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Reductive CO_2 Fixation via the Selective Formation of C−C Bonds: Bridging Enaminones and Synthesis of 1,4-Dihydropyridines

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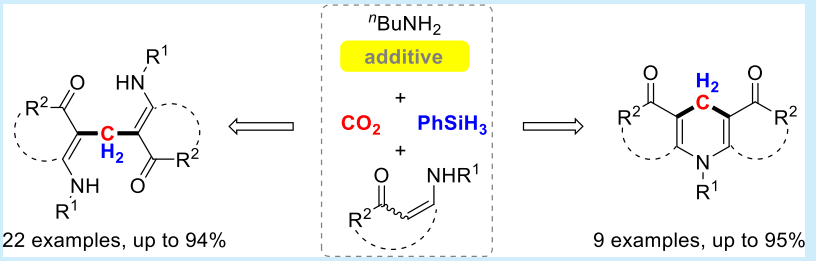

ABSTRACT: Herein, a selective tandem C−C bond-forming reaction with CO_2 was developed to realize the bridging of enaminones and synthesis of 1,4-dihydropyridines, respectively. *n*-Butylamine significantly promoted this CO_2 deoxymethylenation procedure catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and $ZnCl_2$. The mechanism involving the formation of bis(silyl)acetal, nucleophilic addition, and amine elimination was also interpreted to clarify the bridging of two molecules of enaminones with CO_2 and the generation of dihydropyridine derivatives.

As one of the most basic one-carbon (C1) structural units, the methylene structure is widely identified in bioactive molecules and higher value-added chemical structures.[1] Over the past years, carbon dioxide (CO_2) has been regarded as a ubiquitous, green, and recyclable C1 source.[2] The precise introduction of methylene blocks can be achieved by the deoxymethylenenation of CO_2, which has attracted interest from research on the utilization of CO_2. Previously, the oxidation state of carbon (C^{4+}) in CO_2 was reduced to 2+, 0, or 2− valence states (Scheme 1a) through a 2-, 4-, or 6-electron reduction process[3] to achieve the methylation,[4] hydroxylmethylation,[5] deoxymethylenenation,[6] or formylation reaction.[7] Among them, limited attention was paid to deoxymethylenenation of CO_2. Specifically, CO_2 can first be reduced by 2-electron reduction to obtain C^{2+} species, but the subsequent reduction of C^0 to the C^{2-} species is often faster than the reduction of C^{2+} to C^0 species (Scheme 1a), making it difficult to utilize the C^0 species.[6a,3]

The introduction of suitable nucleophilic substrates and the development of mild catalytic systems are feasible solutions to selective deoxymethylenenation. In 2015, Bontemps and Sabo-Etienne et al. developed a (dihydrido)iron complex-catalyzed selective reduction of CO_2 into the methylene group with the hydroborane as a reductant.[6b] In addition, the symmetric $C_{sp2}-C_{sp3}$ bonds were constructed with 2,4-di*tert*-butylphenol as the C-nucleophile (Scheme 1b, total yield for two steps: 39%). In the same year, Cantat and co-workers realized the bridging of two molecules of amines with CO_2 through the organocatalyzed reduction of CO_2 to methylene.[3b]

They found that malonate could efficiently replace the amine reagents to promote the challenging formation of $C_{sp3}-C_{sp3}$ bonds from CO_2 (Scheme 1c, 58%). In addition, the deoxymethylenation of CO_2 was also conducted for the synthesis of aminals (betaine-catalyzed, reported by He et al.[6a] and Han et al.[3a]), dimethoxymethane (Co-catalyzed, reported by Klankermayer et al.[6c]), dithioacetals (under distinctive $NaBH_4/I_2$ system, reported by Xi et al.[6d]), and spiro-indolepyrrolidines (TBD-catalyzed, reported by Xia et al.[6e]), etc.

