$Hf(OTf)_4$-Doped Me_3SiCl-Catalyzed Aminomethylation of Arenes with *N*,*O*-Acetals: Facile Approach to Non-Natural Aromatic Amino Acid Precursors

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Abstract: The authors demonstrated a $Hf(OTf)_4$–Me_3SiCl-system-catalyzed aminomethylation of an aromatic compound, such as a heterocycle or an electron-rich arene, with several new types of *N*,*O*-acetals having both a cyano group and a cyclic amino moiety. This method permits the facile synthesis of artificial aromatic amino acid precursors.

Key words: *N*,*O*-acetal, aminomethylation, amino acid, hafnium

Since the Friedel–Crafts-type reaction is one of the most efficient methods for carbon–carbon bond formation between an aromatic compound and a carbon electrophile, a large number of approaches to establishing synthetic methods have been developed by organic/medicinal chemists.[1] Among these, aminoalkylation is a powerful tool used to directly introduce a nitrogen-containing functional group, specifically an aminomethyl group, onto an aromatic ring. However, most of the electrophilic sources employed have been limited to an imine or an imino ester,[2,3] and the use of an acyclic *N*,*O*-acetal as an aminomethyl group precursor has not been extensively examined.[4] Hafnium-catalyzed aminomethylation of electron-rich aromatic compounds with an *N*-silyl-*N*,*O*-acetal leading to the production of aromatic primary amine derivatives was previously reported.[5,6] During ongoing investigations of aminomethylation of aromatic compounds, the preparation of a new class of an *N*,*O*-acetal having both a cyano group and a cyclic amino moiety was then attempted. In particular, a cyano group was converted into a formyl group and a carboxylic group with a simple operation.[7] In addition, the nitrogen-containing rings, such as piperidine, piperazine, and morpholine, are widely found in the key structure of a number of natural products and biologically active substances.[8] Consequently, development of aminomethylation of an arene with this class of *N*,*O*-acetal would enable a facile approach to producing an aromatic amino acid precursor, which would be expected to show potent biological activity. This report documents the results of $Hf(OTf)_4$-doped Me_3SiCl-catalyzed aminomethylation of an electron-rich arene with an *N*,*O*-acetal having a cyano group leading to the synthesis of an aromatic amino acid precursor. This catalytic system also permitted the facile preparation of an underivatized indolylglycine derivative with another type of *N*,*O*-acetal, such as hydroxyglycine.

Initially, to find the best catalytic system, the aminomethylation of 1-methylindole (**1a**) with *N*,*O*-acetal **2a** using a variety of Lewis acids in the presence of trimethylchlorosilane (Me_3SiCl) as an additive was conducted in CH_2Cl_2 as a model reaction.[9] The results are listed in Table 1. For example, when the reaction ran using a typical Lewis acid, such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $ZnCl_2$, and $Cu(OTf)_2$, the desired product **3a** was obtained in good yield (entries 1–4). With the exception of using a stoichiometric amount of $BF_3{\cdot}OEt_2$, however, most cases required a long reaction time (20–24 h) to complete aminomethylation. Group IV metals also showed a similar effect for the reaction (entries 5–8). In previous work it was noted that when the reaction was conducted using 0.2 equivalent of $Hf(OTf)_4$, the desired indole **3a** was obtained in nearly quantitative yield within five minutes (entry 9). Even when the amount of the hafnium catalyst was decreased to 0.05 equivalent for the acetal, the catalyst showed high catalytic activity and the product **3a** was produced in good yield (entry 11). On the other hand, the reaction without a Lewis acid did not afford the desired product in practical yield (entry 12), and the reaction without Me_3SiCl did not form the product at all (entry 13). Consequently, from the viewpoint of cost, CH_2Cl_2 solution using 0.1 equivalent of $Hf(OTf)_4$ in the presence of Me_3SiCl showed the best conditions for aminomethylation.

