Tetrahedron 64 (2008) 9208–9215

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A practical approach to non-natural or *N*-unsubstituted α-arylglycine derivatives: $Hf(OTf)_4$-doped Me_3SiCl system-catalyzed aminomethylation of electron-rich arenes with a new type of *N*,*O*-acetal

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ARTICLE INFO

Article history:
Received 30 June 2008
Received in revised form 15 July 2008
Accepted 15 July 2008
Available online 18 July 2008

Keywords:
N,*O*-Acetal
Aminomethylation
Amino acid
Hafnium triflate

ABSTRACT

The authors have demonstrated the $Hf(OTf)_4$-doped Me_3SiCl system-catalyzed aminomethylation of electron-rich aromatic compounds, such as indoles and anilines, with new types of *N*,*O*-acetals having a variety of functional groups, such as cyano, ester, bis(trimethylsilyl)amino, diallylamino, and cyclic amino moieties, for the preparation of non-natural aromatic amino acid derivatives. Aminomethylation using an *N*,*O*-acetal with a bis(trimethylsilyl)amino group was particularly successful in the direct preparation of an *N*-unsubstituted α-indolylglycine derivative, which required only a standard aqueous workup.

1. Introduction

Amino acids are among the most important and indispensable materials for the maintenance of human life.[1] Among these, α-arylglycine derivatives constitute the basic and central building blocks necessary to build biologically active substances and naturally occurring compounds, such as vancomycin and nocardicin.[2,3] Thus, several practical approaches to construct these frameworks and their derivatives have been developed by organic/medicinal chemists.[4] Friedel–Crafts-type reactions of electron-rich arenes with a glycine cation equivalent are among the most useful tools in achievement of the facile preparation of these α-aromatic amino acid derivatives. However, most of the electrophilic sources employed in the Friedel–Crafts reaction have been limited to imines or imino esters.[5,6] Moreover, the use of an *N*,*O*-acetal, which functions as a glycine cation equivalent, has not been examined extensively.[7,8] Heaney and co-workers developed an effective preparation of α-aryl-amino acid derivatives using an *N*,*O*-acetal, in the presence of a typical silyl chloride, such as Me_3SiCl; however, most of the reactions required long reaction times to complete.[9] Risch and co-workers demonstrated the aminoalkylation of arenes with benzotriazolyl-substituted *N*,*N*-aminals in the presence of stoichiometric amounts of $AlCl_3$ and $TiCl_4$, leading to the formation of α-aryl-α-amino acid esters.[10] In this context, we designed several types of *N*,*O*-acetals as aminomethyl group equivalents, and found that an $Hf(OTf)_4$-doped Me_3SiCl catalytic system highly and effectively catalyzed the aminomethylation of electron-rich arenes, which led to the production of α-aryl-amino acid precursors.[11] Thus, our next effort focused on the development of an efficient and direct preparation of *N*-underivatized amino acid derivatives using a novel type of *N*,*O*-acetal. In conventional studies, the employed imines and the imino esters typically contained a phenyl group and an electron-withdrawing group on the nitrogen atom of the imine to stabilize the structure. Use of these substituents, however, required severe deprotection conditions, which complicated the otherwise facile synthesis of an *N*-unsubstituted amino acid derivative.[7c,12] To overcome this problem, we utilized an *N*,*N*-bis(trimethylsilyl)-*N*,*O*-acetal and an *N*,*N*-diallylamino-*N*,*O*-acetal as glycine cation equivalents, since it is well-known that an N–Si bond can readily be converted to an N–H bond via the usual aqueous workup,[13] and an allyl group on a nitrogen atom can also be transformed to an N–H bond using the reductive cleavage.[14] Here, we first report the details of the $Hf(OTf)_4$-doped Me_3SiCl-catalyzed aminomethylation of an electron-rich arene using an *N*,*O*-acetal with a cyano group or an ester group, leading to the synthesis of an α-arylglycine derivative. Second, we describe the $Hf(OTf)_4/Me_3SiCl$ catalytic system-catalyzed aminomethylation of indole with an *N*,*N*-bis(trimethylsilyl)-*N*,*O*-acetal that directly produces an *N*-underivatized α-indolylglycine derivative without the deprotection step. Third, we describe a two-step procedure that comprises aminomethylation using an *N*,*O*-acetal with a diallylamino group and the subsequent reductive deprotection of the allyl group with

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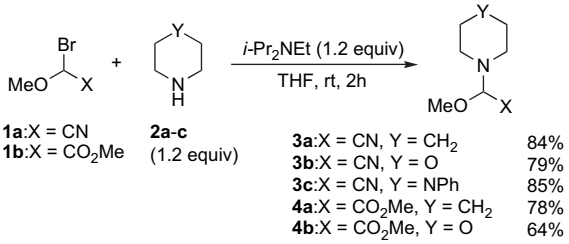
doi:10.1016/j.tet.2008.07.052

palladium to afford the corresponding *N*-unsubstituted α-aryl-amino acid derivatives in good yields.

2. Results and discussion

2.1. Preparation of *N*,*O*-acetals

Initially, a series of *N*,*O*-acetals **3** and **4** possessing a cyano group or an ester group were prepared via the reaction of brominated compound **1** with the corresponding cyclic secondary amine **2** in the presence of a base, as shown in Scheme 1. A representative reaction was as followed: 2-bromo-2-methoxyacetonitrile (**1a**) was treated with piperidine (**2a**) in the presence of a 1.2 equiv of the base, *i*-Pr_2EtN, in THF at room temperature for 2 h, followed by non-aqueous isolation and standard distillation (Kugelrohr), which gave the desired methoxy(piperidino)acetonitrile (**3a**) in 84% yield. Aqueous isolation and silica gel column purification of the acetal **3** resulted in decomposition of the *N*,*O*-acetals.



Scheme 1. Preparation of *N*,*O*-acetals **3** and **4**.

2.2. Aminomethylation with *N*,*O*-acetals having a cyano group and an ester group

Based on our previous studies,[11] the aminomethylation of a variety of heterocycles with *N*,*O*-acetals **3**, which possess a cyano group, was then examined using an $Hf(OTf)_4/Me_3SiCl$ catalytic system. The results of these reactions are summarized in Table 1. Most of the reactions involving substituted indoles, which had either an electron-donating group or an electron-withdrawing group, and *N*,*O*-acetals with a cyano group were completed within 0.5 h, yielding the corresponding amino acid precursors in good to excellent yields (runs 1–4 and 6). In addition, the aminomethylation successfully accommodated acetal substrates that had either an *N*-phenyl-piperazine or a morpholine moiety (runs 5,7, and 8). Other nucleophilic heterocycles, such as pyrrole and furan, were efficiently aminomethylated in good yield (runs 9–18).

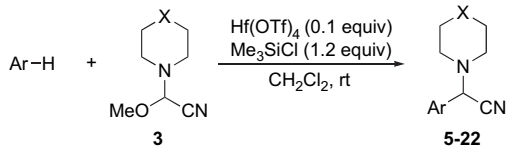
To produce a variety of aromatic glycine derivatives, aminomethylation using *N*,*O*-acetals **4** with an ester group was performed using the $Hf(OTf)_4/Me_3SiCl$ catalytic system (Table 2). As a result, most of the reactions that used an electron-rich heterocycle, such as indoles, pyrroles, furans, and thiophenes, proceeded smoothly to produce the corresponding amino acid derivatives **23**–**35** in good to excellent yields. In particular, when aminomethylation of a substrate consisting of both pyrrole and furan skeletons was conducted, the aminomethyl group was selectively introduced onto the pyrrole ring that showed a stronger nucleophilicity giving the corresponding amino acid derivative **34** in a nearly quantitative yield (run 12). Moreover, aminomethylation of acetal **4a** with an electron-rich arene, such as *N*,*N*-dimethylaniline, under optimized conditions also yielded the aminomethylated product **35** in 91% yield.

