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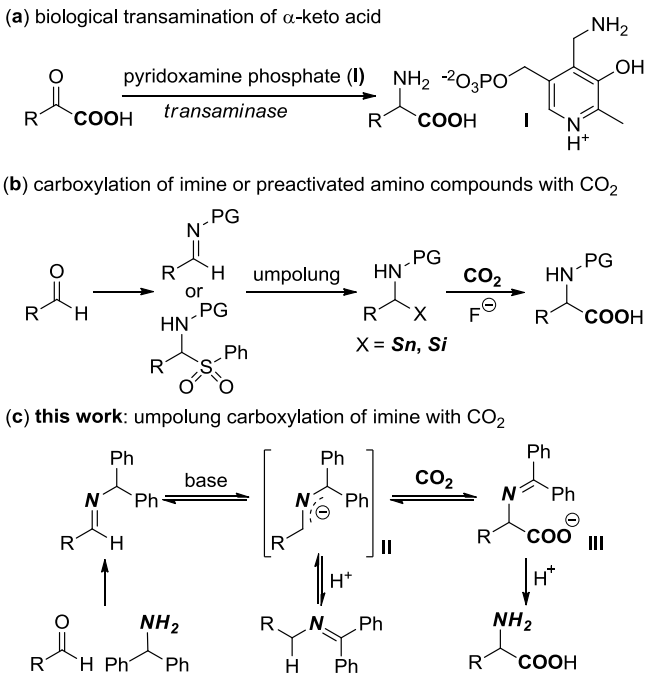
Access to α-Arylglycines via Umpolung Carboxylation of Aromatic Imines with Carbon Dioxide

Chun-Xiao Guo, Wen-Zhen Zhang*, Hui Zhou, Ning Zhang and Xiao-Bing Lu

Abstract: A straightforward and transition-metal-free approach for the efficient synthesis of α-arylglycine derivatives from aromatic imines and carbon dioxide was enabled by umpolung carboxylation reaction. Various substituted diphenylmethimines underwent the carboxylation smoothly with carbon dioxide in the presence of potassium *tert*-butoxide and 18-crown-6 to give the corresponding carboxylated products in good to high yields. Besides the enhancement of solubility of potassium *tert*-butoxide in THF, 18-crown-6 also plays key roles in suppressing reverse protonation or 1, 3-proton shift isomerization as well as stabilizing the carboxylated intermediate.

As a class of non-proteinogenic α-amino acids, α-arylglycine is a key structural unit presented in a vast array of important biologically active compounds including many glycopeptide and β-lactam antibiotics.[1] α-Arylglycines have also found various applications in the synthesis of some fine chemicals as privileged building blocks.[2] For the access to α-amino acids, enzymatic transamination of α-keto acids catalyzed by vitamin B_6-dependent aminotransferase is one of the most important ways in biological systems (Scheme 1, a).[3] Artificial method including modification of substrates bearing pre-installed carboxyl group has been mainly developed in the past decades.[4] However, the synthetic strategy via introduction of carboxyl group is less studied and relied heavily on the Strecker reaction using imines and highly toxic cyanide compounds. The development of an efficient and environmentally benign method to prepare α-amino acids from easily available substrates is highly desirable.

Synthesis of α-amino acids using carbon dioxide (CO_2) as a carboxyl source represents a highly attractive route since CO_2 is an abundant, non-toxic and renewable C1 feedstock.[5] Organolithium mediated direct α-carboxylation of amines using CO_2 under harsh reaction conditions was previously documented.[6] Recently, Sato and co-workers reported the synthesis of α-arylglycine from CO_2 under mild reaction conditions via carboxylation of a series of α-amino stannanes or silanes,[7] which were in-situ formed by the reaction of imines or α-amino sulfone with metal reagents (Scheme 1, b). Inspired by recent umpolung conversion of imines,[8] we envisioned that α-amino acid might be directly constructed from diphenylmethimine using CO_2 as a carboxyl source (Scheme 1, c). Although the 2-azaallyl anion intermediate **II** has been used as a nucleophile in various reactions,[9] to the best of our knowledge, the direct umpolung carboxylation of imine has not yet been described. The key to this conversion is to find a suitable base and reaction system to accelerate the carboxylation of the 2-azaallyl anion intermediate **II**, suppress the reverse protonation, and simultaneously stabilize the formed carboxylate **III**. Herein, we report a transition-metal-free, KO^{t}Bu/18-crown-6 mediated synthesis of α-arylglycine derivatives from aromatic imines and carbon dioxide via umpolung carboxylation reaction.[10]



Scheme 1. Biological and artificial synthesis of α-amino acids.