To extend the general process of aminomethylation onto an indole skeleton, reactions of indoles having several substituent groups with three types of *N*,*O*-acetal **2a**–**c** were carried out under the optimized conditions. The results are summarized in Table 2. For example, when reactions of indoles having an electron-donating group with acetal **2a** were examined using the hafnium catalyst, the reactions reached consumption within 10 minutes to produce the 3-substituted amino acid precursors **3a**–**c** in good to excellent yields (entries 1–3). Employment of indoles **1d**,**e** having an electron-withdrawing group, such as an ester group and a halogen substituent, also underwent the desired aminomethylation in good yield (entries 4 and 5). Moreover, when introduction of an aminomethyl group onto an indole ring by acetals **2b**,**c** with *N*-phenylpiperazine or morpholine moiety was conducted, the desired products were also obtained in excellent yields

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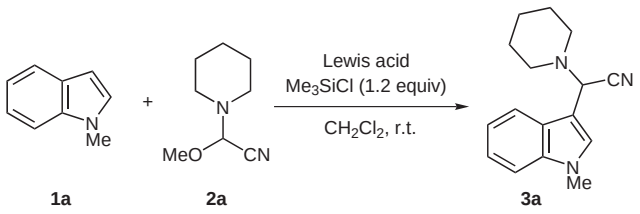
Table 1 Examinations of Lewis Acids



1a **2a** **3a**

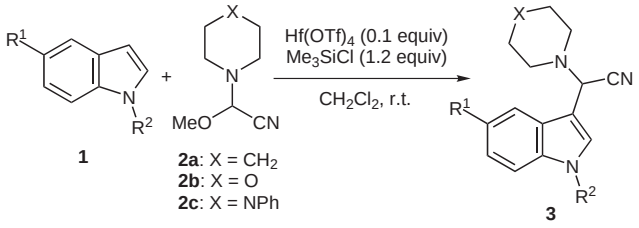
Entry	Lewis acid (equiv)	Time (h)	Yield (%)[a]
1	$BF_3{\cdot}OEt_2$ (1.0)	0.1	98 (84)[b]
2	$AlCl_3$ (0.2)	24	86
3	$ZnCl_2$ (0.2)	24	84
4	$Cu(OTf)_2$ (0.2)	20	84
5	$TiCl_4$ (0.2)	24	63
6	$Ti(O\textit{i}\text{-}Pr)_4$ (0.2)	24	75
7	$ZrCl_4$ (0.2)	24	73
8	$HfCl_4$ (0.2)	24	82
9	$Hf(OTf)_4$ (0.2)	0.1	94
10	$Hf(OTf)_4$ (0.1)	1	97
11	$Hf(OTf)_4$ (0.05)	24	82
12	–	24	39
13[c]	$Hf(OTf)_4$ (0.2)	24	trace

[a] NMR yield.
[b] Yield using 0.2 equiv of $BF_3{\cdot}OEt_2$ is in parentheses.
[c] Reaction was carried out without Me_3SiCl.

(entries 6–9). By contrast, when a similar reaction was examined with the *N*,*O*-acetal containing an *N*-methylpiperazinyl group, the desired product did not form, and the starting indole was recovered. The hafnium catalyst seems to be coordinated on the tertiary amino group rather than the activation of the methoxy substituent.

Aminomethylations of other heterocycles **5**, such as pyrrole and furan, with several types of *N*,*O*-acetal **2** were then investigated with the hafnium–Me_3SiCl catalytic system. The results are summarized in Table 3.[10] Although lowering the nucleophilicity in the pyrrole ring tends to slightly decrease the product yield (entries 1–3), most reactions using a pyrrole derivative produced the corresponding amino acid precursors in good yields. When the reaction using 2-methylfuran (**5**) was conducted under similar conditions, all reactions were completed within three hours to give the corresponding product in satisfactory yields (entries 8–10). Interestingly, when the reaction was carried out with the substrate involving a pyrrole and furan moiety, the desired reaction proceeded with high regioselectivity to yield only the amino acid precursor **8**, where the aminomethyl group was regioselectively introduced onto the pyrrole skeleton. Moreover, aminomethylation of acetal **2** with an electron-rich arene, such as *N*,*N*-dimethylaniline, under optimized conditions also yielded the aminomethylated product **9** (Figure 1).