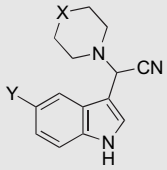
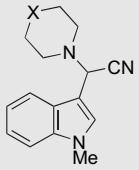
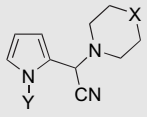
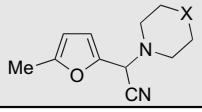
2.3. Preparation of *N*-unsubstituted α-amino acids

To illustrate the utility of this type of *N*,*O*-acetal, we then synthesized an amino acid derivative with an underivatized amino group. Generally, deprotection of an amino group that results in an unsubstituted amino group is complicated and involves reductive cleavage with a metal and hydration under acidic conditions. These harsh experimental conditions may reduce the chemical yield. Therefore, we used a common aqueous workup that readily cleaves N–Si bonds, leading to the formation of N–H bonds, and designed a novel type of *N*,*O*-acetal with a bis(trimethylsilyl)amino group, as follows. Treatment of methyl 2-bromo-2-methoxyacetate (**1b**) with lithium bis(trimethylsilyl)amide in THF at room temperature was followed by non-aqueous isolation and distillation under reduced pressure to give *N*,*O*-acetal **36** in 47% yield (Scheme 2). Subsequently, aminomethylation of indole with the *N*,*O*-acetal **3e** was examined using the $Hf(OTf)_4/Me_3SiCl$ catalytic system. After standard isolation, the desired *N*-unsubstituted indolylglycine **37** was obtained in 35% yield along with the byproduct, bis(indolyl)-methane derivative **38**, in 26% yield (Scheme 3). This result may be due to a reduction in basicity of the amide anion by the inductive effect of two silicon atoms.[15] Namely, the amide group is a better leaving group than the cyclic piperidino anion. When aminomethylation was performed with 1 equiv of $BF_3 \cdot OEt_2$ instead of $Hf(OTf)_4$, the yield did not improve (47% of **37**, 46% of **38**).[16] We showed that the $Hf(OTf)_4/Me_3SiCl$-catalyzed aminomethylation of an electron-rich heterocycle using the *N*,*O*-acetal with a bis-(trimethylsilyl)amino group led to the direct synthesis of an *N*-unsubstituted aromatic glycine derivative without the complicated deprotection step.

Thus, to develop a useful method for the highly efficient preparation of an *N*-underivatized aromatic glycine derivative, we prepared an *N*,*O*-acetal with a diallylamino group. Diallylamino groups can be easily converted to primary amino groups by use of the method described by Guibé and co-workers.[14c] Treatment of methyl 2-bromo-2-methoxyacetate with diallylamine in the

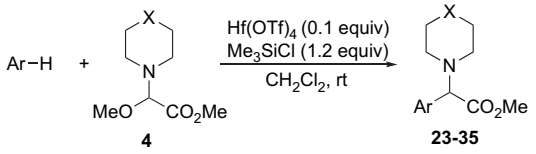
Table 1
Synthesis of a variety of amino acid precursors

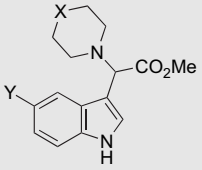
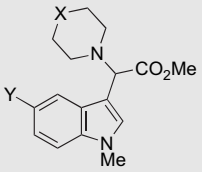
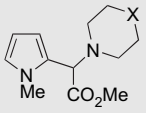
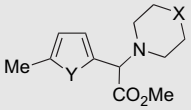
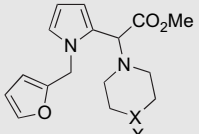
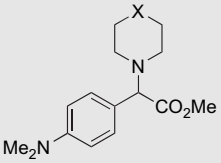


Run	Time (h)	Product	X	Y	Yield[a] (%)
1	0.1		CH_2	H	94 (**5**)
2	0.3		CH_2	MeO	85 (**6**)
3	0.5		CH_2	CO_2Me	89 (**7**)
4	5		CH_2	Br	78 (**8**)
5	0.3		O	H	86 (**9**)
6	0.1		CH_2	—	92 (**10**)
7	0.5		O	—	79 (**11**)
8	0.5		NPh	—	85 (**12**)
9	0.3		CH_2	H	82 (**13**)
10	0.2		CH_2	Me	74 (**14**)
11	0.5		CH_2	Ph	66 (**15**)
12	1		O	H	85 (**16**)
13	1		O	Me	82 (**17**)
14	1		NPh	H	82 (**18**)
15	1		NPh	Me	94 (**19**)
16	0.5		CH_2	—	86 (**20**)
17	3		O	—	63 (**21**)
18	3		NPh	—	83 (**22**)

[a] Isolated yield.

Table 2
Synthesis of a variety of α-arylglycine derivatives

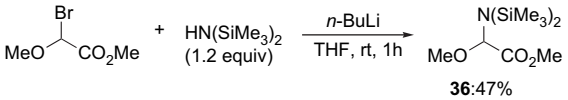


Run	Time (h)	Product	X	Y	Yield[a] (%)
1	0.5		CH_2	H	97 (**23**)
2	1		CH_2	MeO	95 (**24**)
3	2		CH_2	CO_2Me	95 (**25**)
4	1		O	H	95 (**26**)
5	1		CH_2	H	99 (**27**)
6	1		O	H	89 (**28**)
7	1		CH_2	—	98 (**29**)
8	3		O	—	86 (**30**)
9	4		CH_2	O	94 (**31**)
10	4		O	O	96 (**32**)
11	4		O	S	78 (**33**)
12	1		CH_2	—	99 (**34**)
13	3		CH_2	—	91 (**35**)

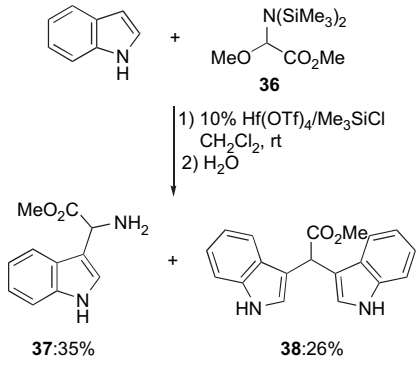
[a] Isolated yield.

presence of Et_3N in THF at room temperature gave *N*,*O*-acetal **39** in 93% yield (Scheme 4).

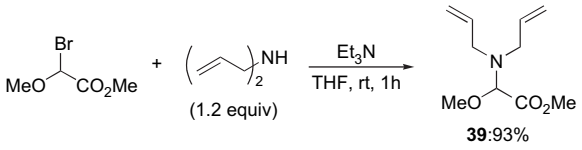
Scheme 5 shows the results of aminomethylation of various heterocycles with *N*,*O*-acetal **39**. In all cases, aminomethylation with both heterocycles and electron-rich arenes proceeded smoothly and efficiently to give the corresponding amino acid derivatives **40**–**47** in good to excellent yields. Finally, deprotection of the diallylamino group on the substituted product was performed with 5% $Pd(PPh_3)_4$ and 6 equiv of 1,3-dimethylbarbituric acid in CH_2Cl_2 at room temperature. The results of this reaction are summarized in Scheme 6. *N*-Substituted α-arylglycine derivatives underwent the reductive deprotection to give the desired *N*-unsubstituted α-arylglycine derivatives **37** and **48**–**51** in moderate to good yields. Thus, we demonstrated that a sequential procedure consisting of $Hf(OTf)_4$-catalyzed aminomethylation



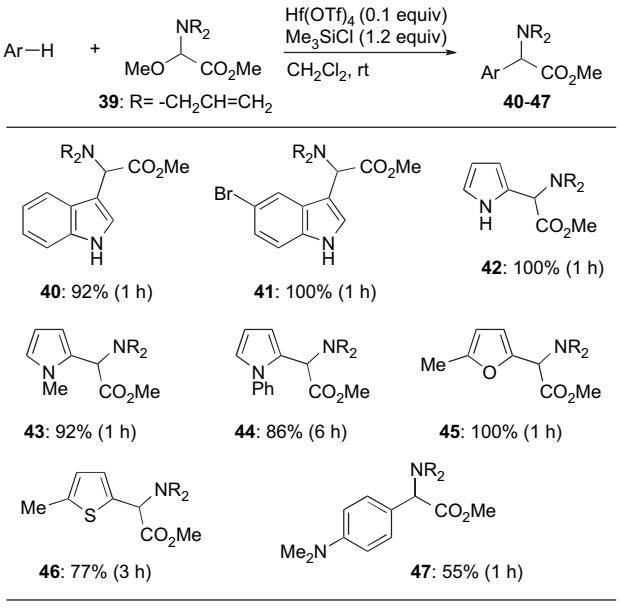
Scheme 2. Preparation of *N*,*O*-acetal **36**.



Scheme 3. Direct synthesis of *N*-unsubstituted indolylglycine **37** via a single-step reaction.



Scheme 4. Preparation of *N*,*O*-acetal **39**.

