).⁹ This catalytic system has the advantage of not requiring additives such as dehydrating reagents or bases. Inspired by the precedent our works on the catalytic activation of carbon dioxide and in continuation with our interest in catalytic synthesis of unsymmetrical ureas, we embarked upon the development of the catalytic system for the synthesis of unsymmetrical ureas from disilylamines, secondary amines, and carbon dioxide as a carbon source in the one-pot, one-step (Scheme 2c).

RESULTS AND DISCUSSION

Our previous paper reported that the reaction of disilylamines with secondary amines in the presence of NH_4VO_3 under ambient pressure of carbon dioxide afforded symmetrical and unsymmetrical ureas simultaneously.⁹ In this paper, we focused on the creation of the catalytic system forming unsymmetrical urea as the main product. The reaction of 2-phenylethyl-*N,N*-bis(trimethylsilyl)amine (**1a**) with morpholine (**2a**) in the presence of NH_4VO_3 (20 mol%) catalyst under ambient pressure of carbon dioxide at 120 °C was found to produce the desired unsymmetrical urea **3aa** in 58% yield with the concomitant formation of the symmetrical urea **4aa** in 36% yield as the by-product (Table 1, entry 1). This catalytic system is heterogeneous at room temperature, but becomes homogeneous when the reaction temperature is raised to 120 °C. The control experiment displayed that NH_4VO_3 catalyst was essential for the catalytic synthesis of the desired unsymmetrical urea from disilylamine and carbon dioxide under ambient pressure (entry 2). Catalytic activities of oxovanadium(V) compounds were examined. NBu_4VO_3 showed moderate catalytic activity (entry 3). NaVO_3 and Na_3VO_4 displayed no desired results (entries 4-5). Similar catalytic activity was performed for $\text{VO(O}^i\text{Pr)}_3$ (entry 6). With V_2O_5 or VO(TEA) ¹⁰, no improvement of the reaction efficiency was observed (entries 7-8). In the catalytic reaction with tetravalent oxovanadium(IV) compounds such as $\text{VOSO}_4 \cdot n\text{H}_2\text{O}$ and VO(acac)_2 , the yields of unsymmetrical urea **3aa** were also lower than that of entry 1 (entries 9-10).

In order to improve the reaction efficiency, the effect of various reaction parameters was investigated (Table 2). The

Table 1. Oxovanadium(V)-Catalyzed Synthesis of Unsymmetrical Ureas from 1a, 2a, and Carbon Dioxide^a



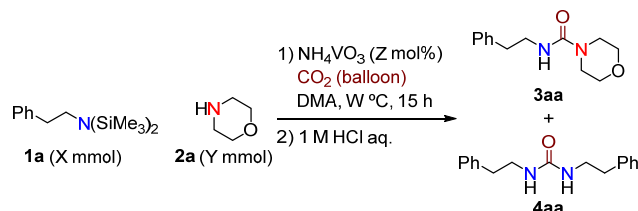
| Entry | catalyst | NMR yield (%) ^b | |
|-------|---|----------------------------|-------------------|
| | | 3aa | 4aa |
| 1 | NH_4VO_3 | 58 | 36 |
| 2 | – | N.D. ^c | N.D. ^c |
| 3 | NBu_4VO_3 | 37 | 45 |
| 4 | NaVO_3 | 8 | 28 |
| 5 | Na_3VO_4 | 12 | 42 |
| 6 | $\text{VO(O}^i\text{Pr)}_3$ | 52 | 33 |
| 7 | V_2O_5 | 44 | 36 |
| 8 | VO(TEA)^d | 18 | 31 |
| 9 | $\text{VOSO}_4 \cdot n\text{H}_2\text{O}$ | 20 | 11 |
| 10 | VO(acac)_2 | 52 | 31 |

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), and catalyst (20 mol%) in DMA (1.0 mL) under CO_2 (balloon) at 120 °C for 15 h. ^b 1,3,5-Trimethoxybenzene was used as an internal standard.