Table 2 Aminomethylation of Indoles with *N*,*O*-Acetals

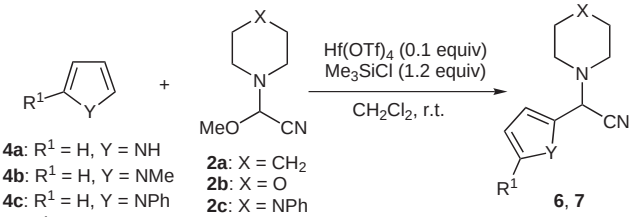


1 **2a**: X = CH_2 **2b**: X = O **2c**: X = NPh **3**

Entry	R^1	R^2		Acetal	Time (h)	Yield (%)[a]
1	H	Me	(**1a**)	**2a**	0.1	92 (**3a**)
2	H	H	(**1b**)	**2a**	0.1	94 (**3b**)
3	MeO	H	(**1c**)	**2a**	0.1	85 (**3c**)
4	MeO_2C	H	(**1d**)	**2a**	0.5	89 (**3d**)
5	Br	H	(**1e**)	**2a**	5	78 (**3e**)
6	H	Me	(**1a**)	**2b**	0.5	79 (**3f**)
7	H	H	(**1b**)	**2b**	0.3	86 (**3g**)
8	H	Me	(**1a**)	**2c**	0.5	85 (**3h**)
9	H	H	(**1b**)	**2c**	0.1	86 (**3i**)

[a] Isolated yield.

Table 3 Aminomethylation of Heterocycles with *N*,*O*-Acetals

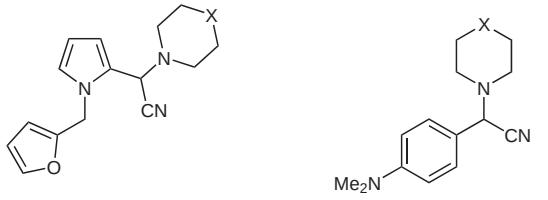


4a: R^1 = H, Y = NH
4b: R^1 = H, Y = NMe
4c: R^1 = H, Y = NPh
5: R^1 = Me, Y = O

2a: X = CH_2 **2b**: X = O **2c**: X = NPh **6**, **7**

Entry	Arene	Acetal	Time (h)	Yield (%)[a]
1	**4a**	**2a**	0.3	82 (**6a**)
2	**4b**	**2a**	0.2	74 (**6b**)
3	**4c**	**2a**	0.5	66 (**6c**)
4	**4a**	**2b**	1	85 (**6d**)
5	**4b**	**2b**	1	82 (**6e**)
6	**4a**	**2c**	1	82 (**6f**)
7	**4b**	**2c**	1	94 (**6g**)
8	**5**	**2a**	0.5	86 (**7a**)
9	**5**	**2b**	3	63 (**7b**)
10	**5**	**2c**	3	83 (**7c**)

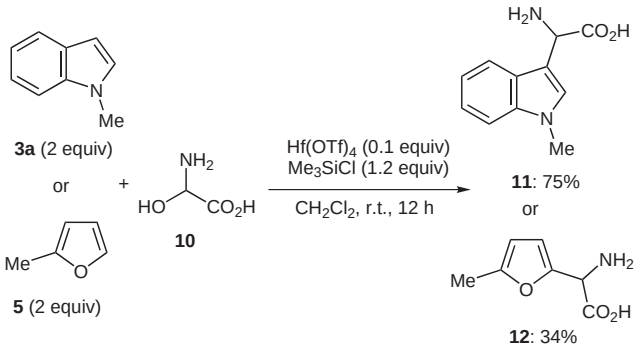
[a] Isolated yield.