In all of the above studies, the methylene group was introduced from CO_2 mainly in a controllable manner. However, these deoxymethylenation reactions primarily emphasized the construction of C−X bonds (where X = N, O, or S). Limited attention was paid to the efficient construction of C−C bonds. Because of our ongoing interest in developing efficient tandem reaction methods,[8] the present research aimed to develop such an alkylamine-promoted deoxymethylenation reaction of CO_2 for the formation of

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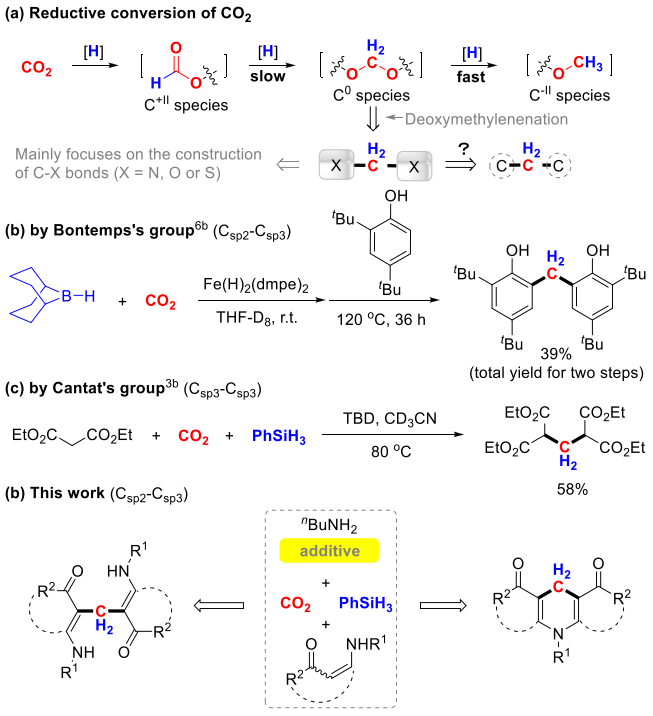
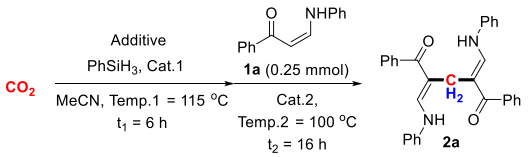
Scheme 1. CO_2 Deoxymethylenation for the Formation of C−C Bonds



C−C bonds. Specifically, the bridging of two molecules of enaminones with CO_2 and the synthesis of 1,4-dihydropyridines were realized.

In terms of high O-,[9] N-,[10] or C-nucleophilicity,[11] enaminones were regarded as useful precursors for synthesis of value-added chemicals. Initially, the reaction of acyclic enaminone **1a**, CO_2, and phenylsilane ($PhSiH_3$) was investigated under different conditions (Scheme 2). To our delight, when the reaction was performed in dry MeCN with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and $ZnCl_2$ as the catalyst under 1 atm of CO_2, the bis-enaminone **2a** was selectively obtained, achieving 88% yield upon isolation (Scheme 2, entry 1). Control experiments then were performed to determine the usefulness of each component (Scheme 2, entries 2−5). Without $PhSiH_3$, no reaction occurred (Scheme 2, entry 2). In contrast, when the reaction was conducted in the absence of *n*-$BuNH_2$, the yield of **2a** only reached 47% (Scheme 2, entry 3), implying the significant role of *n*-$BuNH_2$ in promoting the reaction. As a possible reason, a symbiotic relationship may exist between the CO_2 and amine. CO_2 might react with the primary amine to form carbamic acid, thus essentially increasing the effective concentration of CO_2 in the solution[12] and aiding the subsequent reduction steps. Without TBD, **2a** was not detected (Scheme 2, entry 4), revealing that the TBD was an indispensable catalyst. In the absence of $ZnCl_2$, the yield of **2a** sharply decreased to 39% (Scheme 2, entry 5), identifying $ZnCl_2$ to be a favorable synergistic catalyst. As the amount of $PhSiH_3$, *n*-$BuNH_2$, TBD, and $ZnCl_2$ was decreased, **2a** was also isolated smoothly in a 90% yield (entry 6). When the amount of TBD and $ZnCl_2$ was further reduced to 0.15 equiv, the yield of **2a** was slightly reduced (86%; see Scheme 2, entry 7 vs entry 6). If the dosage of butylamine was reduced from 4 equiv to 2 or 1 equiv, the yield decreased to 83% or 78% (Scheme 2, entries 8 and 9). A