^c N.D. = not detected. ^d $\text{VO(TEA)} =$



Table 2. Optimization of Oxovanadium(V)-Catalyzed Synthesis of Unsymmetrical Ureas^a



| entry | 1a (X mmol) | 2a (Y mmol) | NH_4VO_3 (Z mol%) | temp. (W °C) | NMR yield (%) ^b | |
|-------|----------------|----------------|--------------------------------------|-----------------|----------------------------|------------|
| | | | | | 3aa | 4aa |
| 1 | 0.3 | 0.3 | 20 | 120 | 58 | 36 |
| 2 | 0.3 | 0.3 | 20 | 150 | 50 | 35 |
| 3 | 0.3 | 0.3 | 20 | 100 | 39 | 28 |
| 4 | 0.6 | 0.6 | 8 | 120 | 79 (71) | 21 (16) |
| 5 | 0.6 | 0.6 | 5 | 120 | 70 | 19 |
| 6 | 0.6 | 1.2 | 8 | 120 | 56 | 33 |
| 7 | 0.6 | 2.4 | 8 | 120 | 47 | 44 |

^a Reaction conditions: **1a** (X mmol), **2a** (Y mmol) and catalyst (Z mol%) in DMA (1.0 mL) under CO_2 (balloon) at W °C for 15 h. ^b 1,3,5-Trimethoxybenzene was used as an internal standard. Isolated yields are shown in parentheses.

appropriate reaction temperature under these conditions was found to be 120 °C (entries 1-3). Examination of the optimum catalyst loading amount showed that reducing the loading of NH_4VO_3 from 20 mol% to 8 mol% increased the yield of unsymmetrical urea **3aa** to 79% (entries 4-5). Increasing the amount of **2a** decreased the yield of **3aa**, and the best result was found when 100 mol% **2a** was used (entries 4, 6-7).

In order to inhibit the formation of symmetrical urea, the concentration of disilylamine in the reaction system was studied. To keep the concentration of disilylamine **1a** below that of the catalyst, the reaction was carried out by dropwise addition of disilylamine **1a** in 15 fractions every 30 minutes, producing the unsymmetrical urea **3aa** and symmetrical urea **4aa** in 34% and 35% yields, respectively (Scheme 3). No improvement in yield of the unsymmetrical urea was observed.

Scheme 3. Catalytic Reaction of Disilylamine **1a** with **2a** by Dropwise Addition of **1a**

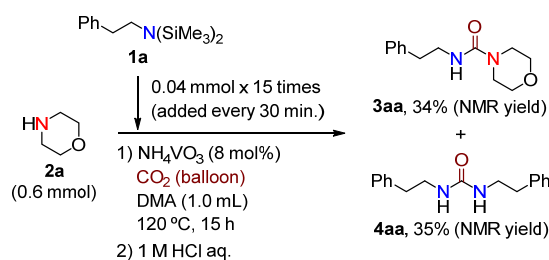


Table 3. Substrate Scope of Secondary Amines in the Catalytic Synthesis of Unsymmetrical Ureas^a

| entry | secondary amine 2 | NMR yield (%) ^b | | entry | secondary amine 2 | NMR yield (%) ^b | |
|-------|--------------------------|----------------------------|------------|-------|--------------------------|----------------------------|------------|
| | | 3 | 4aa | | | 3 | 4aa |
| 1 | | 3ab 74% | 24% | 4 | | 3ae 48% | 37% |
| 2 | | 3ac 64% | 23% | 5 | | 3af 50% | 42% |
| 3 | | 3ad 61% | 38% | 6 | | 3ag 33% | 56% |

^aReaction conditions: **1a** (0.6 mmol), **2** (0.6 mmol) and catalyst (8 mol%) in DMA (1.0 mL) under CO_2 (balloon) at 120 °C for 15 h. ^b1,3,5-Trimethoxybenzene was used as an internal standard.