8a: X = CH_2 4 h, 85% **9a**: X = CH_2 18 h, 38%
8b: X = NPh 5 h, 77% **9b**: X = NPh 15 h, 44%

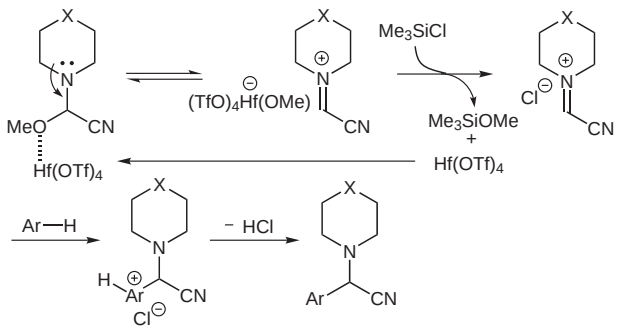
Figure 1

Finally, to illustrate the utility of the Hf–Me_3SiCl catalytic system for an *N*,*O*-acetal, the aminomethylation of *N*-methylindole **3a** with another type of the *N*,*O*-acetal (hydroxyglycine)[11] **10** was examined under optimized conditions, leading to production of the underivatized indolylglycine derivative **11** in 75% yield (Scheme 1). In case using 2-methylfuran (**5**), desired furylglycine derivative **12** was also obtained, but the yield (34%) was not practical, due to low solubility of the product in a typical solvent.



Scheme 1

A plausible mechanism for the aminomethylation of aromatic compounds is shown in Scheme 2. First, the coordination of hafnium triflate to an oxygen atom of acetal **2** forms an iminium complex. Although there is no clear explanation for the role of Me_3SiCl at present,[12] it may trap the in situ generated methoxy ion, thus driving the equilibrium to completion. Finally, the arene would attack the iminium intermediate to produce the corresponding aminomethylated product.



Scheme 2 Plausible reaction path for aminomethylation

In conclusion, it has been demonstrated that the $Hf(OTf)_4$-doped Me_3SiCl system catalyzes the aminomethylation of an aromatic compound, such as a heterocycle or an electron-rich arene, with a new class of *N*,*O*-acetal having a cyano group and leads to the production of an amino acid precursor. This catalytic system was also found to be effective in the one-step preparation of an indolylglycine derivative.

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References and Notes

(1) (a) Olah, G. A. In *Friedel–Crafts Chemistry*; Wiley-Interscience: New York, **1973**. (b) Heaney, H. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 733–752. (c) Olah, G. A.; Krishnamurti, A. R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 293–339. (d) In *Lewis Acids in Organic Synthesis*, Vol. 1 and 2; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, **2000**. (e) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527.

(2) (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.

(3) (a) Xie, W.; Bloomfield, K. M.; Jin, Y.; Dolney, N. Y.; Wan, P. G. *Synlett* **1999**, 498. (b) Johannsen, M. *Chem. Commun.* **1999**, 2233. (c) Gong, Y.; Kato, K.; Kimoto, H. *Synlett* **2000**, 1058. (d) Janczuk, A.; Zhang, W.; Xie, W.; Lou, S.; Cheng, J.; Wang, P. G. *Tetrahedron Lett.* **2002**, *43*, 4271. (e) Lei, F.; Chen, Y.-J.; Sui, Y.; Liu, L.; Wang, D. *Synlett* **2003**, 1160. (f) Piper, S.; Risch, N. *Synlett* **2004**, 1489. (g) Jiang, B.; Huang, Z.-G. *Synthesis* **2005**, 2198.

(4) For selected papers of Friedel–Crafts-type reaction using an acyclic *N*,*O*-acetal, see: (a) O'Donnell, M. J.; Falmagne, J.-B. *Tetrahedron Lett.* **1985**, *26*, 699. (b) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *J. Chem. Soc., Chem. Commun.* **1988**, 1161. (c) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941. (d) DeNinno, M. P.; Eller, C.; Etienne, J. B. *J. Org. Chem.* **2001**, *66*, 6988. (e) Gong, Y.; Kato, K. *J. Fluorine Chem.* **2001**, *108*, 83. (f) Ge, C.-S.; Chen, Y.-J.; Wang, D. *Synlett* **2002**, 37; and references cited therein.

(5) (a) Sakai, N.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2002**, *43*, 4821. (b) Sakai, N.; Hirasawa, M.; Hamajima, T.; Konakahara, T. *J. Org. Chem.* **2003**, *68*, 483.

