

One-Pot Synthesis of α -Amino Acids from Imines through CO₂ Incorporation: An Alternative Method for Strecker Synthesis**

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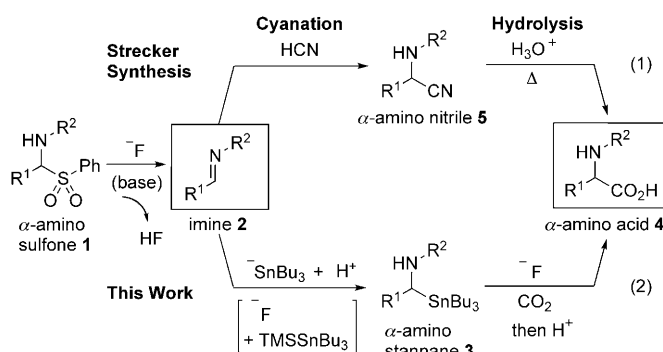
Carbon dioxide is an abundant and inexpensive carbon source (C1 unit); however, its inertness and gaseous character sometimes hamper its use for efficient C–C bond-forming reactions in organic synthesis. To overcome this problem, strongly nucleophilic organometallic reagents, such as RLi and RMgX, are often used for C–C bond construction that incorporates CO₂.^[1] Recently, transition-metal-promoted CO₂ fixation reactions, especially those involving metal-activated/attached unsaturated bonds,^[2–5] have been reported. However, there have been relatively few examples of robust C–C bond-forming reactions between CO₂ and an sp³-hybridized carbon center under mild reaction conditions.^[1,3a,b,6]

In 1850, Strecker pioneered the use of imine hydrocyanation with HCN and subsequent hydrolysis of the resulting α -amino nitrile **5** under acidic conditions to prepare α -amino acids **4** [Eq. (1), Scheme 1].^[7] This remarkable transformation is one of the most reliable methods for α -

amino acid synthesis from imines **2**.^[8] Nevertheless, this classical method has some practical drawbacks including: 1) the use of highly toxic hydrogen cyanide or an equivalent, such as an alkali metal cyanide or TMSCN, and 2) the need for hydrolysis of α -amino nitrile intermediate **5** in strongly acidic media such as aqueous HCl and H₂SO₄ at a high temperature. Replacement of cyanide by CO₂ in the Strecker reaction would lead to direct carboxylation of imines while avoiding the hydrolysis of nitrile **5**. Although the cyanide ion is a strong nucleophile that readily attacks imine groups, the central carbon atom of CO₂ behaves as an electrophile. Therefore, reversal of polarity (umpolung^[9]) on the imino carbon atom is a key to the success of the proposed transformation. For this purpose, we considered the use of a stannyl anion,^[10] which is known to react with imine **2**^[11] so that the resulting α -amino stannane **3** would act as a nucleophile towards CO₂ after metal exchange with Sn.^[12]

Our α -amino acid synthesis from imine **2** and CO₂ is based on several assumptions [Eq. (2), Scheme 1]: 1) imine **2** can be generated in situ from a readily available and stable synthetic precursor of imines, α -amino sulfone **1**,^[13] by treatment with a base, 2) imine **2** can be converted into α -amino stannane **3**^[11] by attack of the tributylstannyl anion generated from TMSnBu₃^[10,14] in the presence of an appropriate fluoride source,^[15] and 3) the fluoride ion can further activate α -amino stannane **3** by attack on the tin atom to exhibit carbanion-like reactivity at the sp³-hybridized carbon atom, thus leading to a C–C bond-forming process with CO₂ and affording α -amino acid derivative **4**.^[12] Ideally, this series of steps could be carried out in one pot with a single fluoride base. The proposed process is complementary to the Strecker amino acid synthesis because readily available and nontoxic CO₂ gas can be employed instead of cyanide as a C1 unit, and also acid-labile substrates would be applicable owing to the avoidance of acid hydrolysis.

For maximum synthetic utility, the *tert*-butoxycarbonyl (Boc) group was chosen as the protecting group for the imino nitrogen atom of the starting imine **2**. *N*-Boc- α -amido stannane **3a** was prepared by a reported procedure^[11] to evaluate the desired fluoride-promoted carboxylation step at 100–110°C under CO₂ (Table 1). During this process, the desired carboxylate **6a**, which was isolated after methyl esterification, and protiodestannylation product **7a** were both obtained. The **6a/7a** ratio depended on the fluoride source employed and the pressure of CO₂. Alkali metal fluorides other than CsF did not mediate carboxylation well, even in combination with a crown ether (Table 1, entries 1–4). In contrast, carboxylation proceeded readily in the presence of CsF. The ratio of **6a/7a** could be further improved by increasing the pressure of CO₂ (Table 1, entries 5–7). When



Scheme 1. Synthetic strategies for α -amino acids from imines. TMS = trimethylsilyl.