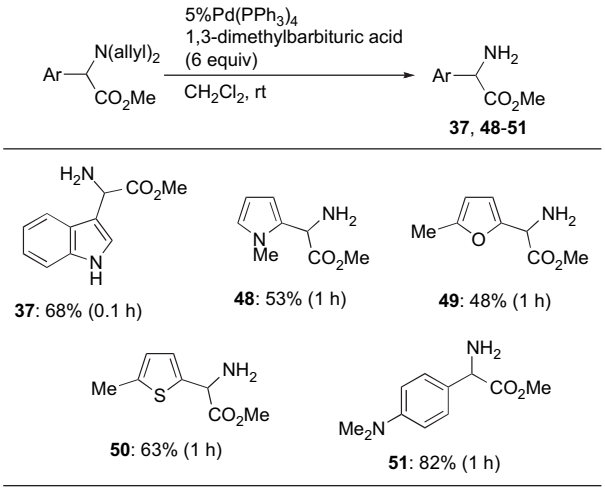


Scheme 5. Synthesis of a variety of α-arylglycine derivatives with acetal **39**. [a]Isolated yield.

using *N*,*O*-acetal with a diallylamino group and deprotection of the diallylamine group on the product successfully produced an *N*-underivatized aromatic amino acid derivative.

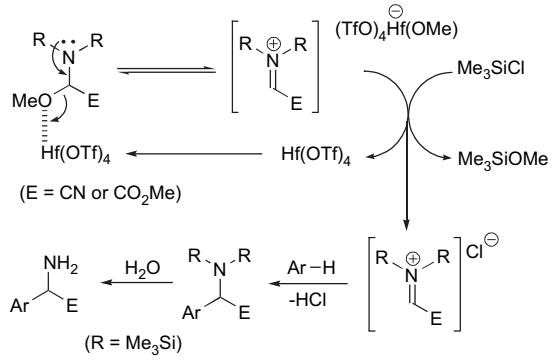
2.4. Plausible mechanism

A plausible mechanism for the aminomethylation of aromatic compounds is shown in Scheme 7. First, coordination of hafnium triflate to an oxygen atom of the starting acetal results in the formation of an iminium complex.[17] Then, Me_3SiCl traps the in situ generated methoxy ion, thus driving the equilibrium to completion and promoting regeneration of the hafnium catalyst, because the use of less than 1 equiv of Me_3SiCl reduces the chemical yield.[5g,18] Finally, the arene attacks the iminium intermediate to produce the corresponding aminomethylated product. When the *N*,*O*-acetal



Scheme 6. Deprotection of diallylamino group. [a]Isolated yield.

with a bis(trimethylsilyl)amino group was used, aqueous workup of the resulting mixture directly gave the corresponding *N*-unsubstituted amino acid.



Scheme 7. Plausible mechanism for the $Hf(OTf)_4/Me_3SiCl$-catalyzed aminomethylation.

3. Conclusion

In conclusion, we demonstrated that the $Hf(OTf)_4$-doped Me_3SiCl system-catalyzed aminomethylation of aromatic compounds, such as electron-rich heterocycles and arenes, using a new class of an *N*,*O*-acetals with a cyano group or an ester group leads to the production of a non-natural amino acid derivative. In addition, we have found that for the $Hf(OTf)_4/Me_3SiCl$ catalytic system, the *N*,*O*-acetal with a bis(trimethylsilyl)amino group functions as an *N*-unsubstituted glycine cation equivalent. Moreover, we have found that a sequential procedure consisting of $Hf(OTf)_4$-catalyzed aminomethylation of *N*,*O*-acetals with a diallylamino group and Pd-catalyzed deprotection of the diallylamino group on the product leads to the preparation of a variety of aromatic glycine derivatives.

4. Experimental

4.1. General experimental

Column chromatography was performed using silica gel. THF was distilled from sodium/benzophenone and dried over 5 Å MS. CH_2Cl_2 was distilled from P_2O_5 and dried over 4 Å MS. Secondary amines **2a–c** were commercially available and distilled prior to use. All reactions were carried out under a N_2 atmosphere, unless otherwise noted. ^1H NMR spectra were recorded at 500 or 300 MHz using tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 125 or 75 MHz using TMS or a center peak of chloroform (77.0 ppm) as an internal standard. High-resolution mass spectra were recorded using NBA (3-nitrobenzylalcohol) as a matrix. $Hf(OTf)_4$,[19] 2-bromo-2-methoxyacetonitrile (**1a**),[20] and methyl 2-bromo-2-methoxyacetate[20] (**1b**) were prepared according to the previously reported procedure.

4.2. General procedure for the synthesis of *N*,*O*-acetals 3

To a freshly distilled THF solution (100 mL), the corresponding secondary amine **2** (24 mmol), diisopropylethylamine (4.1 mL, 24 mmol), and bromomethoxyacetonitrile (11.5 mL, 20.0 mmol) were successively added, and the resulting solution was stirred for 2 h at room temperature. The mixture was then filtered without any aqueous workup and the filtrate was directly distilled (Kugelrohr) to give the corresponding *N*,*O*-acetal **3**.

4.2.1. 2-Methoxy-2-(piperidin-1-yl)acetonitrile[21] (***3a***)
Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (m, 2H), 1.58 (m, 4H), 2.66 (m, 4H), 3.43 (s, 3H), 4.56 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 25.2, 48.4, 55.8, 87.1, 114.4.

4.2.2. 2-Methoxy-2-(morpholin-4-yl)acetonitrile[21] (***3b***)
Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 2.67 (t, 4H, J=5.0 Hz), 3.40 (s, 3H), 3.69 (m, 4H), 4.54 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.4, 55.8, 66.3, 86.3, 113.9.

4.2.3. 2-Methoxy-2-(4-phenyl-piperazin-1-yl)acetonitrile[21] (***3c***)
Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 2.88 (t, 4H, J=5.0 Hz), 3.23 (m, 4H), 3.46 (s, 3H), 4.66 (s, 1H), 6.88 (t, 1H, J=8.0 Hz), 6.92 (d, 2H, J=8.0 Hz), 7.27 (t, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.3, 48.9, 55.9, 86.2, 114.0, 116.4, 120.1, 129.1, 151.0.

4.3. General procedure for the synthesis of *N*,*O*-acetals 4 and 39

To a freshly distilled THF solution (100 mL), the corresponding secondary amine **2** (24 mmol), diisopropylethylamine (4.1 mL, 24 mmol), and methyl 2-bromo-2-methoxyacetate (11 mL, 20 mmol) were successively added, and the solution was stirred at room temperature. After 2 h, the reaction was quenched by adding a saturated aqueous solution (2 mL) of $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$, the organic phase was combined, dried over anhydrous Na_2CO_3, filtered, and evaporated under reduced pressure. The crude product was distilled (Kugelrohr) to give the corresponding *N*,*O*-acetals.

4.3.1. Methyl 2-methoxy-2-(piperidin-1-yl)acetate[9a] (***4a***)
Bp 71–72 °C/5 mmHg (colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ 1.3–1.4 (m, 2H), 1.5–1.6 (m, 4H), 2.5–2.8 (m, 4H), 3.39 (s, 3H), 3.77 (s, 3H), 4.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.8, 48.4, 51.4, 55.5, 94.0, 168.7.

4.3.2. Methyl 2-methoxy-2-(morpholin-4-yl)acetate[9a] (***4b***)
Bp 84–86 °C/5 mmHg (colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ 2.6–2.8 (m, 4H), 3.42 (s, 3H), 3.6–3.7 (m, 4H), 3.79 (s, 3H), 4.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.6, 51.7, 55.8, 66.9, 93.4, 168.2.

4.3.3. Methyl 2-(diallylamino)-2-methoxyacetate (***39***)
Bp 69–70 °C/5 mmHg (colorless oil); ^1H NMR (300 MHz, $CDCl_3$) δ 3.2–3.3 (m, 4H), 3.36 (s, 3H), 3.76 (s, 3H), 4.45 (s, 1H), 5.1–5.2 (m, 4H), 5.7–5.8 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 52.1, 55.5, 89.8, 117.5, 135.7, 169.7; MS (ESI) 222 (M^++Na); HRMS (ESI) calcd for $C_{10}H_{17}NNaO_3$: 222.1106, found: 222.1095.

