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One-Pot Synthesis of α-Amino Acids from CO_2 Using a Bismetal Reagent with Si—B Bond

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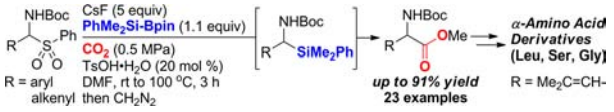
ABSTRACT



In the presence of 1.1 equiv of $PhMe_2Si$-Bpin, 5 equiv of CsF, and 20 mol % of $TsOH \cdot H_2O$, precursors of *N*-Boc-imines can be converted into the corresponding α-aryl or α-alkenyl glycine derivatives under gaseous CO_2 in moderate-to-high yields with a single operation. α-Isobutenyl glycine thus obtained can be further derivatized into various types of α-amino acids including *N*-Boc-leucine, serine, and glycine derivatives in short steps.

α-Amino acids are core molecules exhibiting various functions in bio- and organic chemistry. It is well-known that α-amino acids are critical to life as building blocks of peptides, proteins, and many natural products. Therefore, many practical methods have been developed for the synthesis of chiral/racemic amino acids.[1] However, amino acid synthesis through α-carboxylation of amine derivatives with CO_2 was only achieved by using a strongly basic reagent such as BuLi at a very low temperature.[1g] As part of our ongoing research program aimed at utilization of CO_2 gas, a ubiquitous, inexpensive, and sustainable C1 feedstock, for organic synthesis,[2] we are interested in the synthesis of α-amino acids through CO_2 incorporation by a mild and convenient way. In 2011, we reported a one-pot synthesis of arylglycine derivatives from the corresponding imine equivalents (*N*-Boc-α-amido sulfones **1**) using a combination of TMS-$SnBu_3$ and CsF under a CO_2 atmosphere.[3] However, there are several limitations to overcome: (1) a stoichiometric amount of toxic tin waste was generated after the reaction, (2) only α-aryl-substituted α-amido sulfones were applicable, and (3) a high temperature (100 °C) and high pressure (1 MPa = 10 atm) were necessary to induce efficient carboxylation.[4] Thus, we herein disclose that a less toxic and commercially available silylboron such as $PhMe_2Si$-Bpin[5] is also effective for this one-pot process so that the intermediate α-amido silane is more readily activated by CsF than α-amido stannane, leading to a smooth carboxylation at rt to 100 °C under 0.5 MPa (5 atm) of CO_2 pressure. As a result, not only α-aryl but also α-alkenyl α-amido sulfones were tolerated to afford the corresponding α-amino acid derivatives in moderate-to-good yields.

First, we investigated bismetal reagents without a tin element (Table 1). Several potential bismetal reagents[6] such as Si—Si, Si—Ge, B—B, and Si—B were screened in DMF as a solvent (entries 1—5), among which unsymmetrical bismetals, such as Ph_3Si-$SiMe_3$, $PhMe_2Si$-$GeMe_3$,

(1) For representative reviews, see: (a) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (c) Kreuzfeld, H. J.; Döbler, C.; Schmidt, U.; Krause, H. W. *Amino Acids* **1996**, *11*, 269. (d) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (f) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290. (g) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. *Top. Organomet. Chem.* **2003**, *5*, 139. (h) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.

(2) For reviews on CO_2 incorporation reactions, see: (a) Braunstein, P.; Matt, D.; Nobel, D. *Chem. Rev.* **1988**, *88*, 747. (b) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365. (c) Mori, M. *Eur. J. Org. Chem.* **2007**, 4981. (d) Correa, A.; Martín, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6201. (e) Riduan, S. N.; Zhang, Y. *Dalton Trans.* **2010**, *39*, 3347. (f) Boogaerts, I. I. F.; Nolan, S. P. *Chem. Commun.* **2011**, *47*, 3021. (g) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3842. (h) Zhang, Y.; Riduan, S. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6210. (i) Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W. A.; Kühn, F. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8510.

(3) (a) Mita, T.; Chen, J.; Sugawara, M.; Sato, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 1393. (b) Mita, T.; Higuchi, Y.; Sato, Y. *Chem.—Eur. J.*, doi: 10.1002/chem.201202332.

(4) Mita, T.; Sugawara, M.; Hasegawa, H.; Sato, Y. *J. Org. Chem.* **2012**, *77*, 2159.

(5) For a convenient synthesis of $PhMe_2Si$-Bpin, see: Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647.

(6) For a review on bismetal reagents, see: Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320.