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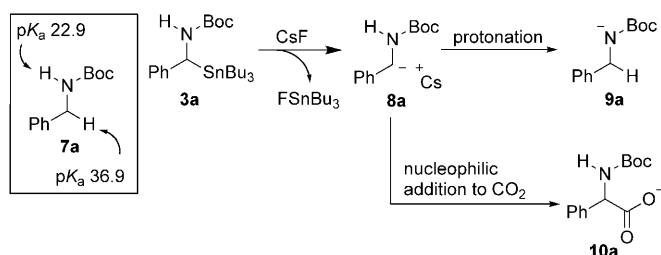
Table 1: Investigation of carboxylation using various fluoride sources.

Entry	Activator	CO ₂ [MPa]	t [h]	Yield [%] ^[a]		
				6a	7a	3a
1	LiF	0.1 (1 atm)	12	–	2	98
2	NaF	0.1	12	–	3	97
3	KF	0.1	12	10	9	59
4	KF + [18]crown-6	0.1	12	22	30	15
5 ^[b]	CsF	0.1	3	62 (60)	21	7
6 ^[b]	CsF	0.5	3	84 (71)	2	4
7 ^[b]	CsF	1	3	86 (75)	< 1	–
8 ^[b]	TBAT	1	3	49	1	10

[a] Yields were determined by using ¹H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. The values in parentheses represent the yields of isolated product. [b] The reaction was performed at 110 °C. TBAT = Tetrabutylammonium triphenyldifluorosilicate.

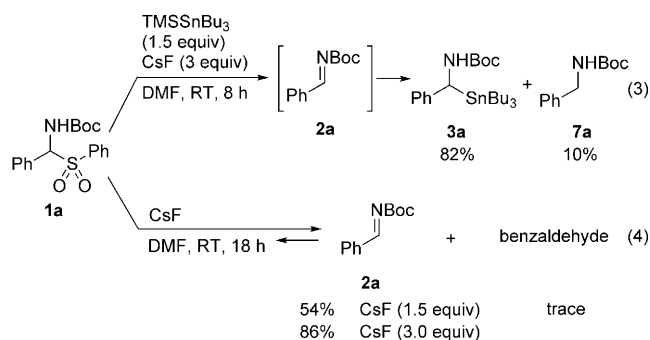
the reaction was performed under 1 MPa of CO₂, the desired carboxylation proceeded efficiently and afforded **6a** in 86 % yield (75 % yield of isolated product^[16]). The fluorosilicate TBAT also mediated the carboxylation, albeit with somewhat decreased yield (Table 1, entry 8).

A reasonable mechanism for the formation of **7a** is shown in Scheme 2. Based on calculated pK_a values in DMSO for *N*-Boc-protected benzyl amine **7a**,^[17] its amide N–H moiety is expected to be 14 orders of magnitude more acidic than its

**Scheme 2.** Estimated pK_a values of **7a** and possible reaction pathways.

proton at the benzylic position; therefore, carbanion-like species **8a**, which is generated by the attack of CsF, can undergo proton transfer in an intra- or intermolecular manner to afford **9a** or **7a**, respectively, under low concentrations of CO₂. At higher CO₂ pressures, carboxylation of **8a** is favored to afford **10a**. Remarkably, even under ambient pressure (Table 1, entry 5), **6a** was afforded as the major product (62 %), thus clearly demonstrating that carboxylation is faster than protonation under fluoride-mediated conditions, despite the large difference in predicted pK_a values.^[18]

Next, we investigated the preparation of α-amino stannane **3a** from imine **2a** (Scheme 3). After some experimentation, we found that the readily available *N*-Boc-protected imine precursor α-amino sulfone **1a**,^[13] which was prepared from benzaldehyde, was actually a better substrate for stannylation^[19] than imine **2a** itself, probably as a result of

**Scheme 3.** Investigation of stannylation. DMF = *N,N*-dimethylformamide.

the inherent instability of imine **2**. Direct stannylation of **1a** was effected by TMSSnBu₃^[14] in the presence of CsF and afforded α-amino stannane **3a** in 82 % yield along with protiodestannylation product **7a** in 10 % yield at room temperature [Eq. (3), Scheme 3]. In the absence of TMSSnBu₃, imine **2a** was still generated along with a trace amount of benzaldehyde, a product of imine hydrolysis, thus indicating that CsF is a competent base during this step [Eq. (4), Scheme 3]. Imine formation, which is an equilibrium favoring imine **2a**, was enhanced by increasing the amount of CsF. In light of these observations, stannylation of **1a** is believed to proceed via imine **2a**. During imine formation, CsF·HF has to be generated and it might act as a proton donor to cause the protiodestannylation of **3a** to produce **7a** (10 %). This pathway is in contrast to the assumed proton-transfer process that gave **7a** as depicted in Scheme 2.