4.4. Preparation of *N*,*O*-acetal 36

To a freshly distilled THF solution (100 mL), hexamethyldisilazane (5.5 mL, 24 mmol), *n*-BuLi (15 mL, 24 mmol in 1.6 M hexane solution), and the methyl 2-bromo-2-methoxyacetate (11 mL, 20 mmol) were successively added, and the resulting solution was stirred at room temperature. After 1 h, the reaction was quenched by adding a saturated aqueous solution (2 mL) of $NaHCO_3$. The mixture was poured into AcOEt (50 mL) and the organic layer was washed by H_2O (20 mL×3). Then, the organic phase was dried over anhydrous Na_2CO_3, filtered, and evaporated under reduced pressure. The crude product was distilled to give the corresponding *N*,*O*-acetal **36**.

4.4.1. Methyl 2-(1,1,1,3,3,3-hexamethyldisilazan-2-yl)-2-methoxyacetate (**36**)

Bp 74–75 °C/3 mmHg (colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.111 (s, 18H), 3.30 (s, 3H), 3.68 (s, 3H), 4.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.2, 52.1, 55.0, 87.7, 172.1; MS (ESI) 286 (M^++Na); HRMS (ESI) calcd for $C_{10}H_{25}NNaO_3Si_2$: 286.1270, found: 286.1248.

4.5. General procedure for the Hf(OTf)$_4$-catalyzed aminomethylation of aromatics with an *N*,*O*-acetal

An *N*,*O*-acetal (0.60 mmol), an aromatic compound (0.50 mmol), and freshly distilled trimethylchlorosilane (0.60 mmol) were successively mixed together in CH_2Cl_2 (2 mL) at room temperature with stirring. After 1 min, $Hf(OTf)_4$ (0.050 mmol) was added and the resulting thick suspension was stirred until the reaction reached completion, as shown by TLC (SiO_2: hexane/AcOEt=2:1). The reaction was quenched with a saturated aqueous solution (2 mL) of $NaHCO_3$. The combined organic layer was dried over sodium carbonate and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt) to afford indolylglycine derivatives.

4.5.1. 2-(1H-Indol-3-yl)-2-(piperidin-1-yl)acetonitrile (**5**)

Mp 139–140 °C (colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4–1.6 (m, 6H), 2.4–2.6 (m, 4H), 5.07 (s, 1H), 7.12 (t, 1H, *J*=7.0 Hz), 7.22 (t, 1H, *J*=7.0 Hz), 7.35 (s, 1H), 7.37 (d, 1H, *J*=7.0 Hz), 7.83 (d, 1H, *J*=7.0 Hz), 8.24 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 25.9, 50.7, 56.4, 109.6, 111.3, 116.1, 120.1, 122.8, 123.9, 125.7, 136.7; MS (FAB) 240, 215, 84. Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.17; H, 7.31; N, 17.71.

4.5.2. 2-(5-Methoxy-1H-indol-3-yl)-2-(piperidin-1-yl)-acetonitrile (**6**)

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4–1.5 (m, 2H), 1.5–1.6 (m, 4H), 2.4–2.6 (m, 4H), 3.85 (s, 3H), 5.02 (s, 1H), 6.87 (d, 1H, *J*=8.5 Hz), 7.23 (d, 1H, *J*=8.5 Hz), 7.30 (m, 2H), 8.26 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.9, 50.6, 55.8, 56.4, 101.9, 111.9, 112.9, 116.1, 124.6, 126.2, 131.8, 154.1; MS (FAB) 269, 244, 185, 84; HRMS (FAB) calcd for $C_{16}H_{19}N_3O$: 269.1528, found: 269.1526.

4.5.3. Methyl 3-(cyano(piperidin-1-yl)methyl)-1H-indole-carboxylate (**7**)

Mp 153–155 °C (white powder); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.4–1.5 (m, 2H), 1.5–1.6 (m, 4H), 2.5–2.6 (m, 4H), 3.95 (s, 3H), 5.10 (s, 1H), 7.39 (d, 1H, *J*=7.0 Hz), 7.44 (s, 1H), 7.94 (d, 1H, *J*=7.0 Hz), 8.51 (br s, 1H), 8.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 25.8, 51.9, 56.2, 111.1, 111.3, 115.8, 122.3, 123.1, 124.2, 125.2, 125.4, 139.3, 168.0; MS (FAB) 298, 271, 213. Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.38; H, 6.28; N, 14.16.

4.5.4. 2-(5-Bromo-1H-indol-3-yl)-2-(piperidin-1-yl)acetonitrile (**8**)

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4–1.5 (m, 2H), 1.5–1.6 (m, 4H), 2.4–2.6 (m, 4H), 5.00 (s, 1H), 7.2–7.4 (m, 3H), 7.97 (s, 1H), 8.37 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 25.8, 50.7, 56.3, 109.4, 112.8, 113.3, 115.8, 122.6, 124.9, 125.8, 127.4, 135.4; MS (FAB) 318, 293, 291, 235, 233; HRMS (FAB) calcd for $C_{15}H_{17}N_3Br$: 318.0606, found: 318.0615 (M^++H).

4.5.5. 2-(1H-Indol-3-yl)-2-(morpholin-4-yl)acetonitrile (**9**)

Mp 148–149 °C (a colorless crystal); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (m, 4H), 3.72 (m, 4H), 5.05 (s, 1H), 7.16 (t, 1H, *J*=7.5 Hz), 7.25 (t, 1H, *J*=7.5 Hz), 7.35 (m, 2H), 7.80 (d, 1H, *J*=7.5 Hz), 8.48 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.7, 55.7, 66.7, 108.2, 111.5, 115.7, 119.7, 120.2, 122.9, 124.3, 125.5, 136.7; MS (FAB) 241, 215, 86. Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.75; H, 6.67; N, 17.41.

4.5.6. 2-(1-Methyl-1H-indol-3-yl)-2-(piperidin-1-yl)acetonitrile (**10**)

Mp 143–144 °C (a colorless crystal); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.4–1.6 (m, 6H), 2.5–2.6 (m, 4H), 3.79 (s, 3H), 5.06 (s, 1H), 7.14 (t, 1H, *J*=7.5 Hz), 7.26 (s, 1H), 7.27 (t, 1H, *J*=7.5 Hz), 7.31 (d, 1H, *J*=7.5 Hz), 7.82 (d, 1H, *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) 254, 227, 169. 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.

4.5.7. 2-(1-Methyl-1H-indol-3-yl)-2-(morpholin-4-yl)-acetonitrile (**11**)

Mp 161–162 °C (a colorless crystal); ^{1}H NMR (500 MHz, DMSO) δ 2.53 (m, 4H), 3.62 (m, 4H), 3.82 (s, 3H), 5.51 (s, 1H), 7.12 (t, 1H, *J*=7.5 Hz), 7.23 (t, 1H, *J*=7.5 Hz), 7.50 (m, 2H), 7.75 (d, 1H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, DMSO) δ 32.4, 49.4, 54.0, 66.0, 105.9, 110.1, 116.4, 119.3, 119.4, 121.9, 125.8, 129.3, 137.0; MS (FAB) 256, 229, 169. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.28; H, 7.06; N, 16.33.

4.5.8. 2-(1-Methyl-1H-indol-3-yl)-2-(4-phenyl-piperazin-1-yl)-acetonitrile (**12**)

Mp 153–154 °C (a colorless crystal); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (m, 4H), 3.20 (m, 4H), 3.78 (s, 3H), 5.13 (s, 1H), 6.85 (t, 1H, *J*=7.5 Hz), 6.89 (d, 2H, *J*=7.5 Hz), 7.14 (t, 1H, *J*=8.5 Hz), 7.22–7.34 (m, 5H), 7.81 (d, 1H, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.9, 49.2, 49.4, 55.4, 107.1, 109.6, 115.8, 116.2, 119.8, 119.9, 120.0, 122.5, 126.1, 128.8, 129.4, 137.6, 151.1; MS (FAB) 330, 304, 169. Anal. Calcd for $C_{21}H_{22}N_4$: C, 76.33; H, 6.71; N, 16.96. Found: C, 76.16; H, 6.70; N, 16.82.

4.5.9. 2-(Piperidin-1-yl)-(1H-pyrrol-2-yl)acetonitrile (**13**)

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4–1.5 (m, 2H), 1.6–1.7 (m, 4H), 2.5–2.6 (m, 4H), 4.81 (s, 1H), 6.15 (s, 1H), 6.35 (s, 1H), 6.79 (s, 1H), 8.52 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 25.8, 50.9, 57.2, 108.5, 108.7, 118.9, 123.7; MS (FAB) 189, 163, 84; HRMS (FAB) calcd for $C_{11}H_{15}N_3$: 189.1266, found: 189.1263 (M^+).