Scheme 2. Optimization of the Reaction Conditions



Entry	$PhSiH_3$ (eq.)	Additive (eq.)	Cat.1 (eq.)	Cat.2 (eq.)	Yield[a] (%)
1	6.0	*n*-$BuNH_2$ (6.0)	TBD (0.5)	$ZnCl_2$ (0.5)	88
2	-	*n*-$BuNH_2$ (6.0)	TBD (0.5)	$ZnCl_2$ (0.5)	n.r.
3	6.0	-	TBD (0.5)	$ZnCl_2$ (0.5)	47
4	6.0	*n*-$BuNH_2$ (6.0)	-	$ZnCl_2$ (0.5)	n.d.
5	6.0	*n*-$BuNH_2$ (6.0)	TBD (0.5)	-	39
6	**4.0**	***n*-$BuNH_2$ (4.0)**	**TBD (0.3)**	**$ZnCl_2$ (0.3)**	**90**
7	4.0	*n*-$BuNH_2$ (4.0)	TBD (0.15)	$ZnCl_2$ (0.15)	86
8	4.0	*n*-$BuNH_2$ (2.0)	TBD (0.3)	$ZnCl_2$ (0.3)	83
9	4.0	*n*-$BuNH_2$ (1.0)	TBD (0.3)	$ZnCl_2$ (0.3)	78
10	2.0	*n*-$BuNH_2$ (4.0)	TBD (0.3)	$ZnCl_2$ (0.3)	34
11	4.0	$BnNH_2$ (4.0)	TBD (0.3)	$ZnCl_2$ (0.3)	71
12	4.0	*t*-$BuNH_2$ (4.0)	TBD (0.3)	$ZnCl_2$ (0.3)	84
13	4.0	$(CH_2NH_2)_2$ (4.0)	TBD (0.3)	$ZnCl_2$ (0.3)	trace
14	4.0	Et_2NH (4.0)	TBD (0.3)	$ZnCl_2$ (0.3)	50
15	4.0	Et_3N (4.0)	TBD (0.3)	$ZnCl_2$ (0.3)	34
16	4.0	*n*-$BuNH_2$ (4.0)	GB (0.3)	$ZnCl_2$ (0.3)	61
17	4.0	*n*-$BuNH_2$ (4.0)	DBU (0.3)	$ZnCl_2$ (0.3)	47
18	4.0	*n*-$BuNH_2$ (4.0)	Cs_2CO_3 (0.3)	$ZnCl_2$ (0.3)	44
19	4.0	*n*-$BuNH_2$ (4.0)	*t*-BuONa (0.3)	$ZnCl_2$ (0.3)	10
20	4.0	*n*-$BuNH_2$ (4.0)	TBD (0.3)	$FeCl_3$ (0.3)	38
21	4.0	*n*-$BuNH_2$ (4.0)	TBD (0.3)	$AlCl_3$ (0.3)	trace
22	4.0	*n*-$BuNH_2$ (4.0)	TBD (0.3)	$AgNO_3$ (0.3)	11
23	4.0	*n*-$BuNH_2$ (4.0)	TBD (0.3)	HOTf (0.3)	32

[a]Isolated yield, n.r. = no reaction, n.d. = no detected.

further reduction of the amount of silane to 2 equiv led to a sharp decrease in the yield of **2a** (Scheme 2, entry 10).

Based on the significant role of butylamine in promoting the reaction, other amines were also screened (Scheme 2, entries 11−15). When other monobasic primary alkylamines (e.g., benzylamine and *tert*-butylamine) were used to replace *n*-butylamine, good yields of **2a** could still be obtained (Scheme 2, entries 11 and 12). Nonetheless, ethylenediamine showed little effect in promoting this reaction (Scheme 2, entry 13). Similarly, diethylamine and triethylamine had no prominent promoting effect, only furnishing **2a** in a 50% and 34% yield, respectively (Scheme 2, entries 14 and 15). Combined with the above results, we used *n*-butylamine in subsequent investigations. When glycine betaine (GB) rather than TBD was adopted, the yield of **2a** only reached 61% (Scheme 2, entry 16). Common basic catalysts (e.g., DBU, Cs_2CO_3, and *t*-BuONa) and Lewis acids (e.g., $AlCl_3$, $FeCl_3$, and $AgNO_3$) also failed to result in a better yield of **2a**. When trifluoromethanesulfonic acid (HOTf) was taken as the Brønsted acid catalyst, only a 32% yield of **2a** was generated. Finally, different silanes were screened. Other hydrosilanes, including Ph_3SiH,