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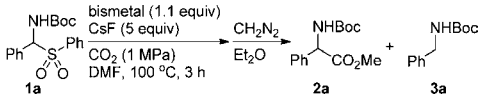
and $PhMe_2Si$-Bpin, somewhat promoted the desired one-pot reaction to afford the corresponding phenyl glycine **2a** in around 10% yield after methyl esterification with CH_2N_2 (for the purpose of determination of yields by ^1H NMR analysis and further purification), accompanied by a trace amount of protodesilylation product **3a**. To induce an efficient silylation of the imine intermediate using $PhMe_2Si$-Bpin,[7] we then examined protic additives such as H_2O, $KF\cdot HF$, $(CF_3)_2CHOH$, 2,6-dimethylphenol, propanoic acid, NH_4Cl, and $TsOH\cdot H_2O$ (entries 6–12). As a result, the use of a catalytic amount of $TsOH\cdot H_2O$ (20 mol %) gave the best yield and **2a** was obtained in 93% yield. Even when the reaction was performed at rt under 0.5 MPa and ambient CO_2 pressure (using a CO_2 balloon), the product was still obtained in 91 and 66% yields, respectively (entries 13 and 14), the trend of which is different from that of carboxylation of *N*-Boc-α-amido stannanes that requires a high temperature (100 °C).[3,4]

In order to elucidate the intermediate of this one-pot sequence, reactions were conducted without CO_2 (Scheme 1). In the presence of 20 mol % of $TsOH\cdot H_2O$, α-amido silane **4a**[8] was obtained in 67% yield, while no reaction occurred in the absence of any protic additives.

In contrast, fluoride-mediated carboxylation of **4a** with CO_2 proceeded smoothly to afford **2a** in excellent yields at rt both under 0.5 MPa and ambient CO_2 even without any protic additives (Table 2, entries 1 and 2).[9] These observations suggested that protic additives only affected the formation of α-amido silane. Notably, the use of both electron-deficient and -rich substrates (**4d** and **4k**) afforded the products in high yields with suppression of formation

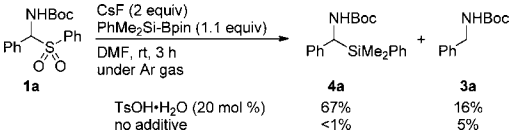
Table 1. Investigation of Bismetals and Protic Additives



			yield (%)[a]	
entry	bismetal reagent	additive (20 mol %)	**2a**	**3a**
1	Me_3Si-$SiMe_3$	–	–	–
2	Ph_3Si-$SiMe_3$	–	11	4
3	$PhMe_2Si$-$GeMe_3$	–	16	1
4	pinB-Bpin	–	–	–
5	$PhMe_2Si$-Bpin	–	10	<1
6		H_2O	10	2
7		$KF\cdot HF$	13	2
8		$(CF_3)_2CHOH$	8	1
9		2,6-dimethylphenol	13	2
10		$C_2H_5CO_2H$	25	2
11		NH_4Cl	53	2
12		$TsOH\cdot H_2O$	93	3
13[b]		$TsOH\cdot H_2O$	91	2
14[c]		$TsOH\cdot H_2O$	66	5

[a] Yields were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [b] The reaction was performed at rt under 0.5 MPa of CO_2. [c] The reaction was performed at rt under ambient CO_2 pressure (0.1 MPa).

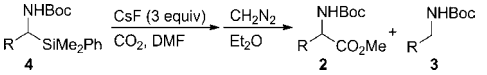
Scheme 1. Isolation of α-Amido Silane **4a**



of protodesilylation product **3** (entries 3 and 4), indicating that the electronic effect on the aromatic ring is not so critical for the yields of carboxylation of α-amido silanes in contrast to our previous system using α-amido stannanes.[4] Furthermore, less reactive α-alkenyl substrate **4s** was also compatible when the reaction was conducted at 100 °C (entries 5 and 6).

On the basis of these experimental results, the whole reaction pathway of this one-pot process is proposed below (Figure 1). Since a higher level of conversion was guaranteed at 100 °C (> 74%) with at least 3 equiv of CsF (1 equiv: 22%; 2 equiv: 54%; 3 equiv: 74%; 4 equiv: 75%; 5 equiv: 93%), only 1 equiv of fluoride ion might be sufficient for Si–B bond cleavage. Another 1 equiv of CsF works as a base to facilitate imine formation, and the final 1 equiv is consumed for silicon activation to generate cesium carbanion **8**[10,11] or fluorosilicate **8′**, leading to carboxylation with CO_2. Isolation of α-amido silane **4a** strongly indicates that selective boron activation of $PhMe_2Si$-Bpin by CsF initially occurs because of a stronger B–F bond compared to a Si–F bond (bond dissociation energy: 613 kJ/mol for B–F and 565 kJ/mol for Si–F).[12] To the best of our knowledge, there are no precedents of the generation of a silyl anion equivalent being triggered by fluoride through Si–B bond cleavage.[13–15] We believe that a protic additive would activate imine **6** as a Brønsted acid catalyst to promote its silylation.[7,16] HF, which is released during imine formation, would act as a proton donor to trap the generated amido anion **7**. This protonolysis of **7** is a crucial step because α-carbanion would be hardly generated directly from **7**