4.5.10. 2-(1-Methyl-1H-pyrrol-2-yl)-2-(piperidin-1-yl)-acetonitrile (**14**)

Mp 127–128 °C (a colorless crystal); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.4–1.6 (m, 6H), 2.4–2.5 (m, 4H), 3.61 (s, 3H), 4.71 (s, 1H), 6.04 (t, 1H, *J*=3.5 Hz), 6.33 (d, 1H, *J*=3.5 Hz), 6.62 (d, 1H, *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) 203, 177, 119. 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.

4.5.11. 2-(1-Phenyl-1H-pyrrol-2-yl)-2-(piperidin-1-yl)-acetonitrile (**15**)

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3–1.5 (m, 6H), 2.33 (m, 2H), 2.59 (m, 2H), 4.52 (s, 1H), 6.25 (t, 1H, *J*=3.5 Hz), 6.51 (d, 1H, *J*=3.5 Hz), 6.87 (d, 1H, *J*=3.5 Hz), 7.3–7.5 (m, 5H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 23.9, 25.7, 49.7, 55.3, 108.1, 112.1, 115.1, 123.7, 124.1, 124.9, 125.9, 127.5, 128.9, 129.6, 139.4; MS (FAB) 265, 240, 181; HRMS (FAB) calcd for $C_{17}H_{19}N_3$: 265.1579, found: 265.1587 (M^+).

*4.5.12. 2-(Morpholin-4-yl)-(1H-pyrrol-2-yl)acetonitrile (**16**)*

Mp 129–131 °C (a colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (m, 4H), 3.73 (m, 4H), 4.82 (s, 1H), 6.17 (d, 1H, J=5.0 Hz), 6.38 (s, 1H), 6.82 (s, 1H), 8.47 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.8, 56.6, 66.6, 108.7, 109.5, 114.4, 119.4, 122.5; MS (FAB) 191, 86. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.84; H, 6.69; N, 22.31.

*4.5.13. 2-(1-Methyl-1H-pyrrol-2-yl)-2-(morpholine-4-yl)-acetonitrile (**17**)*

Mp 107–108 °C (a colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (m, 4H), 3.66 (s, 3H), 3.70 (m, 4H), 4.75 (s, 1H), 6.07 (s, 1H), 6.38 (s, 1H), 6.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.9, 49.4, 55.6, 66.6, 106.7, 111.3, 114.3, 114.3, 122.4, 124.7; MS (FAB) 205, 179, 119; HRMS (FAB) calcd for $C_{11}H_{15}N_3O$: 205.1215, found: 205.1214 (M^+).

*4.5.14. 2-(4-Phenyl-piperazin-1-yl)-2-(1H-pyrrol-2-yl)-acetonitrile (**18**)*

Mp 123–125 °C (a colorless crystal); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71 (m, 4H), 3.20 (m, 4H), 4.91 (s, 1H), 6.19 (s, 1H), 6.41 (s, 1H), 6.83 (s, 1H), 6.88 (t, 1H, J=8.5 Hz), 6.91 (d, 2H, J=8.5 Hz), 7.27 (t, 2H, J=8.5 Hz), 8.43 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.1, 49.6, 56.3, 108.7, 109.3, 114.5, 116.3, 119.4, 120.1, 122.9, 129.2, 150.9; MS (FAB) 266, 240,161; HRMS (FAB) calcd for $C_{16}H_{18}N_4$: 266.1531, found: 266.1533 (M^+).

*4.5.15. 2-(1-Methyl-1H-pyrrol-2-yl)-2-(4-phenyl-piperazin-1-yl)-acetonitrile (**19**)*

Mp 135–137 °C (a colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (m, 4H), 3.16 (m, 4H), 3.64 (s, 3H), 4.80 (s, 1H), 6.07 (s, 1H), 6.38 (s, 1H), 6.65 (s, 1H), 6.85–6.90 (m, 3H), 7.22 (t, 2H, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.1, 40.4, 49.1, 55.5, 106.8, 111.4, 114.4, 116.3, 120.0, 122.9, 124.8, 129.1, 151.0; MS (FAB) 280, 254, 161. Anal. Calcd for $C_{17}H_{20}N_4$: C, 72.83; H, 7.19; N, 19.98. Found: C, 72.82; H, 7.33; N, 20.00.

*4.5.16. 2-(5-Methylfuran-2-yl)-2-(piperidin-1-yl)acetonitrile (**20**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4–1.5 (m, 2H), 1.6–1.7 (m, 4H), 2.30 (s, 3H), 2.5–2.6 (m, 4H), 4.78 (s, 1H), 5.95 (d, 1H, J=3.5 Hz), 6.39 (d, 1H, J=3.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 23.8, 25.5, 50.8, 56.9, 106.4, 111.4, 114.2, 144.3, 153.7; MS (FAB) 204, 178, 147, 84; HRMS (FAB) calcd for $C_{12}H_{16}N_2O$: 204.1263, found: 204.1255 (M^+).

*4.5.17. 2-(5-Methylfuran-2-yl)-2-(morpholine-4-yl)-acetonitrile (**21**)*

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.53 (m, 4H), 3.69 (m, 4H), 4.72 (s, 1H), 5.90 (d, 1H, J=3.0 Hz), 6.35 (d, 1H, J=3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 49.7, 56.1, 66.4, 106.5, 111.9, 113.8, 143.2, 154.0; MS (FAB) 206, 177, 84; HRMS (FAB) calcd for $C_{11}H_{14}N_2O_2$: 205.0977, found: 205.0983 (M^+).

*4.5.18. 2-(5-Methylfuran-2-yl)-2-(4-phenyl-piperazin-1-yl)-acetonitrile (**22**)*

Mp 112–113 °C (a colorless crystal); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.78 (m, 4H), 3.26 (m, 4H), 4.87 (s, 1H), 5.99 (d, 1H, J=5.0 Hz), 6.46 (d, 1H, J=5.0 Hz), 6.87 (t, 1H, J=7.5 Hz), 6.91 (d, 2H, J=7.5 Hz), 7.27 (t, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 48.9, 49.5, 55.9, 106.5, 111.9, 113.9, 116.3, 120.1, 129.1, 143.6, 151.0, 154.0; MS (FAB) 281, 255, 161. Anal. Calcd for $C_{17}H_{19}N_3$ O: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.35; H, 6.91; N, 14.94.

*4.5.19. Methyl 2-(1H-indol-3-yl)-2-(piperidin-1-yl)acetate (**23**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3–1.4 (m, 2H), 1.5–1.6 (m, 4H), 2.5–2.6 (m, 4H), 3.64 (s, 3H), 4.38 (s, 1H), 7.10 (t, 1H, J=7.5 Hz), 7.14 (t, 1H, J=7.5 Hz), 7.16 (s, 1H), 7.25 (d, 1H, J=7.5 Hz), 7.76 (d, 1H, J=7.5 Hz), 8.96 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.6, 51.7, 52.2, 66.3, 109.9, 111.3, 119.2, 119.5, 121.9, 124.4, 127.2, 135.9, 172.9; MS (FAB) 273, 212, 188; HRMS (FAB) calcd for $C_{16}H_{21}N_2O_2$: 273.1603, found: 273.1596.

*4.5.20. Methyl 2-(5-methoxy-1H-indol-3-yl)-2-(piperidin-1-yl)-acetate (**24**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3–1.4 (m, 2H), 1.5–1.6 (m, 4H), 2.5–2.6 (m, 4H), 3.69 (s, 3H), 3.84 (s, 3H), 4.34 (s, 1H), 6.82 (d, 1H, J=7.5 Hz), 7.20 (d, 1H, J=7.5 Hz), 7.22 (s, 1H), 7.26 (s, 1H), 8.49 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 25.8, 51.7, 52.1, 55.8, 66.6, 101.4, 110.3, 111.8, 112.4, 124.8, 127.7, 131.1, 154.1, 172.7; MS (FAB) 303, 245, 218; HRMS (FAB) calcd for $C_{17}H_{23}N_2O_3$: 303.1709, found: 303.1720.

