CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201202332

One-Step Synthesis of Racemic α-Amino Acids from Aldehydes, Amine Components, and Gaseous CO_2 by the Aid of a Bismetal Reagent

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Abstract: α-Amino acids are essential resources for human life and are highly useful as building blocks for organic synthesis. The core framework of an α-amino acid can be divided into three basic components: an aldehyde, an amine, and carbon dioxide (CO_2). We report herein that a one-step synthesis of α-amino acids has been successfully achieved from these three basic and inexpensive chemicals with a single operation, in which the mixture of an aldehyde, a sulfonamide, and gaseous CO_2 was heated at 100 °C in the presence of Bu_3Sn-$SnBu_3$ and CsF. In this one-pot sequential protocol, two important intermediates (imine and α-amino stannane) are involved and the stannyl anion generated in situ plays a crucial role, particularly for the efficient stannylation of the imine in the presence of proton sources and for promoting retrostannylation of the undesired α-alkoxy stannane owing to its high stability and tolerance of the presence of proton sources. This methodology enabled the synthesis of a wide range of racemic arylglycine derivatives in high yields.

Keywords: aldehydes · amino acids · carbon dioxide · C–C bond formation · umpolung

Introduction

α-Amino acids and their derivatives are essential resources for human life and are very useful for organic synthesis as building blocks. The practical syntheses of α-amino acids have been seen in dozens of pieces of literature.[1] The key steps of these transformations can be majorly classified into 1) hydrogenation of dehydroamino acid derivatives,[1a,c,d,h] 2) elongation of the side chain of glycine-derived skeletons through C–C bond formation (e.g., Michael addition and alkylation, etc.),[1b,c,e–h] 3) Nucleophilic substitutions of imino esters,[1c,e,g,h] and 4) α-amination of carboxylic acid derivatives.[1b,c,g,h] Although some of these methodologies were established in respect of operational convenience[2] in addition to high efficiency,[3] they still require multistep sequences for the preparation of the specific substrates from commercially available materials and/or for the conversion into the desired amino acids after the key step. On the other hand, the classical Strecker α-amino acid synthesis[1b,c,e,h] needs only a two-step sequence from simple starting materials: cyanation of imines derived from aldehydes and amines in situ followed by hydrolysis of α-amino nitriles.[4] However, there is still a disadvantage regarding the intolerability of acid-sensitive functional groups because strongly acidic conditions are often required in the final nitrile hydrolysis. Another well-known method for the synthesis of α-amino acid derivatives (dipeptides) from simple components is the Ugi four-component coupling reaction.[5] Nevertheless, isocyanides, components in this reaction, have to be prepared in advance from the corresponding amines by multistep operations (formylation followed by dehydration).

Our research group has already reported a novel one-pot synthesis of α-amino acids from imine precursors, *N*-Boc-α-amino sulfones (Boc = *tert*-butoxycarbonyl), by using TMS-$SnBu_3$ (TMS = trimethylsilyl) and CsF.[6] This process is efficient and fascinating because three independent reactions (imine formation, stannylation, and carboxylation) proceed sequentially in a specific order in the same flask and CsF plays a different role for each step (base to facilitate imine formation, silicon activator to generate the stannyl anion, and stannane activator to generate a fluorostannate or carbanion). Nevertheless, substrate α-amino sulfones should be prepared in advance from aldehydes, sodium sulfinates, and *N*-Boc carbamates.[7] If aldehydes could be used directly for this synthesis without any treatment, it would be more elegant and practical. In principle, an α-amino acid can be divided into three simple and commercially available components, an aldehyde, an amine component, and a CO_2 unit (Scheme 1). CO_2 is thought to be a primitive and sustainable C1 source, the fixations of which have been intensively studied by organic chemists due to its ubiquitous, inexpensive, and renewable properties.[8] To the best of our knowledge, one-step chemical synthesis of α-amino acids from simple and commercially available materials through CO_2 incorporation has not been reported, and we therefore considered the possibility that those three chemicals can be combined with a single operation, with the aid of a stannyl anion, to synthesize α-amino acids.