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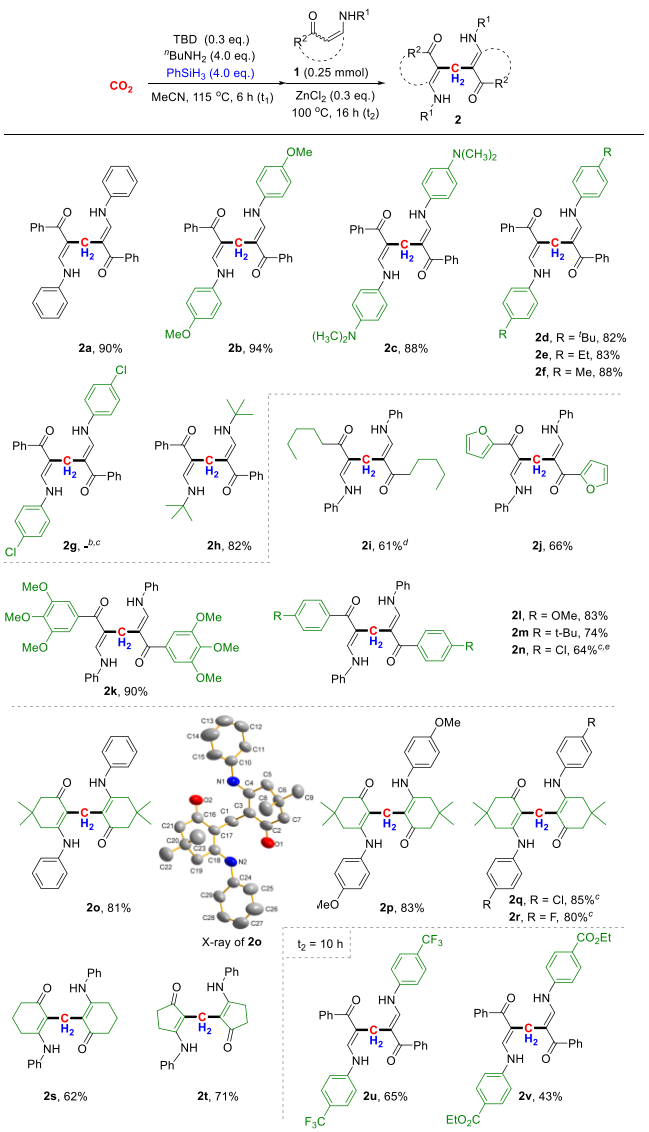
Et_3SiH, EtO_3SiH, Ph_2SiH_2, and polymethylhydrosiloxane were almost ineffective in the formation of **2a**, which may be attributed to the reduction ability of hydrosilane.[13] In addition, when tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, toluene, and 1,2-dichloroethane (DCE) were used as the solvent, the yield of **2a** was no better than that obtained using acetonitrile. Notably, when the reaction temperature in the second step (Temp.2) was increased to 120 °C, **2a** had a tendency to be further converted to 1,4-dihydropyridine.

Under the best reaction conditions (Scheme 2, entry 6), the substrate scope was examined, as shown in Scheme 3. It was found that the reaction of CO_2 with acyclic or cyclic enaminones contributed to a good yield of bis-enaminone formation. First, the R^1 substituents on the acyclic enaminones were studied. Generally, cyclic enaminones bearing electron-donating substituents proceeded well (**2b**−**2f**, 82%−94%), e.g., in substrates with groups such as 4-methoxyphenyl, 4-(dimethylamino)phenyl, and 4-alkylphenyl. Meanwhile, electron-withdrawing substituents (e.g., 4-chlorophenyl) seemed to further accelerate the cyclization reaction to form 1,4-dihydropyridine derivatives. The alkyl group such as *tert*-butyl was suitable for this reaction to produce **2h**. Second, the R^2 substituents were examined (**2i**−**2n**). When R^2 was *n*-butyl, the desired bis-enaminone **2i** was generated in a moderate yield. Furanyl was applicable as well to the production of **2j** in a 66% yield under optimal reaction conditions. The substrates with electron-donating (e.g., **2k**, R^2 = 3,4,5-trimethoxyphenyl, 90%; **2l**, R^2 = *p*-methoxyphenyl, 83%) groups were tolerable to furnish the corresponding products in good yields. When the R^2 substituent was *p*-chlorophenyl, the bis-enaminone **2n** was obtained in a moderate yield. Finally, the cyclic enaminones were investigated (**2o**−**2t**). Good yields of the corresponding bis-enaminones were produced, regardless of electron-donating (**2p**, R^1 = *p*-methoxyphenyl, 83%) or electron-withdrawing (**2q**, R^1 = *p*-chlorophenyl, 85%; **2r**, R^1 = *p*-fluorophenyl, 80%) groups on the benzene ring. Enaminones that were prepared from 1,3-cyclohexanedione and 1,3-cyclopentanedione also performed well, resulting in the 62% and 71% yields of the desired **2s** and **2t**, respectively. In addition, when the reaction time (t_2) was shortened, substrates containing electron-withdrawing trifluoromethyl and ester groups were also tolerated (**2u**, $-CF_3$, 65%; **2v**, $-CO_2Et$, 43%). When different enaminones were used simultaneously (e.g., **1b**:**1o** = 1:1), **2b**, **2o** and the corresponding unsymmetric bis-enaminone were obtained as a mixture. The structure of the products was characterized by nuclear magnetic resonance (NMR) analysis and further confirmed by X-ray analysis of **2o**.