*4.5.21. Methyl 3-(2-methoxy-2-oxo-1-(piperidin-1-yl)ethyl)-1H-indole-5-carboxylate (**25**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3–1.4 (m, 2H), 1.5–1.6 (m, 4H), 2.5–2.6 (m, 4H), 3.69 (s, 3H), 3.91 (s, 3H), 4.46 (s, 1H), 7.27 (s, 1H), 7.34 (d, 1H, J=7.5 Hz), 7.86 (d, 1H, J=7.5 Hz), 8.55 (s, 1H), 9.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 25.6, 51.8, 52.1, 65.9, 111.1, 111.6, 121.6, 122.2, 123.3, 125.7, 126.9, 138.6, 168.2, 172.6; MS (FAB) 331, 271, 246; HRMS (FAB) calcd for $C_{18}H_{23}N_2O_4$: 331.1658, found: 331.1658.

*4.5.22. Methyl 2-(1H-indol-3-yl)-2-(morpholin-4-yl)acetate (**26**)*

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.4–2.5 (m, 4H), 3.5–3.7 (m, 4H), 3.59 (s, 3H), 4.32 (s, 1H), 7.05 (t, 1H, J=7.5 Hz), 7.10 (t, 1H, J=7.5 Hz), 7.14 (s, 1H), 7.22 (d, 1H, J=7.5 Hz), 7.75 (d, 1H, J=7.5 Hz), 8.75 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2, 51.7, 66.1, 66.8, 109.5, 111.2, 119.5, 119.8, 122.2, 124.3, 126.8, 136.1, 172.1; MS (FAB) 275, 215, 188; HRMS (FAB) calcd for $C_{15}H_{18}N_2O_3$: 275.1396, found: 275.1369.

*4.5.23. Methyl 2-(1-methyl-1H-indol-3-yl)-2-(piperidin-1-yl)-acetate (**27**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3–1.4 (m, 2H), 1.5–1.6 (m, 4H), 2.5–2.6 (m, 4H), 3.67 (s, 3H), 3.70 (s, 3H), 4.38 (s, 1H), 7.11 (t, 1H, J=7.5 Hz), 7.14 (s, 1H), 7.20 (d, 1H, J=7.5 Hz), 7.24 (t, 1H, J=7.5 Hz), 7.76 (d, 1H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.7, 32.6, 51.5, 52.0, 66.2, 108.8, 109.1, 119.2, 119.6, 121.6, 127.7, 128.5, 136.6, 172.6; MS (FAB) 287, 227, 202; HRMS (FAB) calcd for $C_{17}H_{23}N_2O_2$: 287.1760, found: 287.1746.

*4.5.24. Methyl 2-(1-methyl-1H-indol-3-yl)-2-(morpholin-4-yl)-acetate (**28**)*

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.4–2.5 (m, 4H), 3.6–3.7 (m, 4H), 3.64 (s, 3H), 3.68 (s, 3H), 4.31 (s, 1H), 7.06 (t, 1H, J=7.5 Hz), 7.08 (s, 1H), 7.16 (t, 1H, J=7.5 Hz), 7.21 (d, 1H, J=7.5 Hz), 7.73 (t, 1H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.8, 51.2, 51.8, 66.0, 66.9, 108.1, 109.3, 119.5, 119.7, 121.9, 127.4, 128.8, 136.9, 172.0; MS (FAB) 287, 229, 202; HRMS (FAB) calcd for $C_{16}H_{21}N_2O_3$: 289.1552, found: 289.1568.

*4.5.25. Methyl 2-(1-methyl-1H-pyrrol-2-yl)-2-(piperidin-1-yl)-acetate (**29**)*

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.4–1.5 (m, 2H), 1.5–1.6 (m, 4H), 2.4–2.5 (m, 4H), 3.69 (s, 3H), 3.70 (s, 3H), 4.26 (s, 1H), 6.03 (t, 1H, J=3.5 Hz), 6.09 (d, 1H, J=3.5 Hz), 6.59 (d, 1H, J=3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 26.1, 34.1, 50.7, 51.3, 66.2, 106.4, 109.7, 123.4, 126.2, 171.0; MS (FAB) 237, 177, 152; HRMS (FAB) calcd for $C_{13}H_{21}N_2O_2$: 237.1603, found: 237.1611.

*4.5.26. Methyl 2-(1-methyl-1H-pyrrol-2-yl)-2-(morpholin-4-yl)-acetate (**30**)*

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.4–2.6 (m, 4H), 3.5–3.6 (m, 4H), 3.70 (s, 3H), 3.71 (s, 3H), 4.28 (s, 1H), 6.03 (t, 1H, J=3.5 Hz), 6.11 (d, 1H, J=3.5 Hz), 6.60 (d, 1H, J=3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1, 50.1, 51.5, 65.7, 67.0, 106.7, 110.3, 123.7, 125.1, 170.4; MS (FAB) 239, 179, 152; HRMS (FAB) calcd for $C_{12}H_{19}N_2O_3$: 239.1396, found: 239.1407.

*4.5.27. Methyl 2-(5-methylfuran-2-yl)-2-(piperidin-1-yl)-acetate (**31**)*

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.4–1.5 (m, 2H), 1.5–1.6 (m, 4H), 2.28 (s, 3H), 2.4–2.5 (m, 4H), 3.73 (s, 3H), 4.17 (s, 1H), 5.91 (d, 1H, J=3.0 Hz), 6.22 (d, 1H, J=3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 24.0, 25.6, 51.7, 51.9, 67.4, 106.1, 110.6, 146.8, 152.5, 170.1; MS (FAB) 238, 178, 153; HRMS (FAB) calcd for $C_{13}H_{20}NO_3$: 238.1443, found: 238.1446.

*4.5.28. Methyl 2-(5-methylfuran-2-yl)-2-(morpholin-4-yl)-acetate (**32**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.3–2.5 (m, 4H), 3.5–3.7 (m, 4H), 3.61 (s, 3H), 4.05 (s, 1H), 5.79 (d, 1H, J=3.5 Hz), 6.11 (d, 1H, J=3.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 50.8, 52.0, 66.5, 66.7, 106.2, 111.2, 145.7, 152.8, 169.4; MS (FAB) 240, 180, 158; HRMS (FAB) calcd for $C_{12}H_{18}NO_4$: 240.1236, found: 240.1235.

*4.5.29. Methyl 2-(5-methylthiophen-2-yl)-2-(morpholin-4-yl)-acetate (**33**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.4–2.6 (m, 4H), 3.7–3.8 (m, 4H), 3.74 (s, 3H), 4.24 (s, 1H), 6.60 (d, 1H, J=3.5 Hz), 6.83 (d, 1H, J=3.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 51.1, 52.1, 66.7, 69.3, 124.5, 127.6, 135.0, 141.3, 170.7; MS (FAB) 256, 196, 169; HRMS (FAB) calcd for $C_{12}H_{18}NO_3S$: 256.1007, found: 256.0995.

*4.5.30. Methyl 2-(1-(furan-2-ylmethyl)-1H-pyrrol-2-yl)-2-(piperidin-1-yl)acetate (**34**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4–1.6 (m, 6H), 2.4–2.5 (m, 4H), 3.68 (s, 3H), 4.37 (s, 1H), 5.12 (d, 1H, J=16.0 Hz), 5.44 (d, 1H, J=16.0 Hz), 6.06 (m, 2H), 6.17 (d, 1H, J=3.5 Hz), 6.30 (d, 1H, J=3.5 Hz), 6.67 (t, 1H, J=3.5 Hz), 7.34 (t, 1H, J=3.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 26.1, 43.4, 50.5, 51.3, 66.2, 107.1, 107.7, 110.0, 110.2, 122.6, 125.9, 142.2, 151.2, 170.7; MS (FAB) 303, 244, 218; HRMS (FAB) calcd for $C_{17}H_{23}N_2O_3$: 303.1709, found: 303.1716.

*4.5.31. Methyl 2-(4-(dimethylamino)phenyl)-2-(piperidin-1-yl)-acetate (**35**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3–1.4 (m, 2H), 1.5–1.6 (m, 4H), 2.3–2.4 (m, 4H), 2.87 (s, 6H), 3.60 (s, 3H), 3.78 (s, 1H), 6.59 (d, 2H, J=10 Hz), 7.20 (d, 2H, J=10 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 25.6, 40.3, 51.6, 52.4, 112.0, 123.4, 129.5, 150.2, 172.8; MS (FAB) 277, 218, 192; HRMS (FAB) calcd for $C_{16}H_{25}N_2O_2$: 277.1916, found: 277.1900.