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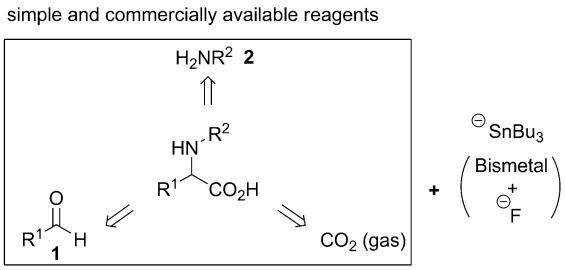
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202332.

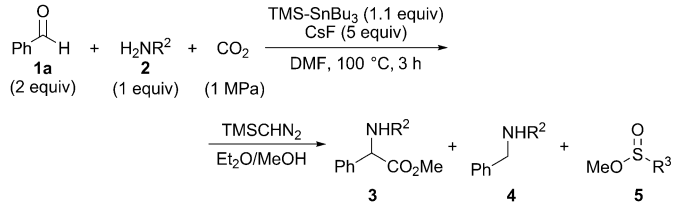


Scheme 1. Division into three simple components in an α-amino acid structure.

Results and Discussion

First, we investigated the effect of amine components for the synthesis of α-phenyl α-amino acid (phenylglycine; Table 1). All reactions were carried out in the presence of two equivalents of benzaldehyde (**1a**), one equivalent of amine component **2**, and 1.1 equivalents of TMS-$SnBu_3$ under 1 MPa (10 atm) of CO_2 pressure. Yields of the corresponding carboxylic acids were determined after methyl esterification with $TMSCHN_2$. Although Boc and Cbz (Cbz = carbobenzyloxy) carbamates (**2a** and **2b**) did not promote the desired one-pot reaction efficiently (Table 1, entries 1 and 2), sulfonamide derivatives **2c**–**h**, except **2f**, exhibited moderate reactivities, in which electron-rich substitutions (Ts, *para*-methoxybenzenesulfonyl) enhanced the formation of amino acids (Table 1, entries 4 and 5), whereas electron-withdrawing nosyl amide **2f** did not provide any products, probably due to retardation of the condensation between benzaldehyde (**1a**) and the amide **2f** (Table 1, entry 6). Alkyl-substituted sulfonamides (**2g** and **2h**) also displayed similar reactivities (Table 1, entries 7 and 8). For the use of sulfonamides as substrates, protonated compound **4** and sulfinyl ester **5** were produced, the latter of which was thought to be generated by elimination of the sulfonyl group followed by methyl esterification (Table 1, entries 3–5). Since eliminated products **5** derived from **2g** and **2h** are, however, low-boiling-point materials, the usual workup and evaporation sequence resulted in their elimination from the reaction mixture (Table 1, entries 7 and 8). Other primary amides and amines, such as diphenyl phosphinamide, diethyl phosphoramidate, *tert*-butylsulfinamide, acetamide, benzyl amine, allyl amine, and aniline did not promote the desired reaction at all, but benzaldehyde starting material **1a** and/or the corresponding imine were recovered.

Table 1. Amide screening.

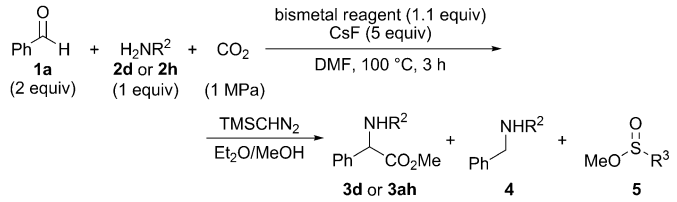


Entry	Amide (R^2)		Yield [%][a]		
			3	**4**	**5**
1	−Boc	**2a**	13	3	–
2	−Cbz	**2b**	6	5	–
3	$-SO_2C_6H_5$ (Bs)	**2c**	33	28	21
4	$-SO_2C_6H_4$*p*-Me (Ts)	**2d**	37	32	25
5	$-SO_2C_6H_4$*p*-OMe	**2e**	40	20	22
6	$-SO_2C_6H_4$*p*-NO_2	**2f**	–	–	–
7	$-SO_2$Me (Ms)	**2g**	36	13	–[b]
8	$-SO_2t$Bu (Bus)	**2h**	40	22	–[b]

[a] Yields were determined by ^{1}H NMR spectroscopic analysis by using 1,1,2,2-tetrachloroethane as an internal standard. [b] Low-boiling-point materials.