Table 2. Investigation of Carboxylations of **4**



					yield (%)[a]	
entry	R	CO_2 (MPa)	temp (°C)	time (h)	**2**	**3**
1	Ph (**4a**)	0.5	rt	1	93	2
2	Ph (**4a**)	0.1 (1 atm)	rt	1	90	<1
3	*p*-Cl-C_6H_4– (**4d**)	0.1	rt	1	95	1
4	*p*-OMe-C_6H_4– (**4k**)	0.1	rt	1	81	<1
5	Me_2C=C– (**4s**)	0.1	rt	3	<1	<1
6	Me_2C=C– (**4s**)	0.5	100	3	68	<1

[a] Yields were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

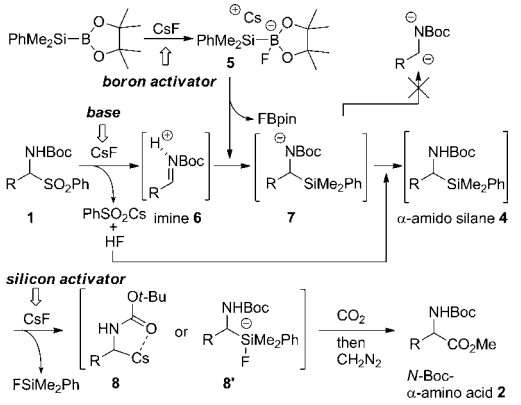


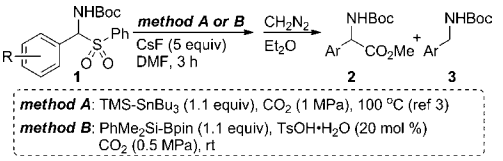
Figure 1. Possible reaction pathways.

because of the instability of the corresponding 1,2-dianion.[4] Because of the higher affinity of fluoride for Si than for Sn (bond dissociation energy: 565 kJ/mol for Si–F and 414 kJ/mol for Sn–F),[12] α-amido silane **4** is more reactive toward a fluoride anion than is α-amido stannane,[4] which allows the carboxylation of **4a** to proceed even at rt.

Next, substrate scope was examined under 0.5 MPa of CO_2 pressure (Table 3 and Figure 2). A wide range of α-aryl α-amido sulfones (**1a**–**1l**) attached with electron-deficient as well as -rich substituents on the aromatic rings with different Hammett σ-values were all active in contrast to the previous system[3] in which protodestannylation products were increased in response to the electron deficiency of aromatic rings, while final carboxylation hardly proceeded for electron-donating substrates (Table 3, method A[3] versus B).[4] In addition, sterically more crowded *ortho*-substitutions also gave high yields (**1g**, **1j**, and **1l**). It is noteworthy that cyano functionality, which is not tolerable in the conventional Strecker synthesis, remained intact in this sequence. Highly electron-donating substrates **1k** and **1l**, which had been sluggish for the previous system (10 and 41%),[3] were also reactive (71 and 85%).

Moreover, methylene catechol **1m**, both α- and β-naphthalene (**1n** and **1o**), and heteroaromatic substrates possessing 2-thienyl and 2-furyl groups (**1p** and **1q**) were all tolerated (Figure 2). Furthermore, one-pot reactions of electron-rich 3-furyl sulfone **1r** as well as substrates having alkenyl groups **1s**–**1w** produced the corresponding α-amino acid derivatives in moderate yields even though they still needed a high temperature condition (100 °C). 3-Furyl and these alkenyl substrates were

Table 3. Substrate Scope for Substituted α-Aryl Sulfones



			A: yield (%)		**B**: yield (%)	
entry	substrate (Hammett σ)		**2**[a]	**3**[a]	**2**[b]	**3**[a]
1	*m*-CN (0.62)	**1b**	31	40	69	6
2	*m*-CF_3 (0.46)	**1c**	37	29	78	6
3	*p*-Cl (0.22)	**1d**	64	17	81	3
4	*m*-OMe (0.10)	**1e**	88	8	82	4
5	*p*-F (0.06)	**1f**	79	11	91	3
6	*o*-F (–)	**1g**	61	12	87	6
7	H (0.00)	**1a**	81	7	87	2
8	*m*-Me (–0.06)	**1h**	74	8	86	5
9	*p*-Me (–0.14)	**1i**	53	6	85	2
10	*o*-Me (–)	**1j**	43	1	79	4
11	*p*-OMe (–0.28)	**1k**	10	5	71[c]	1
12	*o*-OMe (–)	**1l**	41	5	85	3

[a] Yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [b] Isolated yields after column chromatography using 10% KF/SiO_2 as a stationary phase. [c] Reaction time: 16 h.