*4.5.32. Methyl 2-amino-2-(1H-indol-3-yl)acetate (**37**)*

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (br s, 2H), 3.70 (s, 3H), 4.92 (s, 1H), 7.12 (t, 1H, J=7.5 Hz), 7.15 (s, 1H), 7.18 (t, 1H, J=7.5 Hz), 7.32 (d, 1H, J=7.5 Hz), 7.70 (d, 1H, J=7.5 Hz), 8.39 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.8, 52.2, 111.3, 115.3, 119.1, 119.9, 122.2, 122.4, 125.4, 136.4, 174.9; MS (FAB) 205 (M+H, 45%), 188 (M^+-NH_2, 100%), 145 (M^+-CO_2Me, 96%); HRMS (FAB) calcd for $C_{11}H_{13}N_2O_2$: 205.0977, found: 205.0976.

*4.5.33. Methyl 2,2-bis(1H-indol-3-yl)acetate[22] (**38**)*

White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 3H), 5.49 (s, 1H), 6.95 (s, 2H), 7.05 (t, 2H, J=7.5 Hz), 7.13 (d, 2H, J=7.5 Hz), 7.25 (t, 2H, J=7.5 Hz), 7.58 (d, 2H, J=7.5 Hz), 7.95 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 52.2, 111.2, 113.3, 119.1, 119.5, 122.0, 123.3, 126.5, 136.2, 174.0; MS (FAB) 304, 245.

*4.5.34. Methyl 2-(diallylamino)-2-(1H-indol-3-yl)acetate (**40**)*

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.2–3.4 (m, 4H), 3.70 (s, 3H), 4.95 (s, 1H), 5.0–5.2 (m, 4H), 5.8–5.9 (m, 2H), 7.10 (t, 1H, J=7.5 Hz), 7.13 (s, 1H), 7.18 (t, 1H, J=7.5 Hz), 7.30 (d, 1H, J=7.5 Hz), 7.76 (d, 1H, J=7.5 Hz), 8.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.4, 53.3, 60.2, 111.0, 111.1, 117.3, 119.7, 119.8, 122.2, 124.1, 126.9, 136.1, 136.2, 172.9; MS (FAB) 285 (M+H, 33%), 225 ($M-CO_2Me$, 100%); HRMS (FAB) calcd for $C_{17}H_{21}N_2O_2$: 285.1603, found: 285.1606.

*4.5.35. Methyl 2-(5-bromo-1H-indol-3-yl)-2-(diallylamino)-acetate (**41**)*

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.1–3.3 (m, 4H), 3.73 (s, 3H), 4.87 (s, 1H), 5.1–5.3 (m, 4H), 5.8–5.9 (m, 2H), 7.16 (d, 1H, J=7.5 Hz), 7.20 (d, 1H, J=7.5 Hz), 7.25 (s, 1H), 7.91 (s, 1H), 8.40 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.5, 53.3, 60.1, 111.1, 112.6, 113.0, 117.5, 122.5, 125.1, 125.2, 128.6, 134.8, 135.8, 172.6; MS (FAB) 363 (M+H, 22%), 303 ($M-CO_2Me$, 100%) 268; HRMS (FAB) calcd for $C_{17}H_{20}N_2O_2Br$: 363.0708, found: 363.0691.

*4.5.36. Methyl 2-(diallylamino)-2-(1H-pyrrol-2-yl)acetate (**42**)*

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.1–3.3 (m, 4H), 3.73 (s, 3H), 4.60 (s, 1H), 5.1–5.2 (m, 4H), 5.7–5.8 (m, 2H), 6.11 (t, 1H, J=3.0 Hz), 6.14 (d, 1H, J=3.0 Hz), 6.76 (d, 1H, J=3.0 Hz), 8.74 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.7, 53.2, 61.3, 108.0, 108.7, 117.6, 118.1, 125.7, 135.2, 171.9; MS (FAB) 235 (M+H, 19%), 175 ($M-CO_2Me$, 100%); HRMS (FAB) calcd for $C_{13}H_{19}N_2O_2$: 235.1447, found: 235.1453.

*4.5.37. Methyl 2-(diallylamino)-2-(1-methyl-1H-pyrrol-2-yl)-acetate (**43**)*

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.0–3.2 (m, 2H), 3.4–3.6 (m, 2H), 3.61 (s, 3H), 3.72 (s, 3H), 4.71 (s, 1H), 5.0–5.2 (m, 4H), 5.6–5.8 (m, 2H), 6.00 (t, 1H, J=2.0 Hz), 6.02 (d, 1H, J=2.0 Hz), 6.59 (d, 1H, J=2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.9, 51.2, 52.9, 60.0, 106.5, 109.8, 117.0, 123.4, 126.7, 136.3, 171.7; MS (FAB) 248 (M+H, 39%), 189 ($M-CO_2Me$, 100%); HRMS (FAB) calcd for $C_{14}H_{21}N_2O_2$: 249.1603, found: 249.1608.

*4.5.38. Methyl 2-(diallylamino)-2-(1-phenyl-1H-pyrrol-2-yl)-acetate (**44**)*

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.0–3.1 (m, 2H), 3.3–3.4 (m, 2H), 3.66 (s, 3H), 4.61 (s, 1H), 4.9–5.0 (m, 4H), 5.4–5.5 (m, 2H), 6.20 (t, 1H, J=3.0 Hz), 6.28 (d, 1H, J=3.0 Hz), 6.82 (d, 1H, J=3.0 Hz), 7.2–7.5 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2, 52.9, 58.9, 107.9, 111.2, 116.6, 123.6, 126.5, 127.3, 127.6, 128.8, 136.4, 139.8, 171.9; MS (FAB) 311 (M+H, 28%), 251 ($M-CO_2Me$, 100%); HRMS (FAB) calcd for $C_{19}H_{23}N_2O_2$: 311.1760, found: 311.1754.

*4.5.39. Methyl 2-(diallylamino)-2-(5-methylfuran-2-yl)acetate (**45**)*

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.1–3.2 (m, 2H), 3.3–3.4 (m, 2H), 3.73 (s, 3H), 4.66 (s, 1H), 5.1–5.2 (m, 4H), 5.8–5.9 (m, 2H), 5.92 (d, 1H, J=3.5 Hz), 6.17 (d, 1H, J=3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 51.8, 53.8, 60.8, 106.1, 110.5, 117.6, 135.7, 147.4, 152.3, 170.6; MS (FAB) 250 (M+H, 23%) 190 ($M-CO_2Me$, 100%) 153; HRMS (FAB) calcd for $C_{14}H_{20}NO_3$: 250.1443, found: 250.1455.

*4.5.40. Methyl 2-(diallylamino)-2-(5-methylthiophen-2-yl)-acetate (**46**)*

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.2–3.3 (m, 4H), 3.75 (s, 3H), 4.77 (s, 1H), 5.1–5.2 (m, 4H), 5.8–5.9 (m, 2H), 6.59 (d, 1H, J=3.5 Hz), 6.72 (d, 1H, J=3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 51.7, 53.2, 62.6, 117.5, 124.4, 126.6, 135.8, 137.0, 140.3,

171.5; MS (FAB) 266 (M+H, 15%), 206 (M−CO_2Me, 100%), 169; HRMS (FAB) calcd for $C_{14}H_{20}NO_2S$: 266.1215, found: 266.1223.

*4.5.41. Methyl 2-(diallylamino)-2-(4-(dimethylamino)-phenyl)acetate (**47**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (s, 6H), 3.1–3.2 (m, 4H), 3.67 (s, 3H), 4.46 (s, 1H), 5.0–5.2 (m, 4H), 5.8–5.9 (m, 2H), 6.65 (d, 2H, J=8.5 Hz), 7.20 (d, 2H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 51.4, 53.1, 67.3, 112.1, 117.4, 123.6, 129.5, 135.6, 150.1, 173.1; MS (FAB) 289, 229; HRMS (FAB) calcd for $C_{17}H_{25}N_2O_2$: 289.1916, found: 289.1926.

4.6. General procedure for deallylation

A diallylated compound (0.5 mmol), 1,3-dimethylbarbituric acid (458 mg, 3.00 mmol), and $Pd(PPh_3)_4$ (28.9 mg, 0.0250 mmol) were successively mixed together in CH_2Cl_2 (3 mL) at room temperature with stirring. After 1 h, the reaction was quenched with 1 N HCl (3 mL) and the reaction mixture was washed with $CHCl_3$ (5 mL×3). Then, to neutralize the resulting mixture, a saturated aqueous solution (10 mL) of $NaHCO_3$ was then added. The organic layer was dried over Na_2CO_3 and evaporated under reduced pressure to afford the corresponding product.