By linking each reaction described above, we finally achieved a one-pot synthesis of α-amino acids from α-amino sulfones **1** (Table 2). In the presence of 1.1 equivalents of TMSSnBu₃ and 5 equivalents of CsF, α-amino sulfones **1** were transformed into the corresponding α-amino acids in moderate to high yields (49–88 %) within 3 hours under 1 MPa of CO₂ at 100 °C. After treatment with diazomethane and purification of the crude product mixtures to remove **7** and organotin residues,^[16] α-amino acid methyl esters **6** were isolated in 46–79 % yields. When imine **2a** was used instead of **1a**, **7a** was a major product (36 %) and **6a** was obtained in only 28 % yield together with the expected hydrolysis product, benzaldehyde (7 %; Table 2, entry 2). The one-pot reaction was applicable to various substituted α-amino benzyl sulfones (Table 2, entries 1 and 3–9).^[20] Furthermore, both α- and β-naphthyl amino stannane (Table 2, entries 10 and 11) and heteroaromatic substrates (Table 2, entries 12 and 13), which are potentially labile under a strongly acidic condition, were active substrates in this process.

In summary, we have developed a novel one-pot process for the synthesis of α-amino acids from imine equivalents using CO₂ gas as a carbon source. This reaction was made possible by the reagent combination of TMSSnBu₃ and CsF. Three successive reactions (imine formation, stannylation, and carboxylation) proceeded in the same flask under these conditions to give products in up to 79 % yield. The fluoride source CsF functions in a different role for each step. Examination of different substrate types, such as α-alkenyl

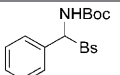
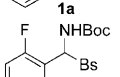
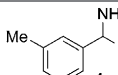
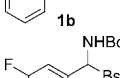
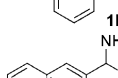
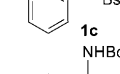
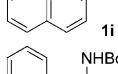
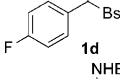
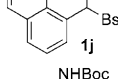
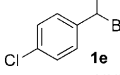
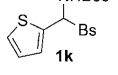
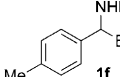
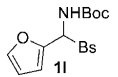
Table 2: One-pot synthesis of α -amino acids.

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$$\begin{array}{c}
 \text{1) TMSSnBu}_3 \text{ (1.1 equiv)} \\
 \text{CsF (5 equiv)} \\
 \text{DMF, RT, 5 min} \\
 \text{2) CO}_2 \text{ (1 MPa)} \\
 \text{100 }^\circ\text{C, 3 h}
 \end{array}
 \xrightarrow{
 \begin{array}{c}
 \text{1) Et}_2\text{O} \\
 \text{HCl (1M)} \\
 \text{2) CH}_2\text{N}_2
 \end{array}
 }$$

$$\text{Ar-CH(NHBoc)-SO}_2\text{-Ph} \rightarrow \text{Ar-CH(NHBoc)-CO-OMe} + \text{Ar-CH(NHBoc)-H}$$

$$\text{1} \quad \quad \quad \text{6} \quad \quad \quad \text{7}$$

Entry	Substrate	Yield [%] ^[a]		Entry	Substrate	Yield [%] ^[a]	
		6	7			6	7
1		81 (78)	7				
2 ^[b]		28	36	8 ^[d]		74 (57)	8
3		61 (52)	12	9		88 (79)	8
4		62 (46)	19	10		73 (66)	15
5		79 (63)	11	11		65 (62)	14
6		64 (51)	17	12		49 (46)	8
7 ^[c]		53 (47)	6	13 ^[e]		62 (55)	6

[a] Yields were determined by using ^1H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. The values in parentheses represent the yields of isolated product. [b] Imine **2a** was used as a substrate and 7% of benzaldehyde was formed. [c] 9% of α -amino stannane **3f** remained. [d] 3% of α -amino stannane **3g** remained. [e] The reaction was performed at 110°C . Bs = benzenesulfonyl.

and α -alkyl α -amino sulfones, as well as asymmetric variants of this transformation are currently underway.

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