Amino Acid Synthesis

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One-Pot Synthesis of α-Amino Acids from Imines through CO_2 Incorporation: An Alternative Method for Strecker Synthesis**

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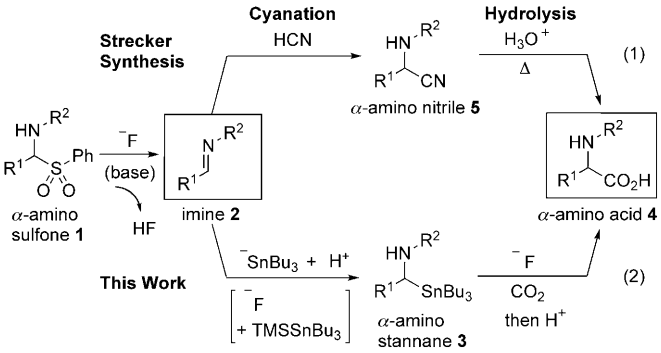
Carbon dioxide is an abundant and inexpensive carbon source (C1 unit); however, its inertness and gaseous character sometimes hamper its use for efficient C–C bond-forming reactions in organic synthesis. To overcome this problem, strongly nucleophilic organometallic regents, such as RLi and RMgX, are often used for C–C bond construction that incorporates CO_2.[1] Recently, transition-metal-promoted CO_2 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 CO_2 and an sp^3-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 a 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 H_2SO_4 at a high temperature. Replacement of cyanide by CO_2 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 CO_2 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 CO_2 after metal exchange with Sn.[12]



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

Our α-amino acid synthesis from imine **2** and CO_2 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 $TMSSnBu_3$[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 sp^3-hybridized carbon atom, thus leading to a C–C bond-forming process with CO_2 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 CO_2 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 CO_2 (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 CO_2. 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 CO_2 (Table 1, entries 5–7). When

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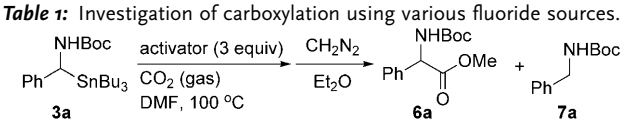
Table 1: Investigation of carboxylation using various fluoride sources.

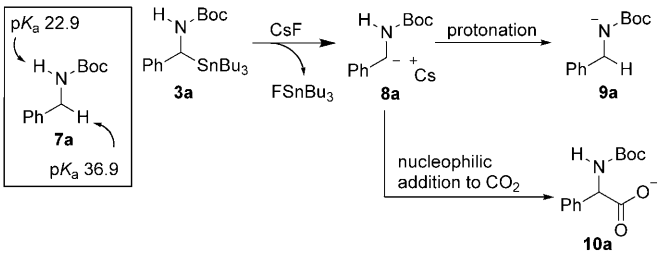


Entry	Activator	CO_2 [MPa]	t [h]	Yield [%][a]		
				6a	**7a**	**3a**
1	LiF	0.1 (1 atm)	12	–	2	98
2	NaF	0.1	12	–	3	97
3	KF	0.1	12	10	9	59
4	KF + [18]crown-6	0.1	12	22	30	15
5[b]	CsF	0.1	3	62 (60)	21	7
6[b]	CsF	0.5	3	84 (71)	2	4
7[b]	CsF	1	3	86 (75)	<1	–
8[b]	TBAT	1	3	49	1	10

[a] Yields were determined by using ^{1}H 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 CO_2, 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).

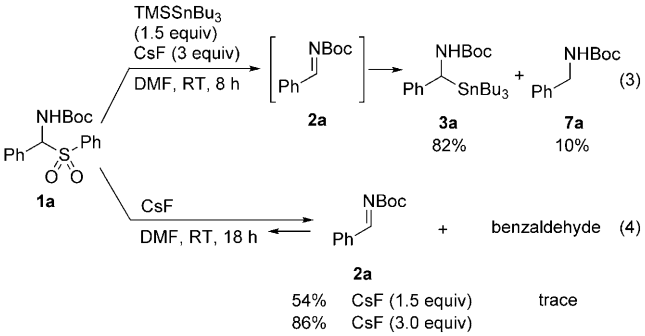
A reasonable mechanism for the formation of **7a** is shown in Scheme 2. Based on calculated pK_a values in DMSO for *N*-Boc-protected benzyl amine **7a**,[17] its amide N–H moiety is expected to be 14 orders of magnitude more acidic than its



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 CO_2. At higher CO_2 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



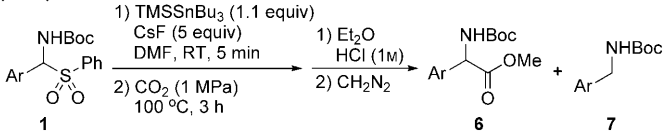
Scheme 3. Investigation of stannylation. DMF = *N*,*N*-dimethylformamide.