(7) (a) Levin., V. V.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Eur. J. Org. Chem.* **2008**, 5226. (b) Gritsenko., R. T.; Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2009**, *50*, 2994. (c) Kosobokov, M. D.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Hu, J. *J. Org. Chem.* **2012**, *77*, 2080.

(8) (a) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403. (b) Vyas, D. J.; Fröhlich, R.; Oestreich, M. *Org. Lett.* **2011**, *13*, 2094.

(9) Carboxylations of C(sp^3)-Si bonds by a fluoride were only achieved using specific substrates such as 1-cyano-1-trimethylsilylcyclopropane and (perfluoroalkyl)trimethylsilanes. See: (a) Ohno, M.; Tanaka, H.; Komatsu, M.; Ohshiro, Y. *Synlett* **1991**, 919. (b) Singh, R. P.; Shreeve, J. M. *Chem. Commun.* **2002**, 1818. (c) Babadzhanova, L. A.; Kirij, N. V.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2004**, *125*, 1095. (d) Petko, K. I.; Kot, S. Y.; Yagupolskii, L. M. *J. Fluorine Chem.* **2008**, *129*, 301. For fluoride-mediated carboxylations of C(sp^2)-Si bonds, see: (e) Effenberger, F.; Spiegler, W. *Chem. Ber.* **1985**, *118*, 3900. For a recent achievement of carboxylation of benzylic silanes using CO_2, see: (f) Mita, T.; Michigami, K.; Sato, Y. *Org. Lett.* **2012**, *14*, 3462.

(10) Optically active **4a** (97% ee) was synthesized according to the reported procedure (ref 8a) and subjected to the fluoride-mediated carboxylation. As a result, **2a** was obtained in racemic form, indicating that carboxylation would proceed via a benzylic anion species **8** rather than a fluorosilicate **8′**.

(11) For the stabilization of lithium carbanion by a Boc group, see: Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574.

(12) Emsley, J. *The Elements*, 3rd ed.; Oxford University Press: New York, 1998.

(13) For transition metal (Rh or Cu)-catalyzed Si–B cleavage to generate silyl anion equivalents, see: (a) Walter, C.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5675. (b) Walter, C.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3818. (c) Walter, C.; Fröhlich, R.; Oestreich, M. *Tetrahedron* **2009**, *65*, 5513. (d) Vyas, D. J.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8513. (e) Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898. (f) Welle, A.; Petrignet, J.; Tinant, B.; Wouters, J.; Riant, O. *Chem.—Eur. J.* **2010**, *16*, 10980. (g) Ibrahem, I.; Santoro, S.; Himo, F.; Córdova, A. *Adv. Synth. Catal.* **2011**, *353*, 245. (h) Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem.—Eur. J.* **2011**, *17*, 13538. (i) Calderone, J. A.; Santos, W. L. *Org. Lett.* **2012**, *14*, 2090. For a transition-metal-free method, see: (j) O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7712.

(14) For silyl anion generation triggered by a fluoride through Si–Si bond cleavage, see: (a) Hiyama, T.; Obayashi, M.; Mori, I.; Nozaki, H. *J. Org. Chem.* **1983**, *48*, 912. (b) Hiyama, T.; Obayashi, M. *Tetrahedron Lett.* **1983**, *24*, 4109. (c) Hiyama, T.; Obayashi, M.; Sawahata, M. *Tetrahedron Lett.* **1983**, *24*, 4113.

(15) For borylation of imines using pinB-Bpin by a methoxide anion without transition metal catalysts, see: Solé, C.; Gulyás, H.; Fernández, E. *Chem. Commun.* **2012**, *48*, 3769.

(16) It is also possible that the boron atom is prone to be activated by a fluoride through the coordination of pinacol oxygen to a protic additive. See: Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738.