Scheme 3. Scope of the Reaction[a]



[a]Yields are of isolated products. [b]Part of the product irrepressibly converted to 1,4-dihydropyridine. [c]Poor solubility in acetonitrile. Using MeCN:THF (2:1, 3 mL) as the solvent. [d]t_2 = 3 h. [e]t_2 = 9 h.

In the above research process, some bis-enaminone, such as **2g** and **2n**, had a tendency to be converted to 1,4-dihydropyrimidine derivatives, which have been widely exploited as reducing agents[14] and are very attractive heterocycles in medicinal chemistry and pharmacology, because of their wide range of biological activities.[15] Afterward, the conditions were optimized. To be more specific, when the reaction temperature was increased to 120 °C, this tandem cyclization reaction was promoted to furnish 1,4-dihydropyrimidine derivatives. To evaluate the scope of this reaction with respect to the formation of 1,4-dihydropyrimidines, we preliminary studied reactions of CO_2 with acyclic or cyclic enaminones (see Scheme 4). The substrates with electron-withdrawing (e.g., **3b**, R^1 = *p*-chlorophenyl, 81%; **3d**, R^2 = *p*-chlorophenyl, 89%) or electron-donating (e.g., **3c**, R^1 = *p*-methoxyphenyl, 89%; **3e**, R^2 = *p*-methoxyphenyl, 71%) groups were all found to help generate the target products in good yields. In addition, fused-dihydropyridine derivatives could also be generated from the reaction between cyclic enaminones and CO_2 (**3f**−**3i**, 77%−95%).

Next, the reaction mechanism was explored and studied. When formaldehyde rather than CO_2 and $PhSiH_3$ was directly adopted, **2a** and **3a** were successfully produced (Scheme 5a). In particular, more **3a** could be obtained at 120 °C, revealing the higher temperature as a favorable condition for the production of **3a**. These results also suggest that formaldehyde or its equivalents (e.g., bis(silyl)acetal) may be intermediates in the tandem reaction. Moreover, when **2a** was subjected to the standard conditions, **3a** was isolated in good yield (Scheme 5b), revealing that dihydropyridine was transformed from bis-enaminone **2**.

Drawing upon our experimental results and the related knowledge in the literatures, we propose the following catalytic

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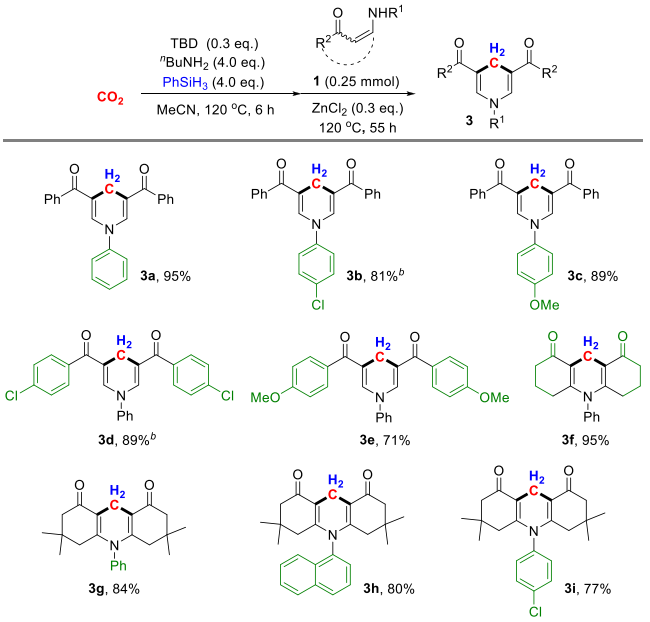
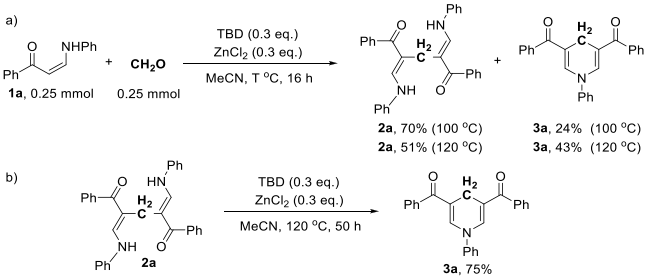
Scheme 4. Scope of the Reaction to Form 1,4-Dihydropyridines[a]



[a]Yields are of isolated products. [b]Using MeCN:THF (2:1, 3 mL) as the solvent.