(6) For selected papers of $Hf(OTf)_4$-catalyzed Friedel–Crafts-type reaction, see: (a) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409. (b) Kobayashi, S.; Iwamoto, S. *Tetrahedron Lett.* **1998**, *39*, 4697. (c) Shiina, I.; Suzuki, M. *Tetrahedron Lett.* **2002**, *43*, 6391. (d) Song, C. E.; Jun, D.-u.; Choung, S.-Y.; Roh, E. J.; Lee, S.-g. *Angew. Chem. Int. Ed.* **2004**, *43*, 6183.

(7) Larock, R. C. In *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, **1999**.

(8) (a) Carceller, E.; Merlos, M.; Giral, M.; Almansa, C.; Bartrolí, J.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **1993**, *36*, 2984. (b) Carceller, E.; Merlos, M.; Giral, M.; Balsa, D.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **1996**, *39*, 487. (c) Yang, R.; Zhao, R.; Chen, D.; Shan, L.; Yun, L.; Wang, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3017.

(9) **General Procedure for the Hf(OTf)$_4$-Catalyzed Aminomethylation of Aromatics with an *N*,*O*-Acetal**
To a CH_2Cl_2 solution (2 mL) was successively added *N*,*O*-acetal **2a** (92.5 mg, 0.600 mmol), 1-methylindole (65.5 mg, 0.500 mmol), and freshly distilled trimethylchlorosilane (65.7 mg, 0.600 mmol) under nitrogen atmosphere. After 1 min, Hf(OTf)$_4$ (38.8 mg, 0.0500 mmol) was added to the solution, and the thick suspension was vigorously stirred until the reaction reached completion, as shown by TLC (hexane–EtOAc, 6:4). The reaction was quenched with a sat. aq solution of $NaHCO_3$. The combined organic layer was dried over Na_2CO_3 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane–EtOAc) to afford the product **3a** in 92% (119.2 mg) yield. All new compounds were fully characterized by their spectral analyses. Spectral data for (1-methyl-1*H*-indol-3-yl)piperidin-1-yl-acetonitrile (**3a**): colorless crystals; mp 143–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40–1.60 (m, 6 H), 2.50–2.60 (m, 4 H), 3.79 (s, 3 H), 5.06 (s, 1 H), 7.14 (t, 1 H, *J* = 7.5 Hz), 7.26 (s, 1 H), 7.27 (t, 1 H, *J* = 7.5 Hz), 7.31 (d, 1 H, *J* = 7.5 Hz), 7.82 (d, 1 H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 25.9, 32.9, 50.7, 56.3, 107.9, 109.4, 116.3, 119.6, 120.1, 122.4, 126.3, 128.5, 137.5. MS–FAB: *m/z* 254 [M$^+$ + H]. Anal. Calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.71. Found: C, 75.77; H, 7.37; N, 16.71.
(1-Methyl-1*H*-pyrrol-2-yl)piperidin-1-yl-acetonitrile (**6b**): colorless crystals; mp 127–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40–1.60 (m, 6 H), 2.40–2.50 (m, 4 H), 3.61 (s, 3 H), 4.71 (s, 1 H), 6.04 (t, 1 H, *J* = 3.5 Hz), 6.33 (d, 1 H, *J* = 3.5 Hz), 6.62 (d, 1 H, *J* = 3.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 25.8, 33.9, 50.3, 56.4, 106.6, 110.8, 114.8, 123.7, 124.4. MS–FAB: *m/z* = 203 [M$^+$ + H]. Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 71.12; H, 8.16; N, 20.91.