To explore the validity of this catalytic system, the substrate scope of secondary amines was examined under the optimized reaction conditions (Table 3). Heterocyclic amines, such as piperidine (**2b**) and 4-phenylpiperidine (**2c**), showed good reactivity and afforded the desired unsymmetrical ureas in 74% and 64 % yields, respectively (entries 1-2). Similarly, thiomorpholine (**2d**) was successfully converted into the corresponding unsymmetrical urea **3ad** in 61% yield (entry 3). This catalytic system was found to be applicable to acyclic amines such as dibutylamine (**2e**) and *N*-methyl-*N*-benzylamine (**2f**) (entries 4-5). The catalytic reaction with *N*-methylprop-2-yn-1-amine gave the desired unsymmetrical urea **3ag** in a low yield probably due to its low boiling point (entry 6).

Our next experiments focused on clarifying the scope of a variety of disilylamines using morpholine (**2a**). As shown in Table 4, aliphatic disilylamines (**1b-1e**) were all suitable substrates, delivering the corresponding unsymmetrical ureas **3ba-3ea** in good yields (entries 1-4). The catalytic reaction of aromatic disilylamines (**1f-1i**) proceeded to afford the corresponding unsymmetrical ureas **3fa-3ia** in good yields, wherein the formation of the symmetrical urea **4** was suppressed

(entries 5-8). Starting from electron donating *p*-OMe substituted phenyldisilylamine **1i**, the unsymmetrical urea **3ia** was obtained in 65% yield with the formation of trace amounts of **4ii** (entry 8). In the case of using electron withdrawing *p*- CF_3 substituted phenyldisilylamine **1j** (entry 9), the yield significantly decreased compared with those of **1f-1i** (entries 5-8). The reason for the decrease in yield is probably that nucleophilicity of the nitrogen atom is lower than any other substrates **1f-1i**.

The effectiveness of this catalytic system was further demonstrated with chiral disilylamine. The catalytic reaction of chiral disilylamine **1k** derived from (*R*)-(+)-1-phenylethylamine with morpholine (**2a**) was found to afford the corresponding chiral unsymmetrical urea **3ka** and symmetrical urea **4kk** with retention of chirality as determined by chiral HPLC analysis (24% and 21% yields, respectively, Scheme 4).¹¹ The low yields are probably due to the effect of the substituent on the α -carbon to the nitrogen atom. Despite the low yield under the present conditions, this catalytic system could be applicable to the synthesis of chiral urea without loss of chirality.

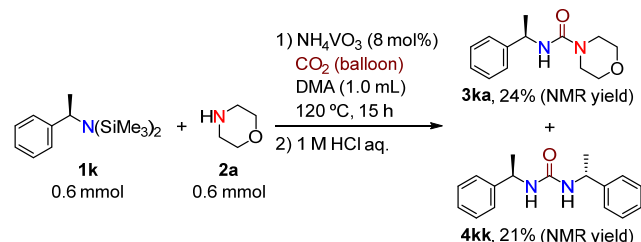
Table 4. Substrate Scope of Disilylamines in the Catalytic Synthesis of Unsymmetrical Ureas^a

1) NH_4VO_3 (8 mol%)
 CO_2 (balloon)
 DMA, 120 °C, 15 h
 2) 1 M HCl aq.

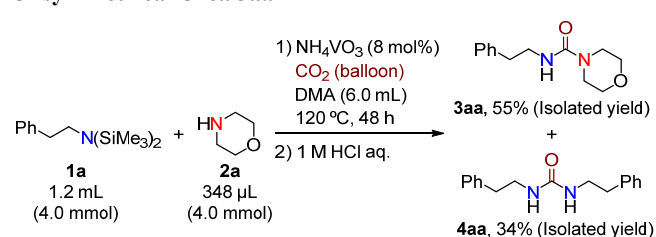
| entry | disilylamine 1 | NMR yield (%) ^b | | entry | disilylamine 1 | NMR yield (%) ^b | |
|-------|-----------------------|----------------------------|--------------------------------|-------|-----------------------|----------------------------|--------------------------------|
| | | 3 | 4 | | | 3 | 4 |
| 1 | | 3ba 65% | 4bb 20% | 6 | | 3ga 51% | 4gg 6% |
| 2 | | 3ca 62% | 4cc 28% | 7 | | 3ha 40% | 4hh 6% |
| 3 | | 3da 58% | 4dd 13% | 8 | | 3ia 65% | 4ii trace |
| 4 | | 3ea 63% | 4ee 33% | 9 | | 3ja 15% | 4jj 11% ^c |
| 5 | | 3fa 45% | 4ff 14% ^c | | | | |