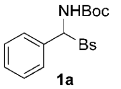
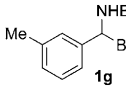
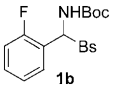
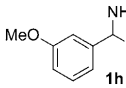
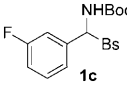
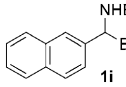
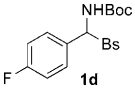
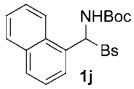
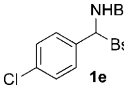
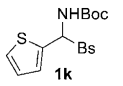
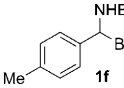
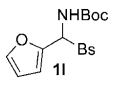
the inherent instability of imine **2**. Direct stannylation of **1a** was effected by $TMSSnBu_3$[14] in the presence of CsF and afforded α-amino stannane **3a** in 82% yield along with protiodestannylation product **7a** in 10% yield at room temperature [Eq. (3), Scheme 3]. In the absence of $TMSSnBu_3$, 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 $TMSSnBu_3$ 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 CO_2 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 CO_2 gas as a carbon source. This reaction was made possible by the reagent combination of $TMSSnBu_3$ 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.



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

[a] Yields were determined by using ^{1}H 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-animo sulfones, as well as asymmetric variants of this transformation are currently underway.

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[1] For selected examples of carboxylation of alkyl lithium species to produce α-amino acids, see: a) G. Katsoulos, M. Schlosser, *Tetrahedron Lett.* **1993**, *34*, 6263–6264; b) Y. S. Park, P. Beak, *J. Org. Chem.* **1997**, *62*, 1574–1575; c) V. Coeffard, I. Beaudet, M. Evain, E. L. Grognec, J.-P. Quintard, *Eur. J. Org. Chem.* **2008**, 3344–3351; d) D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260–7261.

[2] For recent reviews, see: a) T. Sakakura, J.-C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365–2387; b) M. Mori, *Eur. J. Org. Chem.* **2007**, 4981–4993; c) A. Correa, R. Martín, *Angew. Chem.* **2009**, *121*, 6317–6320; *Angew. Chem. Int. Ed.* **2009**, *48*, 6201–6204.

[3] Transition-metal-catalyzed carboxylations of C–Sn and C–B bonds, for Sn: a) M. Shi, K. M. Nicholas, *J. Am. Chem. Soc.* **1997**, *119*, 5057–5058; b) R. Johansson, O. F. Wendt, *Dalton Trans.* **2007**, 488–492; for boron: c) K. Ukai, M. Aoki, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2006**, *128*, 8706–8707; d) J. Takaya, S. Tadami, K. Ukai, N. Iwasawa, *Org. Lett.* **2008**, *10*, 2697–2700; e) T. Ohishi, M. Nishiura, Z. Hou, *Angew. Chem.* **2008**, *120*, 5876–5879; *Angew. Chem. Int. Ed.* **2008**, *47*, 5792–5795.

[4] For recent direct carboxylations of heteroaromatic C–H bonds, see: a) I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858–8859; b) O. Vechorkin, N. Hirt, X. Hu, *Org. Lett.* **2010**, *12*, 3567–3569; c) L. Zhang, J. Cheng, T. Ohishi, Z. Hou, *Angew. Chem.* **2010**, *122*, 8852–8855; *Angew. Chem. Int. Ed.* **2010**, *49*, 8670–8673; d) I. I. F. Boogaerts, G. C. Fortman, M. R. L. Furst, C. S. J. Cazin, S. P. Nolan, *Angew. Chem.* **2010**, *122*, 8856–8859; *Angew. Chem. Int. Ed.* **2010**, *49*, 8674–8677.

[5] a) K. Shimizu, M. Takimoto, Y. Sato, M. Mori, *Org. Lett.* **2005**, *7*, 195–197; b) M. Takimoto, T. Mizuno, Y. Sato, M. Mori, *Tetrahedron Lett.* **2005**, *46*, 5173–5176; c) K. Shimizu, M. Takimoto, M. Mori, Y. Sato, *Synlett* **2006**, 3182–3184; d) M. Takimoto, T. Mizuno, M. Mori, Y. Sato, *Tetrahedron* **2006**, *62*, 7589–7597; e) K. Shimizu, M. Takimoto, Y. Sato, M. Mori, *J. Organomet. Chem.* **2006**, *691*, 5466–5475.