Given that sulfonamides are suitable for this reaction, several silylstannanes with different sizes of silicone moieties, such as TES-$SnBu_3$ (TES = triethylsilyl), TIPS-$SnBu_3$ (TIPS = triisopropylsilyl), and TBS-$SnBu_3$ (TBS = *tert*-butyldimethylsilyl), were prepared and subjected to the reaction with *para*-toluenesulfonamide (**2d**; Table 2, entries 1–4). In response to the steric bulk of the silyl groups, higher yields of α-amino acid **3** were observed, with a decrease in the amount of the protonated compound **4**. Eventually, the use of Bu_3Sn–$SnBu_3$ gave the highest yield along with a small amount of protonated compound **4** (Table 2, entry 5). Furthermore, when *tert*-butylsulfonamide (**2h**) was used instead of **2d**, the yield of α-amino acid **3** slightly increased to 64% (Table 2, entry 6). Finally, by changing the ratio of equivalents for each component to **1a**/**2h**/Bu_3Sn–$SnBu_3$ = 1:1.5:1.5, the yield was further increased to 74% (Table 2, entry 7).[9]

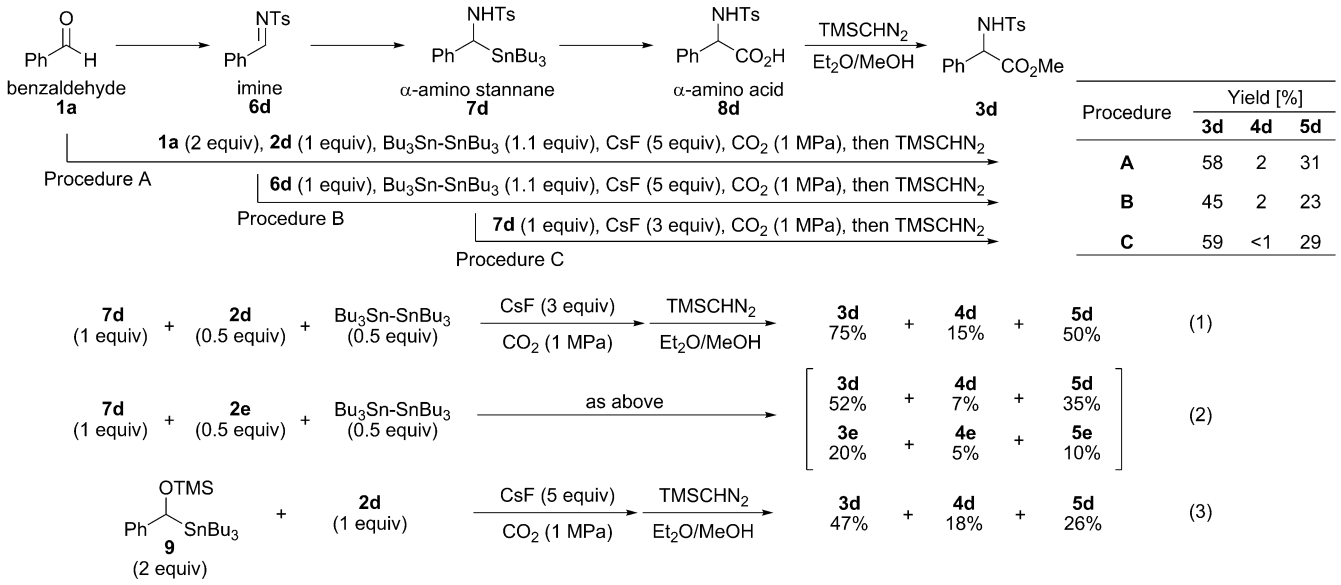
Table 2. Bismetal screening.