Initial investigations were conducted by subjecting *N*-diphenylmethanimine (**1a**), which was readily prepared by reaction of benzaldehyde with diphenylmethamine, to stoichiometric amounts of various bases in THF at 25 °C under CO_2 atmosphere (Table 1). An organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) only gave 13% yield of 1, 3-proton shift by-product ketimine **3a** (entry 1). 14% yield of desired carboxylative product **2a** was obtained when NaHMDS was used as a base (entry 2). Replacement of NaHMDS by stronger base KHMDS provided an improved conversion and selectivity of **2a** (entry 3). KO^{t}Bu gave moderate conversion but relatively low carboxylative selectivity (entry 5). To enhance the solubility of base in THF, crown ethers were then introduced into

[a] C.-X. Guo, Dr. W.-Z. Zhang, Dr. H. Zhou, N. Zhang and Prof. Dr. X.-B. Lu
State Key Laboratory of Fine Chemicals
Dalian University of Technology
Dalian 116024 (China)
E-mail: zhangwz@dlut.edu.cn

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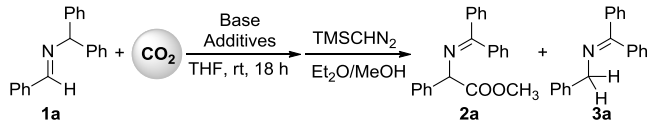
the reaction system.[11] We delightedly found that the combination of KO^{t}Bu and 18-crown-6 led to striking increases in both conversion and selectivity, **2a** was isolated in 93% yield (entry 6). Among the tested solvents (see Supporting Information), THF was revealed as an optimized solvent. Furthermore, reaction temperature and CO_2 pressure had a profound effect on the product selectivity. An increase of temperature to 80 °C caused the major formation of isomerization product **3a** (entry 9). When the reaction was conducted at lower CO_2 pressure, decreased yield and selectivity of **2a** were observed. This indicates that the carboxylation is more predominant than 1, 3-proton shift under high CO_2 pressure (entries 10 and 11). Decreasing the loading of 18-crown-6 from 1.2 to 0.4 equivalent resulted in an obvious negative effect on yield and selectivity of **2a** (entry 12). It's noteworthy that the carboxylative reaction using KO^{t}Bu/18-crown-6 could be completed within 1 h, providing 93% isolated yield of **2a** (entry 13).

Table 1. Development of the reaction conditions.[a]

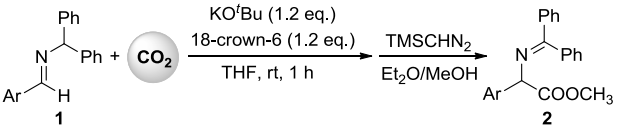


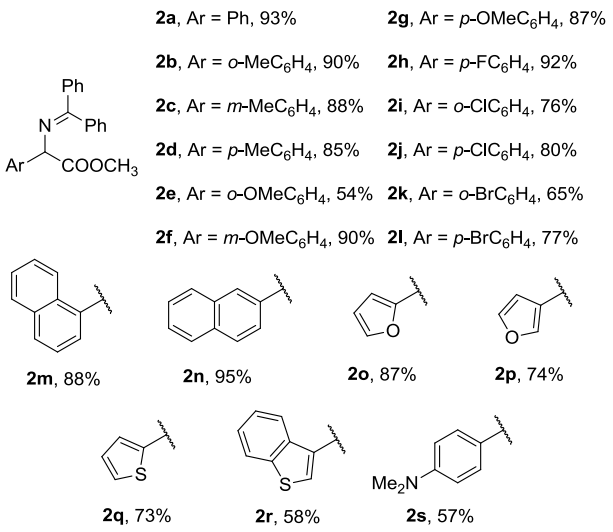
Entry	Base	Additive	Yield [%][b] 2a	3a
1	DBU	-	<1	13
2	NaHMDS	-	14	3
3	KHMDS	-	44	3
4	NaO^{t}Bu	-	<1	17
5	KO^{t}Bu	-	28	33
6	KO^{t}Bu	18-crown-6	95(93)	3
7	LiO^{t}Bu	12-crown-4	<1	<1
8	NaO^{t}Bu	15-crown-5	11	35
9[c]	KO^{t}Bu	18-crown-6	6	79
10[d]	KO^{t}Bu	18-crown-6	90	7
11[e]	KO^{t}Bu	18-crown-6	71	16
12[f]	KO^{t}Bu	18-crown-6	51	23
13[g]	KO^{t}Bu	18-crown-6	93(93)	4