(1-Furan-2-yl-methyl-1*H*-pyrrol-2-yl)piperidin-1-yl-acetonitrile (**8a**): colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (m, 2 H), 1.59 (m, 4 H), 2.52 (m, 4 H), 4.83 (s, 1 H), 4.95 (d, 1 H, *J* = 10.0 Hz), 5.38 (d, 1 H, *J* = 10.0 Hz), 6.08 (t, 1 H, *J* = 5.0 Hz), 6.15 (d, 1 H, *J* = 5.0 Hz), 6.31 (t, 1 H, *J* = 5.0 Hz), 6.37 (s, 1 H), 6.73 (s, 1 H), 7.35 (s, 1 H), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0, 25.7, 43.6, 50.2, 56.3, 107.1, 107.8, 110.4, 111.2, 114.5, 123.2, 123.9, 142.6, 150.6. MS–FAB: *m/z* = 269, 243, 185. HRMS–FAB: *m/z* calcd for $C_{16}H_{19}N_3O$: 269.1528; found: 269.1529.
[4-(Dimethylamino)phenyl]piperidin-1-yl-acetonitrile (**9a**): colorless crystals; mp 148–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.50 (m, 2 H), 1.50–1.60 (m, 4 H), 2.40–2.60 (m, 4 H), 2.96 (s, 6 H), 4.72 (s, 1 H), 6.69 (d, 2 H, *J* = 8.5 Hz), 7.33 (d, 2 H, *J* = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0, 25.8, 40.4, 50.7, 62.5, 112.0, 116.2, 120.7, 128.8, 150.6. MS–FAB: *m/z* = 244 [M$^+$ + H]. Anal. Calcd for $C_{15}H_{21}N_3$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.26; H, 8.79; N, 17.59.
Amino(1-methyl-1*H*-indol-3-yl)acetic acid (**11**): colorless solids; mp 173–174 °C. ^{1}H NMR (300 MHz, DMSO): δ = 3.79 (s, 3 H), 5.27 (s, 1 H), 7.11 (t, 1 H, *J* = 7.8 Hz), 7.21 (t, 1 H, *J* = 7.8 Hz), 7.46 (d, 1 H, *J* = 7.8 Hz), 7.53 (s, 1 H), 7.68 (d, 1 H, *J* = 7.8 Hz), 8.78 (br s, 3 H). ^{13}C NMR (75 MHz, DMSO): δ = 32.6, 48.6, 105.7, 110.1, 119.0, 119.5, 121.9, 125.5, 129.8, 136.5, 170.1. MS–FAB: *m/z* (%) = 205 (5) [M$^+$ + H], 188 (100) [M$^+$ – NH_2], 159 (52) [M$^+$ – CO_2H]. HRMS–FAB: *m/z* calcd for $C_{11}H_{13}N_2O_2$: 205.0977; found: 205.0980 [M$^+$ + H].
Amino(5-methylfuran-2-yl)acetic acid (**12**): pale yellow solids; mp 92–93 °C. ^{1}H NMR (300 MHz, DMSO): δ = 2.18 (s, 3 H), 5.17 (s, 1 H), 6.12 (d, 1 H, *J* = 5.0 Hz), 6.49 (d, 1 H, *J* = 5.0 Hz), 8.80 (br s, 3 H). ^{13}C NMR (75 MHz, DMSO): δ = 9.1, 47.0, 112.3, 121.4, 174.6, 180.1, 190.9. MS–FAB: *m/z* (%) = 156 (80) [M$^+$ + H], 139 (100) [M$^+$ – NH_2]. HRMS–FAB: *m/z* calcd for $C_7H_{10}NO_3$: 156.0661; found: 156.0665 [M$^+$ + H].

(10) When the reaction was examined with an *N*,*O*-acetal having another type of a nitrogen-containing ring, such as pyrrole, the desired amino acid precursor was not obtained, resulting in the production of the unknown product.

(11) (a) Hoefnagel, A. J.; van Bekkum, H.; Peters, J. A. *J. Org. Chem.* **1992**, *57*, 3916. (b) Sugiura, M.; Mori, C.; Hirano, K.; Kobayashi, S. *Can. J. Chem.* **2005**, *83*, 937.

(12) For selected papers on reactions enhanced by a coexistence of Lewis acid and Me_3SiCl, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (b) Mukaiyama, T.; Wariishi, K.; Saito, Y.; Hayashi, M.; Kobayashi, S. *Chem. Lett.* **1988**, 1101. (c) Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159. (d) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 6715. (e) Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646. (f) Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *Chem. Lett.* **2002**, 428. (g) Yang, L.; Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2007**, *48*, 1599.