Entry	Bismetal	Amide	Yield [%][a]		
			3	**4**	**5**
1	TMS−$SnBu_3$	**2d** (R^3 = Tol)[b]	37	32	25
2	TES−$SnBu_3$	**2d**	39	24	26
3	TIPS−$SnBu_3$	**2d**	49	16	26
4	TBS−$SnBu_3$	**2d**	51	6	33
5	Bu_3Sn−$SnBu_3$	**2d**	58	2	31
6	Bu_3Sn−$SnBu_3$	**2h** (R^3 = *t*Bu)	64	3	–[c]
7[d]	Bu_3Sn−$SnBu_3$	**2h**	74	6	–[c]

[a] Yields were determined by ^{1}H NMR spectroscopic analysis by using 1,1,2,2-tetrachloroethane as an internal standard. Each yield was calculated on the basis of amide **2**. [b] Tol = tolyl. [c] A low-boiling-point material. [d] 1 Equivalent of benzaldehyde (**1a**), 1.5 equivalents of amide **2h**, and 1.5 equivalents of tin reagent were used and yields were calculated on the basis of benzaldehyde (**1a**).

Based on the results of our previous study,[6] we speculated that the reaction proceeded via imine **6** and α-amino stannane **7**. To confirm this hypothesis, Ts-protected intermediates (**6d** and **7d**) were prepared independently from



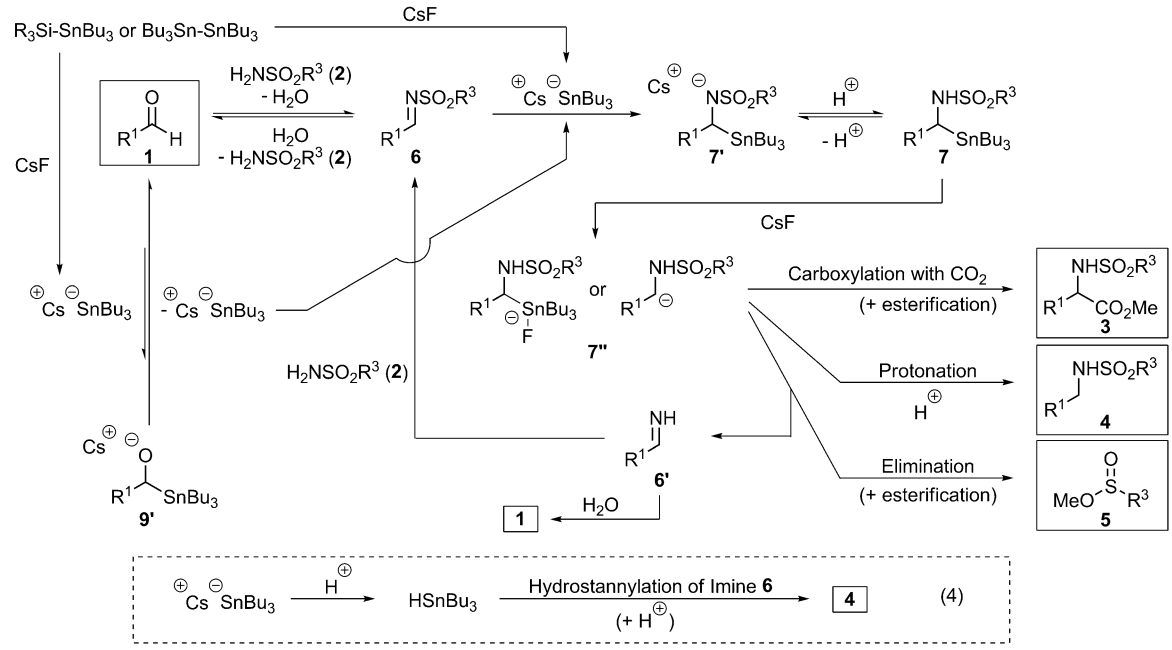
Procedure	Yield [%]		
	3d	4d	5d
A	58	2	31
B	45	2	23
C	59	<1	29

Scheme 2. Elucidation of reaction intermediates in the one-step α-amino acid synthesis. All reactions described above were conducted in autoclaves filled with CO_2 (1 MPa) in DMF at 100 °C for 3 h. Yields were determined by ^{1}H NMR spectroscopic analysis by using 1,1,2,2-tetrachloroethane as an internal standard.