[a] Reaction condition: **1a** (0.2 mmol), base (1.2 equiv.), additive (1.2 equiv.) 2.0 MPa of CO_2, 2 mL THF, 25 °C, 18 h. Followed by treatment with 2.0 equivalent of $TMSCHN_2$ in MeOH/Et_2O. [b] Yields were determined by NMR using 1,1,2,2-tetrachloroethane as an internal standard. Data given in parentheses are isolated yields. [c] 80 °C. [d] 0.5 MPa of CO_2. [e] 1 atm of CO_2. [f] 0.4 equivalent of 18-crown-6 was used. [g] carboxylation reaction time: 1 h.

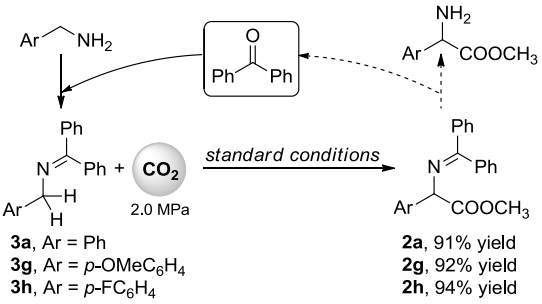
Under the optimized reaction conditions, the scope of the umpolung carboxylation with respect to aldimine substrates was then investigated (Table 2). Aromatic aldimines bearing a wide range of functional groups including electron-donating methyl, methoxy, dimethylamino and electron-withdrawing fluoro, chloro, bromo substituents all reacted smoothly to afford the corresponding α-arylglycine derivatives (**2b** to **2l**, **2s**) in moderate to good yields. Both α-, β-naphthyl substituted substrates participated in the carboxylative reaction quite efficiently to provide the corresponding products **2m** and **2n** in good yields. Furan- and thiophene-containing aldimines (**1o** to **1r**) are also suitable substrates for this reaction.

Table 2. Scope for the carboxylation of aldimines.





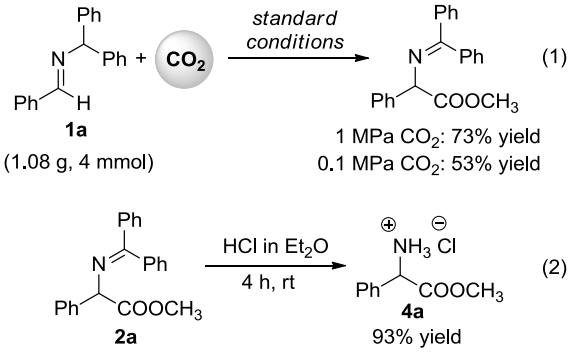
[a] Reaction condition: **1** (0.2 mmol), KO^{t}Bu (1.2 equiv.), 18-crown-6 (1.2 equiv.) 2.0 MPa of CO_2, 2 mL THF, 25 °C, 1 h. Followed by treatment with 2.0 equivalent of $TMSCHN_2$ in MeOH/Et_2O. [b] Isolated yields.



Scheme 2. KO^{t}Bu/18-crown-6 mediated carboxylation of ketimines with CO_2.

Since the aldimine (**2**) and ketimine (**3**) precursors could generate the same 2-azaallyl anion intermediate via

deprotonation, ketimines (**3**) were then used as substrates under the above optimized reaction condition. As shown in Scheme 2, ketimines bearing electron-donating methoxy (**3g**), and electron-withdrawing fluoro (**3h**) all conducted carboxylation smoothly to afford the corresponding α-arylglycine derivatives in good yields. Although the preparation of ketimines is more time-consuming and their starting materials are relatively limited, direct carboxylation of ketimines provided an efficient method to synthesize α-arylglycines under mild conditions via a benzophenone-mediated α-carboxylation of benzyl amines (Scheme 2).



Scheme 3. Gram-scale reaction and hydrolysis of carboxylative product.