^aReaction conditions: **1** (0.6 mmol), **2a** (0.6 mmol) and catalyst (8 mol%) in DMA (1.0 mL) under CO_2 (balloon) at 120 °C for 15 h. ^b1,3,5-Trimethoxybenzene was used as an internal standard. ^cIsolated yield.

Scheme 4. Catalytic Reaction of Chiral Disilylamine 1k with 2a

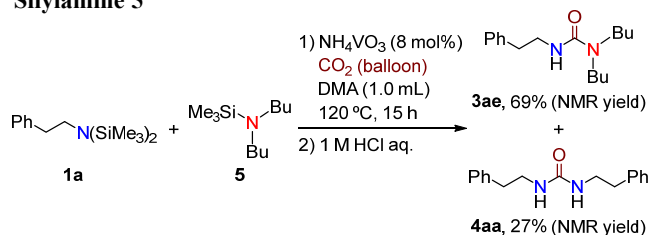


Scheme 5. Gram-Scale NH_4VO_3 -Catalyzed Synthesis of Unsymmetrical Urea 3aa



It is worth mentioning that gram-scale catalytic reaction of disilylamine **1a** (4.0 mmol) with morpholine (**2a**, 4.0 mmol) was successfully performed under ambient pressure of carbon dioxide to produce the desired unsymmetrical urea **3aa** and symmetrical urea **4aa** in 55% and 34% isolated yields, respectively (Scheme 5).

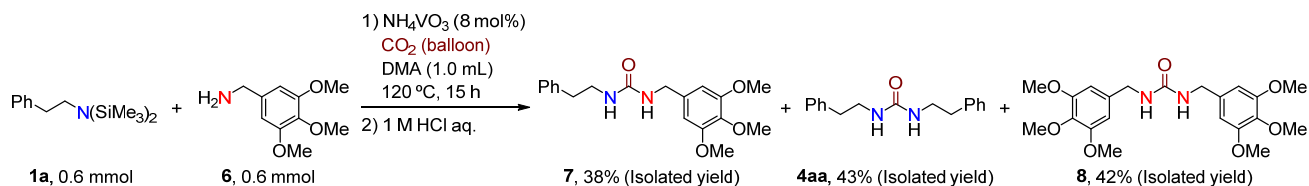
Scheme 6. Catalytic Reaction of Disilylamine 1a with Silylamine 5



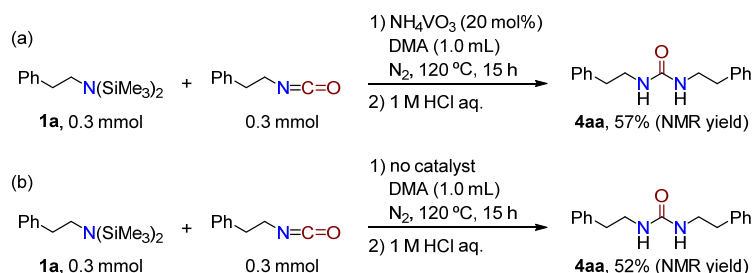
As exemplified in above reactions, the developed protocol is useful for the synthesis of unsymmetrical ureas from disilylamines and secondary amines. Additional examples are showcased in Schemes 6 and 7. The reaction of disilylamine **1a** (0.6 mmol) with *N,N*-dibutyltrimethylsilylamine (**5**, 0.6 mmol) in the presence of NH_4VO_3 (8 mol%) catalyst under the ambient pressure of carbon dioxide was demonstrated, yielding the corresponding unsymmetrical urea **3ae** in 69% yield with the symmetrical urea **4aa** in 27% yield as the by-product (Scheme 6). This result indicates that the use of silylamine (Me_3SiNR_2) instead of secondary amine (HNR_2) (Table 3, entry4) improved the reaction efficiency.