Scheme 5. Verification of Intermediates



cycle for this tandem CO_2 deoxymethylenenation reaction (see Scheme 6). The reaction is initiated by TBD-catalyzed reduction of CO_2, producing bis(silyl)acetal **II**.[16] Then, nucleophilic substitution between **1a** and **II** affords intermediate **IV** (Scheme 6, path a). Alternatively, bis(silyl)acetal **II** undergoes a condensation reaction with *n*-butylamine (or aniline formed in the last step) to form imine **III**,[6b] which is further transformed to **IV′** via the nucleophilic addition with enaminone **1a**. Note that the formation of imine (TBD-catalyzed reduction−condensation of CO_2 with primary amine) in the same system has been supported in our previous work[8c] and Xia's work.[6e] Subsequently, an elimination reaction (**IV** or **IV′** to **V**) occurs to generate terminal olefin **V**, as supported by density functional theory (DFT) calculations in our previous work.[8c] The bridging of enaminones (to form bis-enaminone **2a**) is realized through the nucleophilic addition between **V** and **1a**. Intermediate **VI** then is yielded by further intramolecular nucleophilic addition of nucleophilic N atom to the *β*-position of the carbonyl group on the other side. Finally, after eliminating aniline, 1,4-dihydropyrimidine **3a** is generated. In this procedure, $ZnCl_2$, as a beneficial catalyst, may coordinate with the carbonyl group to enhance its electrophilicity,[17] thereby promoting the corresponding nucleophilic addition or elimination process. In addition, the role of *n*-butylamine may also be reflected in the reaction with CO_2 to form carbamic acid, which essentially increases the concentration of CO_2 in the solution.[12]

In summary, we have developed a new reductive tandem C_{sp2}−C_{sp3} bond-forming reaction with CO_2. The bridging of enaminones and the synthesis of 1,4-dihydropyridines were achieved separately. Control experiments revealed that *n*-butylamine significantly promoted this TBD- and zinc-chloride-catalyzed CO_2 deoxymethylenation procedure. A possible mechanism involving the formation of bis(silyl)acetal, nucleophilic addition, and amine elimination was postulated to clarify the generation of bis-enaminone and dihydropyridine derivatives. Further investigations of the reaction mechanism and the synthetic utility are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

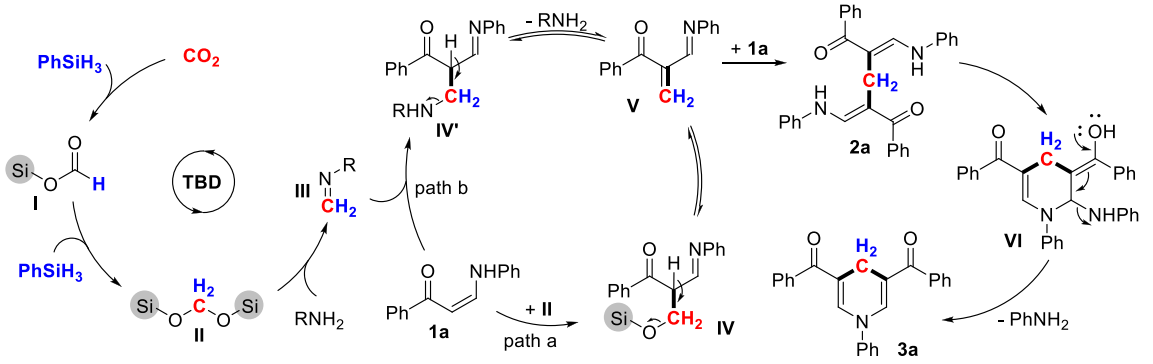
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02963.

Experimental details, synthetic procedures, ^1H and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1896690 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Scheme 6. Proposed Mechanism



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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to Zhao's upcoming child.

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