Gram-scale carboxylation of **1a** was carried out under 1.0 MPa CO_2 pressure and 73% yield of product was isolated. More convenient manipulation using Schlenk tube under 0.1 MPa CO_2 pressure gave 53% isolated yield of **2a** (Scheme 3, 1). This indicated the utility and efficiency of this new reaction in preparative-scale organic synthesis. Moreover, hydrolysis of carboxylative product **2a** readily afforded methyl phenylglycine hydrochloride (**4a**) in 93% yield (Scheme 3, 2).[9c]

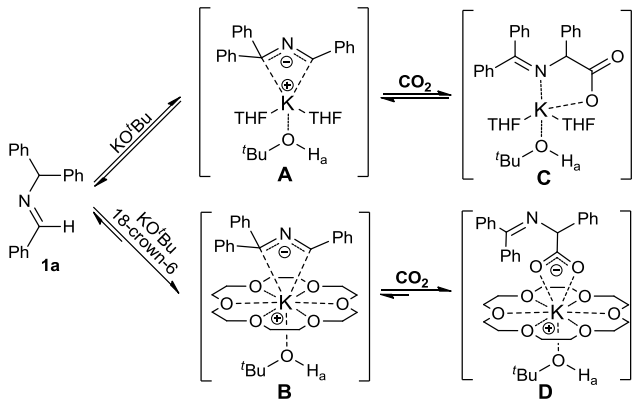


Figure 1. Possible intermediates in the absence (**A**, **C**) and presence (**B**, **D**) of 18-crown-6.

Mechanistic studies were then performed to gain insight into the pivotal role of 18-crown-6 in promoting this carboxylation reaction. Reaction of aldimine **1a** with KO^{t}Bu in THF in the absence or presence of 18-crown-6 should generate 2-azaallyl intermediate **A** or **B** respectively (Figure 1).[12] *In situ* Fourier transform infrared spectroscopy (see Figure S1 in Supporting Information) showed that when KO^{t}Bu was added to THF solution of **1a** and 18-crown-6, absorbance peak at 1641 cm^{-1} disappeared and absorption at 1580 cm^{-1} which could be assigned to intermediate **B** was observed immediately. When CO_2 was bubbled into the reaction system, the C=N absorption of intermediate **D** (1655 cm^{-1}) gradually increased with consecutive decrease of absorbance of intermediate **B**.

^{1}H NMR studies revealed that chemical shift of H_a in intermediate **A** (10.83 ppm) is much higher than that in intermediate **B** (5.18 ppm) (see Figure S3 in Supporting Information), which suggested that intermediate **A** might be more liable to conduct protonation intramolecularly back to form aldimine or ketimine. This implied that the introduction of 18-crown-6 to this reaction system could effectively inhibit the reverse protonation of 2-azaallyl intermediate or 1, 3-proton shift isomerization.

DFT studies showed that when carboxylated intermediate **C** and **D** underwent the reverse decarboxylation, the intermediate **D** with 18-crown-6 had a much higher energy barrier (15.5 kcal/mol) than intermediate **C** without 18-crown-6 (6.5 kcal/mol) (see Supporting Information). This demonstrated another effect of 18-crown-6 which stabilizes the carboxylated intermediate and inhibits its decarboxylation.

In conclusion, we have developed an efficient, transition-metal-free method for the synthesis of α-arylglycine derivatives from aromatic imines and carbon dioxide via umpolung carboxylation reaction. The key to the success of this transformation is the use of 18-crown-6 as a pivotal additive. Besides enhancing the solubility of KO^{t}Bu in THF, 18-crown-6 also plays key roles in suppressing the reverse protonation of 2-azaallyl intermediate or 1, 3-proton shift isomerization and stabilizing the carboxylated intermediate. Further investigations into the detailed mechanism and enantioselective version of this reaction are in progress in our laboratory.

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Keywords: carbon dioxide fixation • umpolung •carboxylation • transition-metal-free •α-amino acids

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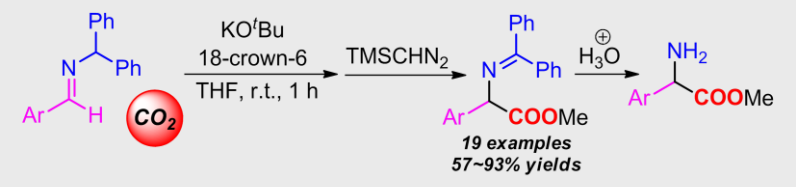

A transition-metal free synthesis of α-arylglycine derivatives from aromatic imines and carbon dioxide via KO^{t}Bu/18-crown-6 promoted umpolung carboxylation reaction is described

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