Subsequently, the reaction with primary amine was evaluated. The NH_4VO_3 catalyzed reaction of disilylamine **1a** (0.6 mmol) with 3,4,5-trimethoxybenzylamine (**6**, 0.6 mmol) under the ambient pressure of carbon dioxide at 120 °C was found to lead to the formation of the desired unsymmetrical urea **7** in 38% isolated yield, wherein the symmetrical urea **4aa** derived from disilylamine **1a** and the symmetrical urea **8** derived from primary amine **6** were produced in 43% and 42% isolated yields, respectively (Scheme 7).

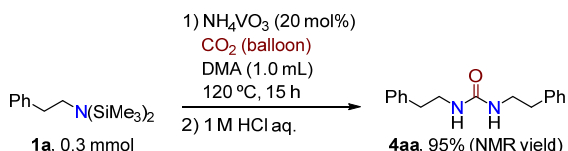
Scheme 7. Catalytic Reaction of Disilylamine 1a with Primary Amine 6



Scheme 8. Reaction of Disilylamine 1a with 2-Phenylethyl Isocyanate



Scheme 9. Catalytic Reaction of Disilylamine 1a

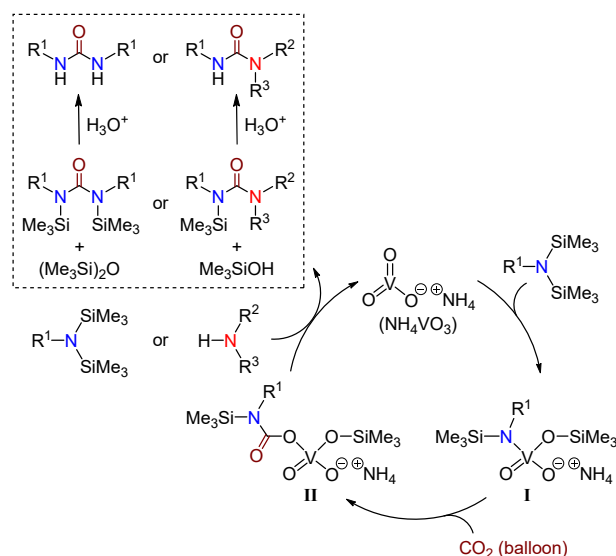


To gain insight into the reaction mechanism, the reaction of disilylamine **1a** with 2-phenylethyl isocyanate was conducted (Scheme 8). The reaction of **1a** with 2-phenylethyl isocyanate in the presence of NH_4VO_3 catalyst under nitrogen atmosphere led to the formation of the symmetrical urea **4aa** in 57% yield (Scheme 8a). Without NH_4VO_3 catalyst, the symmetrical urea **4aa** was obtained in 52% yield (Scheme 8b). On the other hand, NH_4VO_3 catalyst facilitated the catalytic transformation of disilylamine **1a** with carbon dioxide into the symmetrical urea **4aa** in 95% yield as shown in Scheme 9. These results suggest that isocyanate might not be generated in this catalytic system. The proposed catalytic cycle for oxovanadium(V)-catalyzed synthesis of ureas based on the above-mentioned results is illustrated in Scheme 10. The reaction of NH_4VO_3 catalyst with disilylamine produces the vanadium-silylamide intermediate **I**, in which carbon dioxide insertion into V–N bond occurs to afford the intermediate **II**.¹² Subsequent reaction with disilylamine or secondary amine yields the corresponding silylurea.