benzaldehyde (**1a**) and *para*-toluenesulfonamide (**2d**) and subjected to the reactions indicated in Scheme 2 (procedures B and C). Even when the reactions were commenced at different stages, the target α-amino acid derivative **3d** could be obtained. However, the yield of each product (**3d**, **4d**, and **5d**) was slightly different depending on the starting material employed. When using imine **6d**, which is inherently unstable under these fluoride-mediated conditions,[6,10] the yield of **3d** decreased to 45% and **4d** and **5d** were obtained in 2 and 23% yields, respectively, probably because slight imine decomposition occurred to produce benzaldehyde (**1a**; procedure B, Scheme 2). By comparison with procedure A, almost the same distributions were observed when the reaction began with α-amino stannane **7d** by using CsF (procedure C; **3d**: 59; **4d**: <1; **5d**: 29%). These experimental results strongly suggested that this one-step reaction actually proceeded through the proposed pathway, but a high concentration of imine **6d** at one time gave the worse result (procedure B). Next, to clarify the reason why the modified reagent ratio (aldehyde **1**/amide **2**/Bu_3Sn–$SnBu_3$ = 1:1.5:1.5) resulted in higher yields, carboxylation of intermediate **7d** was performed in the presence of extra amide **2d** and Bu_3Sn–$SnBu_3$ [0.5 equiv each; Scheme 2, Eq. (1)]. As a result, **3d** was obtained in 75% yield with respect to **7d**, along with **4d** and **5d** in 15 and 50% yields, respectively. The increase in total yield with respect to **7d** to 140% was probably due to transformation of extra **2d** into **3d**, **4d**, and **5d** during the reaction. Furthermore, carboxylation of **7d** was conducted in the presence of a different amide, such as *para*-methoxybenzensulfonamide (**2e**), leading to the incorporation of these two sulfonyl groups onto the product [Scheme 2, Eq. (2)]. This scrambling phenomenon strongly indicated that there should be a step for the regeneration of imine **6** during this sequential process (vide infra): *N*-methoxybenzensulfonyl imine **6e** was considered to be generated after elimination of the *para*-toluenesulfonyl group.

We also used α-silyloxy stannane **9** as a potential source for producing the stannyl anion. It is known that silylstannnaes are reacted easily with aldehydes in the presence of an activator (cyanide, fluoride, or N-heterocyclic carbene) to afford α-silyloxy stannane even below room temperature.[11] This process seems to be much faster than imine formation from the aldehyde and sulfonamide, which usually requires azeotropic dehydration in the presence of a Lewis acid at a high temperature.[12] If retrostannylation is more favorable than stannylation of an aldehyde, the stannyl anion would be regenerated. Therefore, the reaction of **9** was tested in the presence of amide **2d**, CsF, and CO_2 [Scheme 2, Eq. (3)], thus affording the desired amino acid **3d** in 47% yield, which strongly indicated that after the generation of cesium alkoxide, retrostannylation[13] occurred to produce benzaldehyde **1a** and a stannyl anion that kept silent during imine formation and then reacted with imine **6d** as soon as it was generated (maintaining a low concentration of the imine).

Based on the above-described experimental results, plausible reaction pathways are proposed (Scheme 3).[14] Imine **6** would be generated by the condensation of aldehyde **1** with primary sulfonamide **2**, which is stannylated by the stannyl anion generated from a bismetal and CsF. Imine formation is a slow equilibrium because of the low nucleophilicity of the nitrogen atom attached to a strongly electron-withdrawing sulfonyl group. However, since the corresponding amide anion **7′** would be stabilized by the sulfonyl substitution, the stannylation of an imine might be irreversible and the equilibrium of imine formation eventually shifts in favor of

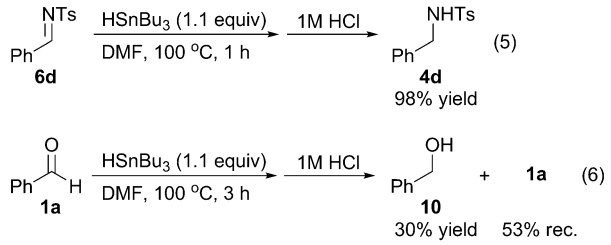


Scheme 3. Entire reaction processes for the one-step synthesis of α-amino acids from aldehyde **1**, sulfonamide **2**, and CO_2 gas in the presence of a bismetal reagent.