[6] For recent advances in carboxylation of alkyl zinc reagents under mild conditions, see: a) C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 7826–7827; b) H. Ochiai, M. Jang, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 2681–2683; c) K. Kobayashi, Y. Kondo, *Org. Lett.* **2009**, *11*, 2035–2037; d) A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem.* **2010**, *122*, 4769–4773; *Angew. Chem. Int. Ed.* **2010**, *49*, 4665–4668.

[7] A. Strecker, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–45.

[8] A number of catalytic asymmetric Strecker reactions have also been reported, see: M. Shibasaki, M. Kanai, T. Mita in *Organic Reactions, Vol. 70* (Ed.: L. E. Overman), Wiley, New York, **2008**, pp. 1–119; for a recent excellent example of catalytic asymmetric Strecker reaction for preparing chiral *N*-Boc-α-amino acids, see: S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968–971.

[9] For reviews on umpolung of amine reactivity, see: a) D. Seebach, D. Enders, *Angew. Chem.* **1975**, *87*, 1–18; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 15–32; b) P. Beak, D. B. Reitz, *Chem. Rev.* **1978**, *78*, 275–316.

[10] a) M. Mori, N. Isono, N. Kaneta, M. Shibasaki, *J. Org. Chem.* **1993**, *58*, 2972–2976; b) T. Honda, M. Mori, *Chem. Lett.* **1994**, 1013–1016; c) A. Kinoshita, M. Mori, *Chem. Lett.* **1994**, 1475–1478.

[11] Conventional methods for the preparation of α-amino stannanes from imines using either $LiSnBu_3$ or $Et_2ZnLiSnBu_3$ as a nucleophile, see: a) K. W. Kells, J. M. Chong, *Org. Lett.* **2003**, *5*, 4215–4218; b) K. W. Kells, J. M. Chong, *J. Am. Chem. Soc.* **2004**, *126*, 15666–15667; c) A. He, J. R. Falck, *Angew. Chem.* **2008**, *120*, 6688–6691; *Angew. Chem. Int. Ed.* **2008**, *47*, 6586–6589.

[12] Tin/lithium exchange of *N*-Boc-*N*-(*p*-methoxyphenyl)-α-(tributylstannyl)benzylamine proceeded by treatment of *n*BuLi in the

presence of (−)-sparteine to generate lithium carbanions, which then reacted with CO_2 to afford α-phenyl glycine derivatives, see Ref. [1b].
[13] a) A. M. Kanazawa, J.-N. Denis, A. E. Greene, *J. Org. Chem.* **1994**, *59*, 1238 – 1240; b) T. Mecozzi, M. Petrini, *J. Org. Chem.* **1999**, *64*, 8970 – 8972; c) J.-N. Desrosiers, A. Côté, A. A. Boezio, A. B. Charette, *Org. Synth.* **2006**, *83*, 5 – 17.
[14] Commercially available from Aldrich. For its application to organic synthesis, see Ref. [10].
[15] $TMSSnBu_3$ reacts with an aldehyde in the presence of CsF–CsOH. See: J. Busch-Petersen, Y. Bo, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 2065 – 2068.
[16] 10% K_2CO_3/silica gel was employed as a stationary phase on column chromatography to remove organotin residues, see: D. C. Harrowven, D. P. Curran, S. L. Kostiuk, I. L. Wallis-Guy, S. Whiting, K. J. Stenning, B. Tang, E. Packard, L. Nanson, *Chem. Commun.* **2010**, *46*, 6335 – 6337.
[17] Calculations were performed on Jaguar 7.7 at the B3LYP/6-31G + (d,p) level. See the Supporting Information for details.
[18] Without CO_2, the protonation proceeded selectively. We also considered the possibility that pentacoordinated fluorostannylate species react with CO_2 directly without the generation of the naked cesium carbanion.
[19] For direct stannylations from α-amino sulfones, see: a) D. MacLeod, P. Quayle, G. M. Davies, *Tetrahedron Lett.* **1990**, *31*, 4927 – 4930; b) W. H. Pearson, A. C. Lindbeck, J. W. Kampf, *J. Am. Chem. Soc.* **1993**, *115*, 2622 – 2636.
[20] Electron-rich substrates which destabilize benzylic carbanions gave worse results. For example, *p*-OMe and *o*-OMe phenyl glycines were obtained in 10% and 41% yields, respectively, while the yield of *m*-OMe phenyl glycine was 88% (Table 2, entry 9).