CONCLUSIONS

In conclusion, a commercially available easy-to-handle NH_4VO_3 was demonstrated to serve as an efficient catalyst for the one-pot, one-step synthesis of unsymmetrical ureas from disilylamines through catalytic activation of carbon dioxide as a C1 building block under ambient pressure. The catalytic system was also demonstrated to be potentially applicable to the synthesis of chiral urea without loss of chirality. Efficient utilization of carbon dioxide as a carbon source is considered essential for a sustainable society in the future. This sustainable approach is characterized by utilization of carbon dioxide under ambient pressure, application of a wide range of substrates without the use of dehydration reagents or bases, and easy

Scheme 10. Proposed Catalytic Cycle for Oxovanadium(V)-Catalyzed Synthesis of Ureas



scalability. Studies on the detailed reaction mechanism of this reaction and application of this practical catalytic carbon dioxide activation system to other reactions are now in progress.

EXPERIMENTAL SECTION

General Information. Disilylamines (**1b-1e**¹³ and **1f-1j**¹⁴) and $\text{VO}(\text{TEA})^{10}$ were prepared according to the literature method. The other reagents and solvents were purchased from commercial sources and further purified by the standard methods if necessary. ^1H NMR, ^{13}C NMR, ^{19}F NMR, and ^{29}Si NMR spectra were recorded in CDCl_3 or C_6D_6 on a JEOL JNM-ECS 400 MHz spectrometer. Chemical shifts of ^1H NMR and ^{13}C NMR spectra were given in δ (ppm) relative to the residual solvent signal as an internal standard. Chemical shifts of $^{29}\text{Si}\{^1\text{H}\}$ NMR spectra were reported relative to the external reference Me_4Si ($\delta = 0$ ppm). Chemical shifts of $^{19}\text{F}\{^1\text{H}\}$ NMR spectra were referenced to an external PhCF_3 ($\delta = -63.7$ ppm). High resolution mass spectroscopy (HRMS) was performed on a JEOL JMS-700 spectrometer. Gel permeation chromatography (GPC) was performed on a YMC-GPC-T2000. The analysis of chiral ureas was carried out

using HPLC (Chiralpak IA, hexane/CHCl₃/EtOH = 8:2:1, flow 0.5 mL/min, 254 nm).

General procedure for oxovanadium(V)-catalyzed synthesis of ureas. In a 10 mL two-necked flask, disilylamine **1a-1j** (0.60 mmol), amines **2a-2g** (0.60 mmol) NH₄VO₃ (5.6 mg, 0.048 mmol), and DMA (1.0 mL) were placed in a glovebox filled with nitrogen. Next, nitrogen in the flask was replaced with CO₂. The mixture was stirred at 120 °C for 15 h, followed by treatment with 1 M HCl aq. and extraction with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtrated, and removed under reduced pressure. Unsymmetrical ureas and symmetrical ureas was isolated by preparative TLC (ethyl acetate/CH₂Cl₂ = 1:1 for **3aa-3ja**, **3ae**, **7**, and **8**) or GPC (gel permeation chromatography) (**3ab-3ad**, and **3af-3ag**). 1,3,5-Trimethoxybenzene was used as an internal standard, and ¹H NMR analysis was performed to determine the NMR yield. Spectral data of the products were identical with those of authentic samples.

Procedure for gram-scale NH₄VO₃-catalyzed synthesis of unsymmetrical urea 3aa. In a 200 mL three-necked flask, 2-phenylethyl-*N,N*-bis(trimethylsilyl)amine (**1a**) (1.2 mL, 4.0 mmol), morpholine (**2**, 348 μL, 4.0 mmol), NH₄VO₃ (37.4 mg, 0.32 mmol), and DMA (6.0 mL) were placed in a glovebox filled with nitrogen. Next, nitrogen in the flask was replaced with CO₂. The mixture was stirred at 120 °C for 48 h, followed by treatment with 1 M HCl aq. and extraction with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtrated, and removed under reduced pressure. The residue was isolated by preparative TLC (ethyl acetate/CH₂Cl₂ = 1:1) to give 518 mg (2.2 mmol, 55% yield) of *N*-(2-phenylethyl)-4-morpholinecarboxamide (**3aa**).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/>.

¹H NMR, ¹³C NMR, and ¹⁹F NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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University and the Analytical Center, Graduate School of Science, Osaka Metropolitan University.

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