imine **6**. After the protonation of amide anion **7′**, either hypercoordinate stannate or carbanion species **7″**[6,13] would be generated by the attack of a fluoride anion, which exhibits nucleophilic character at the α-position of amines (umpolung reactivity[15]). Then this species undergoes the desired carboxylation to afford α-amino acid **3** by nucleophilic addition to CO_2. At the same time, the undesired protodestannylation caused by proton sources, such as sulfonamide **2** and H_2O, generated during imine formation, as well as elimination of the sulfony group, somewhat proceeds to afford benzyl amine derivative **4** and sulfinic acid **5**, respectively. During the elimination step, NH-imine **6′** is generated, and part of it might be hydrolyzed to aldehyde **1**. Both **6′** and the regenerated **1** could react with sulfonamide **2** to reproduce *N*-sulfonyl imine **6** to participate in the reaction sequence. Meanwhile, the stannyl anion can react with aldehyde **1**.[11] However, although α-alkoxy stannane **9′** is generated, retrostannylation would be favorable [Scheme 2, Eq. (3)]. Therefore, aldehyde **1** and the stannyl anion are regenerated, the latter of which should be consumed for stannylation of imines. When other bismetal reagents, such as Si–B and Si–Si were employed for the purpose of the generation of the silyl anion, both benzyl alcohol and pinacol derivatives were observed as major products,[9] which indicates that the silylation of aldehyde **1** actually proceeded, but the desilylation by fluoride was much faster than the retrosilylation. It is notable that this α-amino acid synthesis takes advantage of the properties of the stannyl anion being relatively stable in the presence of proton sources, leading to the enhancement of retrostannylation from the undesired α-alkoxy stannane **9′**. The reported pK_a values of $HSnMe_3$ in DMSO and $HSnBu_3$ in 1,2-dimethoxyethane were 23.4 and 25.0, respectively,[16] which support the proposed stability of the stannyl anion, especially towards H_2O generated during imine formation (H_2O: pK_a = 32.0 in DMSO; $MsNH_2$ (**2g**): pK_a = 17.5 in DMSO).

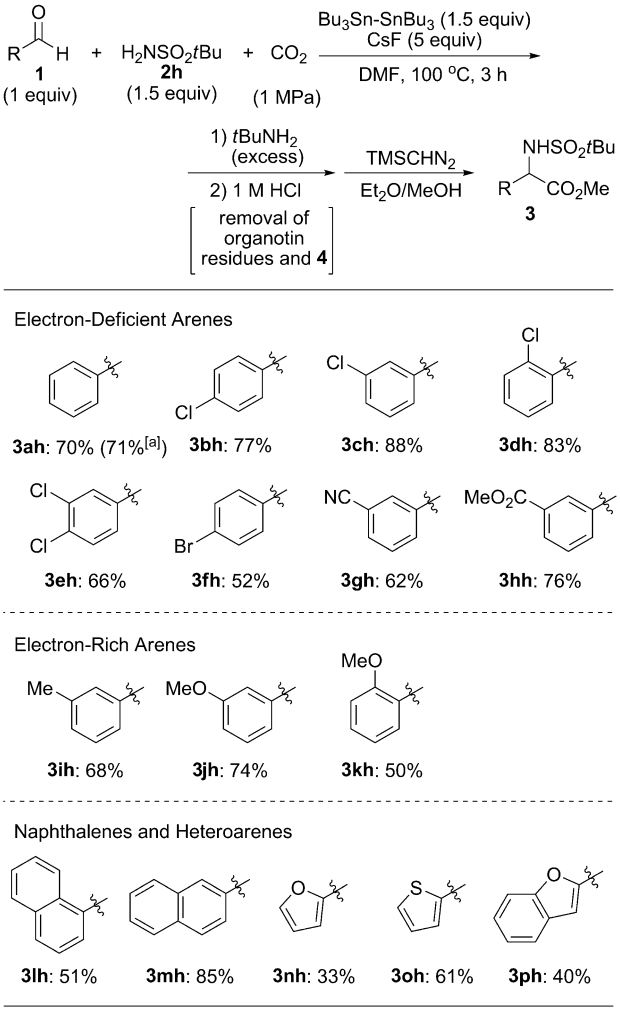
The decrease in the yield of the benzylamine derivative **4** in response to the steric bulk of the silicone moiety (Table 2) might be attributed to the speed of generation of the stannyl anion. If stannyl anion formation is fast in the case of sterically smaller silylstannanes, the stannyl anion can be partly protonated during slow imine formation, producing $HSnBu_3$, which might reduce sulfonyl imine **6** to afford **4** through hydrostannylation [Scheme 3, Eq. (4)]. On the other hand, when the formation of the stannyl anion is slow and it is gradually produced in the case of sterically bulkier silylstannanes and ditin reagents, the generated stannyl anion would be adjusted to react with imine **6** before its protonation. We consider that **4** could be generated through two pathways (protodestannylation of **7**[6,13] and hydrostannylation of **6**) and that the hydrostannylation is the main pathway when using sterically smaller silylstannanes that are more susceptible to a fluoride source. To confirm this hypothesis, **6d** and **1a** were treated with commercially available $HSnBu_3$ in DMF at 100 °C (Scheme 4). As a result, without any activators or catalysts, hydrostannylation of **6d** was completed within 1 h to afford **4d** in 98% yield [Scheme 4, Eq. (5)]. However, the reaction of **1a** with $HSnBu_3$ was slower and benzyl alcohol (**10**) was obtained in only 30% yield even after 3 h [Scheme 4, Eq. (6)]. The results of this study indicate the possibility that $HSnBu_3$ generated in situ can reduce imine **6** efficiently and preferentially.

