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Facile Approach to Natural or Non-Natural Amino Acid Derivatives: Me_3SiCl-Promoted Coupling Reaction of Organozinc Compounds with N,O-Acetals

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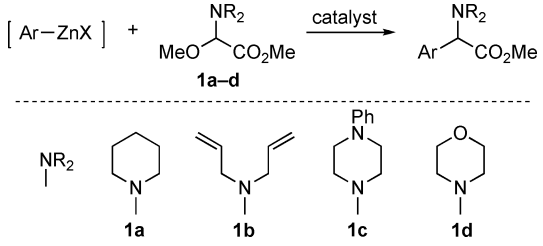
We have developed a Me_3SiCl-promoted coupling reaction of aryl- and alkylzinc compounds, in-situ generated either by transmetalation of the corresponding organometallic reagents or by insertion of zinc metal into organic halides, with several N,O-acetals, which leads to the preparation of a variety of natural and non-natural amino acid derivatives.

Introduction

α-Aryl amino acid derivatives are important and indispensable materials for the maintenance of human life.[1] Approaches that employ Friedel–Crafts-type reactions of aromatics with imine (iminoesters),[2] N,O-acetals,[3] and N,N-acetals[4] as glycine cation equivalents are among the most useful and representative tools for the preparation of these α-aromatic amino acid derivatives. In this type of reaction, aromatic compounds with electron-donating groups, such as an alkyl or alkoxy group and an amino group, and electron-rich heterocycles, such as indole, pyrrole, and furan, have generally been utilized. However, reactions in which less-activated aryl compounds, such as benzene and toluene, and aromatic compounds with an electron-withdrawing group, such as a halogen substituent and an ester group, are used have been unsuccessful due to lower nucleophilicity. A $Hf(OTf)_4$-doped Me_3SiCl catalytic system was also found to effectively catalyze the aminomethylation of electron-rich arenes with several N,O-acetals, which led to the production of α-aryl amino acid derivatives.[5] Unfortunately, aminomethylation with the use of aromatic compounds with electron-deficient substituents was entirely unproductive. Thus, it was necessary to focus on the development of an efficient process, which could undertake the aminomethylation of aromatic compounds having an electron-withdrawing group with N,O-acetals.

Organozinc reagents, which are tolerant for a variety of functional groups, generally show lower reactivity to typical organic electrophiles than the corresponding organolithium compounds and Grignard reagents. However, these reagents display a potential advantage for carbon–carbon bond formation with organic compounds having electron-withdrawing groups, such as ketones, aldehydes, nitriles, and esters.[6] In addition, organozinc compounds can be easily prepared either by transmetalation of organolithium reagents or Grignard reagents or by insertion of zinc metal into organic halides. Consequently, the coupling reaction of such arylzinc compounds with N,O-acetals, activated by a proper catalyst, would be suitable for the preparation of α-aryl amino acid derivatives having electron-deficient groups (Scheme 1).[7,8]



Scheme 1. Metal-promoted coupling reaction of arylzinc compounds with N,O-acetals **1** as a glycine moiety precursor.

In this paper, the authors report a Me_3SiCl-promoted coupling reaction of arylzinc compounds, prepared by transmetalation of the corresponding aryllithium compounds having electron-deficient groups, with N,O-acetals as a glycine cation equivalent, leading to the synthesis of a variety of α-arylglycine derivatives. The authors also demonstrate that this method can be applied to the coupling reaction of benzyl- and alkylzinc species with N,O-acetals, which leads to the preparation of standard amino acid derivatives such as glycine, phenylalanine, aspartic acid, valine, and leucine.

Results and Discussion

On the basis of previous studies, when the reaction of in situ generated phenylzinc bromide with N,O-acetal[9] **1a** was initially performed with the use of $Hf(OTf)_4$ (5 mol-%) and

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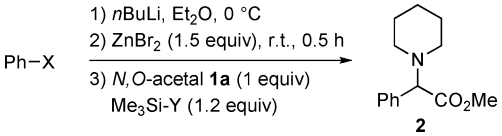
chlorotrimethylsilane (Me_3SiCl, 1.2 equiv.), the desired aminomethylated product **2a** was obtained in 95% yield (Table 1, run 1). When the reaction was attempted without the hafnium catalyst, the same result was obtained (Table 1, run 2); moreover, without the addition of hafnium and Me_3SiCl, starting N,O-acetal **1a** was recovered (Table 1, run 3). Consequently, it was found that Me_3SiCl activates the N,O-acetal, to make up for the low nucleophilicity of the arylzinc reagent, and promotes the coupling reaction. In order to better adjust the reaction conditions, a counteranion exchange on a silicon catalyst was carried out, which resulted in a decreased yield (Table 1, runs 4 and 5). In contrast, the use of chlorobenzene instead of the bromide resulted in the recovery of the starting acetal. In the case of iodobenzene, the yield decreased slightly (Table 1, runs 6 and 7).

Table 1. Optimization of reaction conditions.