*4.6.1. Methyl 2-amino-2-(1-methyl-1H-pyrrol-2-yl)acetate (**48**)*

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88 (br s, 2H), 3.67 (s, 3H), 3.74 (s, 3H), 4.65 (s, 1H), 6.01 (t, 1H, J=3.5 Hz), 6.05 (d, 1H, J=3.5 Hz), 6.57 (d, 1H, J=3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.9, 51.6, 52.3, 106.6, 106.8, 123.1, 130.6, 173.9; MS (FAB): 169, 152; HRMS (FAB) calcd for $C_8H_{13}N_2O_2$: 169.0977, found: 169.0979.

*4.6.2. Methyl 2-amino-2-(5-methylfuran-2-yl)acetate[23] (**49**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (br s, 2H), 2.27 (s, 3H), 3.75 (s, 3H), 4.43 (s, 1H), 5.90 (d, 1H, J=3.5 Hz), 6.15 (d, 1H, J=3.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 51.5, 58.2, 106.2, 108.9, 116.9, 135.7, 171.5; MS (FAB): 170, 153.

*4.6.3. Methyl 2-amino-2-(5-methylthiophen-2-yl)acetate (**50**)*

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (br s, 2H), 2.44 (s, 3H), 3.75 (s, 3H), 4.78 (s, 1H), 6.60 (d, 1H, J=3.5 Hz), 6.80 (d, 1H, J=3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 52.5, 54.6, 124.6, 124.8, 139.7, 140.9, 173.4; MS (FAB): 186, 169; HRMS (FAB) calcd for $C_8H_{12}NO_2S$: 186.0589, found: 186.0607.

*4.6.4. Methyl 2-amino-2-(4-(dimethylamino)phenyl)acetate (**51**)*

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (br s, 2H), 2.93 (s, 6H), 3.68 (s, 3H), 4.52 (s, 1H), 6.68 (d, 2H, J=8.5 Hz), 7.21 (d, 2H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.4, 52.1, 58.1, 112.5, 127.4, 133.9, 150.2, 174.9; MS (FAB) 210, 192; HRMS (FAB) calcd for $C_{11}H_{17}N_2O_2$: 209.1290, found: 209.1287.

Acknowledgements

This work was partially supported by a grant for the 'High-Tech Research Center' Project for Private Universities: a matching fund subsidy from MEXT, 2000–2004, and 2005–2007. N.S. acknowledges the TORAY Award in Synthetic Organic Chemistry, Japan.

References and notes

1. (a) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584; (b) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360; (c) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816; (d) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989; Vol. 7.
2. Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.
3. Salituro, G. M.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 760.
4. (a) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222; (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 135; (c) O'Donnell, M. J., Ed. α-Amino acid synthesis (Tetrahedron Symposia in Print). *Tetrahedron* **1988**, *44*, 5253.
5. For selected papers and reviews on the preparation of α-aryl amino acid derivatives, see: (a) Soueidan, M.; Collin, J.; Gil, R. *Tetrahedron Lett.* **2006**, *47*, 5467; (b) Jiang, B.; Huang, Z.-G. *Synthesis* **2005**, 2198; (c) Lei, F.; Chen, Y.-J.; Sui, Y.; Liu, L.; Wang, D. *Synlett* **2003**, 1160; (d) Janczuk, A.; Zhang, W.; Xie, W.; Lou, S.; Cheng, J.; Wang, P. G. *Tetrahedron Lett.* **2002**, *43*, 4271; (e) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221; (f) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817; (g) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 6715; (h) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114; (i) Johannsen, M. *Chem. Commun.* **1999**, 2233; (j) Ben-Ishai, D.; Sataty, I.; Peled, N.; Goldshare, R. *Tetrahedron* **1987**, *43*, 439.
6. For selected reviews and papers for the reaction of carbon nucleophiles with *N*,*O*- and *N*,*N*-acetals, leading to the amino acid derivatives, see: (a) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10; (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044; (c) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683; (d) Katritzky, A. R.; Kirichenko, N.; Rogovoy, B. V.; He, H. Y. *J. Org. Chem.* **2003**, *68*, 9088; (e) Lebouvier, N.; Laroche, C.; Huguenot, F.; Brigaud, T. *Tetrahedron Lett.* **2002**, *43*, 2827; (f) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477; (g) Ferraris, D.; Young, B.; Dudding, T.; Drury, W. J., III; Lectka, T. *Tetrahedron* **1999**, *55*, 8869; (h) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168; (i) Kobayashi, S.; Ishitani, H.; Komiyama, S.; Oniciu, D. C.; Katritzky, A. R. *Tetrahedron Lett.* **1996**, *37*, 3731; (j) Tsukamoto, T.; Kitazume, T. *Chem. Lett.* **1992**, *21*, 1377; (k) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121; (l) Katritzky, A. R.; Shobana, N.; Harris, P. A. *Tetrahedron Lett.* **1990**, *31*, 3999.
7. (a) Ge, C.-S.; Chen, Y.-J.; Wang, D. *Synlett* **2002**, 37; (b) DeNinno, M. P.; Eller, C.; Etienne, J. B. *J. Org. Chem.* **2001**, *66*, 6988; (c) O'Donnell, M. J.; Falmagne, J.-B. *Tetrahedron Lett.* **1985**, *26*, 699.
8. For papers on the reaction of boronic acids with α-hydroxyglycine, see: Sugiura, M.; Mori, C.; Hirano, K.; Kobayashi, S. *Can. J. Chem.* **2005**, *83*, 937.
9. (a) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941 and references cited therein; (b) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *J. Chem. Soc., Chem. Commun.* **1988**, 1161.
10. (a) Piper, S.; Risch, N. *Synlett* **2004**, 1489; (b) Grumbach, H.-J.; Merla, B.; Risch, N. *Synthesis* **1999**, 1027.
11. For detailed examinations of Lewis acids for aminomethylation of electron-rich arenes with *N*,*O*-acetals, see our preliminary papers: (a) Sakai, N.; Asano, J.; Shimano, Y.; Konakahara, T. *Synlett* **2007**, 2675; (b) Sakai, N.; Hirasawa, M.; Hamajima, T.; Konakahara, T. *J. Org. Chem.* **2003**, *68*, 483; (c) Sakai, N.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2002**, *43*, 4821.
12. Gong, Y.; Kato, K.; Kimoto, H. *Synlett* **2000**, 1058.
13. (a) Gong, Y.; Kato, K. *J. Fluorine Chem.* **2001**, *108*, 83; (b) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157; (c) Okano, K.; Morimoto, T.; Sekiya, M. *Chem. Pharm. Bull.* **1985**, *33*, 2228; (d) Bestmann, H. J.; Wölfel, G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 53; (e) Hirao, A.; Hattori, I.; Yamaguchi, K.; Nakahama, S.; Yamazaki, N. *Synthesis* **1982**, 461.
14. (a) Hirner, S.; Panknin, O.; Edefuhr, M.; Somfai, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1907; (b) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535; (c) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109.
15. (a) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7068; (b) Grimm, D. T.; Bartmess, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 1227.
16. The aminomethylation of *N*,*O*-acetal **36** with other electron-rich arenes, such as pyrrole, furan, and aniline derivative, did not produce the corresponding amino acid derivatives.
17. For mechanistic work on an intermediate in the alkylation of acyclic acetals, see: Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915.
18. When the reaction was carried out in the presence of 0.5 equiv of Me_3SiCl, the yield of the aminomethylated product was less than 50%. 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) Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646; (e) Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *Chem. Lett.* **2002**, 428; (f) Yang, L.; Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2007**, *48*, 1599.
19. Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409.
20. Dinzo, S. E.; Freeksen, R. W.; Pabst, W. E.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 2846.
21. Kantlehner, W.; Haug, E. *Synthesis* **1982**, 146.
22. Earle, M. J.; Fairhurst, R. A.; Heaney, H. *Tetrahedron Lett.* **1991**, *32*, 6171.
23. Mueller, U.; Connell, R.; Goldmann, S.; Mohrs, K.H.; Angerbauer, R.; Matthias, M.G.; Niewoehner, U.; Gruetzmann, R.; Beuck, M. Ger. Offen. 1996, 156; *Chem. Abstr.* **1996**, *125*, 142561.