Next, under the optimal conditions, substrate scope was examined by using the optimal amide **2h** (Scheme 5). To



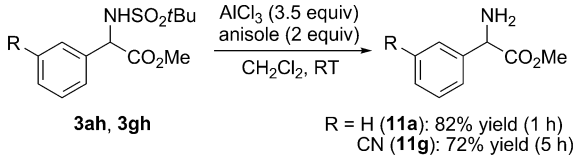
Scheme 4. Hydrostannylation reactions of imine **6d** and benzaldehyde (**1a**).

remove organotin residues and neutral compound **4**, the crude mixture was treated with an excess amount of tBuNH$_2$ to convert it into its stable tBuNH$_3$ salt.[3] After fine solids had been washed with hexane to completely remove those materials,[13] pure methyl *N*-sulfonylamino carboxylates **3** could be obtained through acid treatment followed by methyl esterification with TMSCHN$_2$. A variety of aldehydes possessing electron-withdrawing groups on the aromatic ring (**1a–h**) were applicable and afforded the corresponding α-amino acid derivatives **3** in up to 88% yield. It is noteworthy that cyano functionality, which is not tolerated under the conventional Strecker synthesis, remained intact in this sequence (**3gh**). In addition, the ester moiety could survive even though the stannyl anion was generated in situ (**3hh**).[10] Moreover, aldehydes possessing electron-rich arenes (**1i–k**) were also suitable candidates. Both 1- and 2-naphthaldehydes (**1l** and **1m**), as well as heteroaromatic aldehydes possessing 2-furyl, 2-thienyl, and 2-benzofuryl groups (**1n–p**), were all active under these conditions. A larger-scale reaction (1 mmol scale) proceeded without any problems, giving **3ah** with an identical yield (71%). Although these amino acids were obtained as the racemic form and only limited to arylglycine derivatives,[17] it is noteworthy that only a single operation enables their syntheses with high efficiency.



Scheme 5. Substrate scope for the one-step α-amino acid synthesis from aldehydes **1**, *tert*-butylsulfonamide (**2h**), and CO_2. Yields of the isolated products are shown. All reactions were performed by using 0.1 mmol of **1**. [a] 1 mmol of **1a** was used (10-times larger scale).