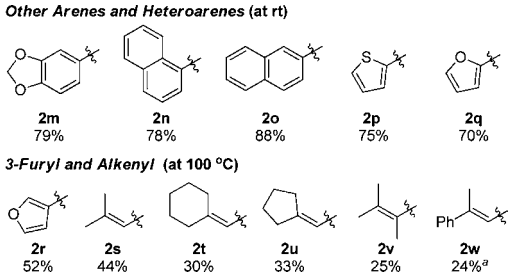
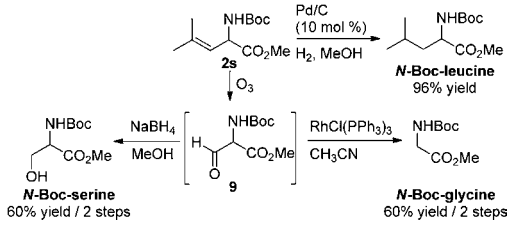


Figure 2. Substrate scope for other arenes and heteroarenes as well as 3-furyl and alkenyl sulfones using **method B** ($PhMe_2Si$-Bpin (1.1 equiv), CsF (5 equiv), $TsOH \cdot H_2O$ (20 mol %), CO_2 (0.5 MPa), DMF, 3 h, then CH_2N_2). Isolated yields are shown unless otherwise noted. [a] The yield was determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Scheme 2. Derivatization of Product **2s**



totally inactive under the previous condition,[3] highlighting the successful use of $PhMe_2Si$-Bpin.[17]

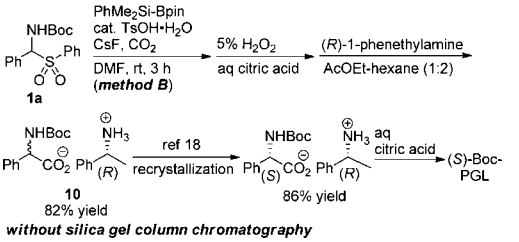
Considering the synthetic utility of this one-pot reaction, α-amino acid derivative **2s** obtained by this procedure was transformed into several useful α-amino acids (Scheme 2). *N*-Boc-leucine was obtained in 96% yield by hydrogenation of **2s**. *N*-Boc-serine was obtained in 60% yield through ozonolysis with O_3 followed by reduction with $NaBH_4$. *N*-Boc-glycine was synthesized through Tsuji–Wilkinson decarbonylation from the same intermediate **9**. Although their amino acids are racemic, it is noteworthy that these simple manipulations enable the synthesis of these basic α-amino acids only in a few steps using CO_2 gas.

Finally, we demonstrated practical preparation of α-amino acids without purification by silica gel column chromatography (Scheme 3). After completion of the reaction, 1 equiv of benzenesulfinic acid and 0.2 equiv of TsOH existed in the reaction mixture as acidic components in addition to the desired *N*-Boc-α-amino acid. However, benzenesulfinic acid could not be removed by simple extraction with Et_2O from aq citric acid solution. Therefore, the

(17) Although the intermediate α-amino silane **4** was produced smoothly when using α-alkyl sulfones, the final carboxylation reaction did not proceed at all. See the Supporting Information for details.

(18) (a) Lipkowski, A. W. *Pol. J. Chem.* **1981**, *55*, 1725. For the use of 1-phenethylamine as a resolving agent, see: (b) Juaristi, E.; Escalante, J.; Leon-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmerty* **1998**, *9*, 715.

Scheme 3. Salt Formation with (*R*)-1-Phenethylamine and Optical Resolution of the Salt



crude mixture was treated with H_2O_2 in aq citric acid to convert it into benzenesulfonic acid. In this stage, separation of the α-amino acid from these sulfonic acids worked very well, and the resulting extract was treated with (*R*)-1-phenethylamine to afford the corresponding pure diastereomer mixture salt **10** in 82% yield as white precipitates. This salt **10** can be transformed into chiral (*S*)-*N*-Boc-phenyl glycine (Boc-PGL) following a conventional optical resolution by simple recrystallizations.[18]

In summary, we could successfully utilize $PhMe_2Si$-Bpin for one-pot α-amino acid synthesis from α-amido sulfones through CO_2 incorporation. Addition of a catalytic amount of a protic additive plays a crucial role in efficient silylation. Compared to the previous system using TMS-$SnBu_3$, toxic organotin reagents could be avoided, and the yields of α-amino acids were generally higher. In addition, substrate scope was expanded to tolerate α-alkenyl α-amido sulfones, which is a big advantage for replacement with $PhMe_2Si$-Bpin. The product obtained by this procedure was successfully transformed into several α-amino acids within two steps. Furthermore, without purification by silica gel column chromatography, amino acids were easily converted to their (*R*)-1-phenethylamine salts, which would then provide chiral phenyl glycine after recrystallizations. Examination of catalytic enantioselective variants of this transformation is now actively ongoing.

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Supporting Information Available. Details of experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.