Finally, considering the utility of the products, removal of the *tert*-butylsulfonyl group in **3ah** and **3gh** was demonstrated (Scheme 6). By following the Enders' procedure[18] with a different quenching method, the *tert*-butylsulfonyl group was cleaved in the presence of $AlCl_3$ and anisole, affording the corresponding free amines **11a** and **11g** in 82 and 72% yield, respectively. Notably, the free amino ester **11g** possessing a cyano moiety, which cannot be synthesized by the conventional Strecker method, could be accessed by this protocol. The use of *tert*-butylsulfonamide (**2h**) has a great advantage for deprotection of the *tert*-butylsulfonyl group of the product under mild conditions owing to the facile generation of the *tert*-butyl carbocation in the presence of a Lewis acid.



Scheme 6. Removal of the *tert*-butylsulfonyl group.

Conclusion

We have developed a one-step convergent synthesis of α-amino acids from aldehydes, sulfonamides, and gaseous CO_2. This new method is quite efficient and the corresponding α-amino acids were obtained in moderate-to-high yields with a single operation (up to 88% yield). This sequential reaction proceeds via two intermediates, an imine and an α-amino stannane. The use of a stannyl anion is key because it is relatively stable against proton sources such as sulfonamides and H_2O that exist in the reaction and because it facilitates the retrostannylation of the undesired α-alkoxy stannanes. This novel method proposes a new strategy for

the synthesis of α-amino acids from simple and commercially available materials with a single operation.

Experimental Section

Preparative scale (1 mmol) procedure for the one-step synthesis of 3 ah: Dry CsF (760 mg, 5.0 mmol, 5 equiv), which was preheated for 10 min by a heat gun under vacuum before use (<5 mm Hg at ca. 400 °C), was quickly mixed with *tert*-butylsulfonamide (**2 h**; 206 mg, 1.5 mmol, 1.5 equiv). After addition of dry DMF (3.0 mL), benzaldehyde (**1 a**; 102 μL, 1.0 mmol) was added, followed by hexabutylditin (758 μL, 1.5 mmol, 1.5 equiv). The mixture was placed inside an autoclave and sealed tightly. CO_2 gas was introduced into the autoclave (1 MPa), which was heated at 100 °C for 5 h. After the mixture had cooled to room temperature, water and Et_2O were added, and the pH of the mixture was adjusted to 2 by using 1 M HCl. The organic layer was extracted with Et_2O, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was diluted with Et_2O (ca. 2 mL) followed by treatment with an excess of *tert*-butylamine (ca. 500 μL). After 20 min, hexane was added, and the resultant solids were filtrated and washed with hexane. The solids were placed into water followed by addition of AcOEt, and the pH of the mixture was adjusted to 2 by using 1 M HCl. The organic layer was extracted with AcOEt and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was diluted with Et_2O/MeOH = 4:1 (ca. 4 mL) followed by treatment with $TMSCHN_2$ (2 M in Et_2O). After 1 h, the mixture was directly concentrated under high vacuum to afford the crude product. The crude product was then purified by silica gel column chromatography (hexane/AcOEt, 3:1), affording methyl 2-(1,1-dimethylethylsulfonamido)-2-phenylacetate (**3 ah**; 203 mg, 0.71 mmol) in 71 % yield as a white solid.

Removal of the *tert*-butylsulfonyl group: In a drying tube, the α-amino acid derivative **3 ah** (57.1 mg, 0.20 mmol) was dissolved in dry dichloromethane (5.0 mL). Anisole (45.3 μL. 0.40 mmol, 2.0 equiv) and aluminum chloride (93.3 mg, 0.70 mmol, 3.5 equiv) were added successively in one portion to the reaction mixture. After stirring for 1 h at room temperature, the resulting yellow solution was diluted with dichloromethane (16 mL) and 30 % ammonia solution (14 mL). The organic layer was extracted six times with dichloromethane. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was then purified by silica gel column chromatography (dichloromethane-MeOH, 97:3), affording methyl 2-amino-2-phenylacetate (**11 a**; 27.1 mg, 0.16 mmol) in 82 % yield as a yellow oil.

Acknowledgements

This work was financially supported by Grants-in-Aid for Young Scientists (B; no. 24750081) and for Scientific Research (B) (no. 23390001) from the Japan Society for the Promotion of Science (JSPS), by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis (no. 23105501)" from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by the Uehara Memorial Foundation.

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Received: June 30, 2012
Revised: October 2, 2012
Published online: November 26, 2012