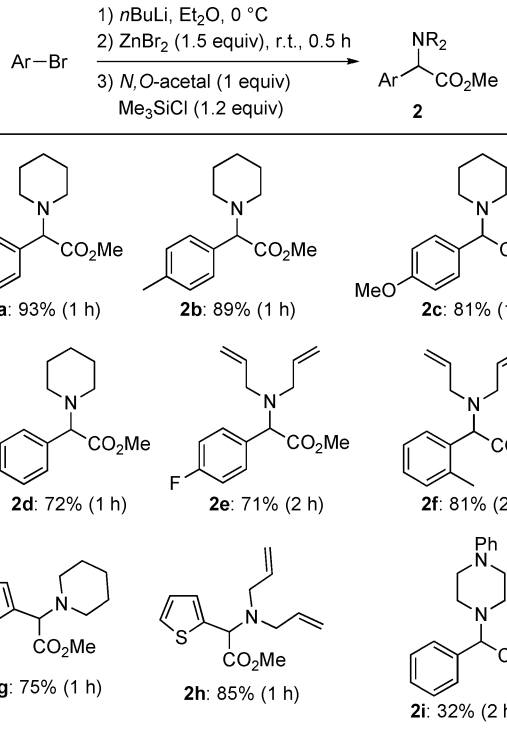
Run	Ph–X	Me_3Si–Y	Time [h]	Yield [%][a]
1	PhBr	Me_3SiCl	1	95[b]
2	PhBr	Me_3SiCl	1	93
3	PhBr	none	1	NR
4	PhBr	Me_3SiI	1.5	ND
5	PhBr	Me_3SiOTf	1	33
6	PhCl	Me_3SiCl	1	NR
7	PhI	Me_3SiCl	0.5	77

[a] Isolated yield. [b] Reaction was carried out in the presence of $Hf(OTf)_4$ (5 mol-%).

Preparation of a variety of α-arylglycine derivatives with several N,O-acetals was then examined, and the results are summarized in Table 2. The reaction can be successfully adapted to aryl bromides with either an electron-donating or an electron-withdrawing group, as well as to a heterocycle such as 2-bromothiophene. It was particularly successful in the one-pot synthesis of arylglycine derivatives **2d**,**e** having an electron-withdrawing group as a fluorine substituent. The location of a methyl group on the benzene ring did not affect the reactivity, and the corresponding amino acid derivative **2f** was produced in good yield. The use of N,O-acetal **1c** markedly decreased the yield of **2i**. Me_3SiCl seems to prefer to coordinate to the *N*-phenylpiperazine rather than to serve as an activator for the methoxy substituent.

The reaction of N,O-acetals with benzyl halide derivatives instead of aryl bromide derivatives was the carried out for the preparation of phenylalanine derivatives, and the results are shown in Table 3. The reaction with benzyl bromide did not need the generation of the corresponding benzyl anion from the halide with *n*BuLi and proceeded through a standard Reformatsky-type reaction with metallic zinc to produce expected phenylalanine derivatives **3**. For example, when the reaction with benzyl bromide and 3-methylbenzyl bromide was carried out in the presence of granular zinc, the corresponding phenylalanine derivatives

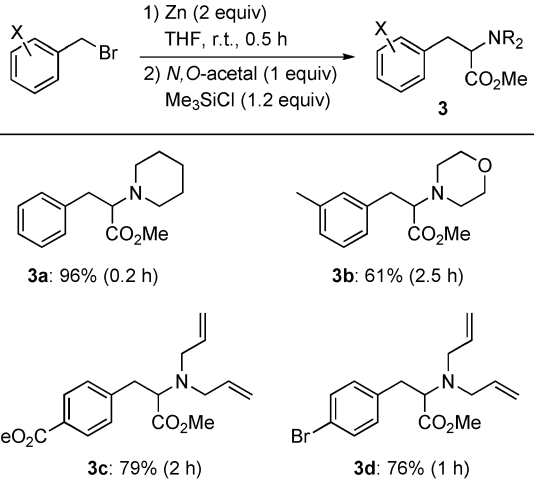
Table 2. Synthesis of α-arylglycine derivatives.[a]



[a] Isolated yield.

3a,**b** were obtained in 96 and 61% yield, respectively. The reactions with substrates having an electron-withdrawing group, such as an ester group or a bromine substituent, were also successful and produced expected phenylalanine derivatives **3c**,**d** in good yields.

Table 3. Synthesis of phenylalanine derivatives.[a]

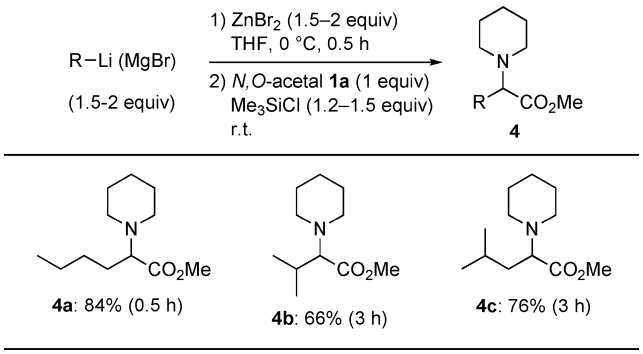


[a] Isolated yield.

The present method was used to prepare several amino acid derivatives with aliphatic chains, as shown in Table 4. For example, with the use of *n*BuLi in the presence of $ZnBr_2$ the reaction proceeded to give desired amino acid **4a** in 84% yield. Similar cases in which isopropyl or *sec*-butyl

Grignard reagents were used were also successful in producing valine derivative **4b** and leucine derivative **4c** in practical yields.

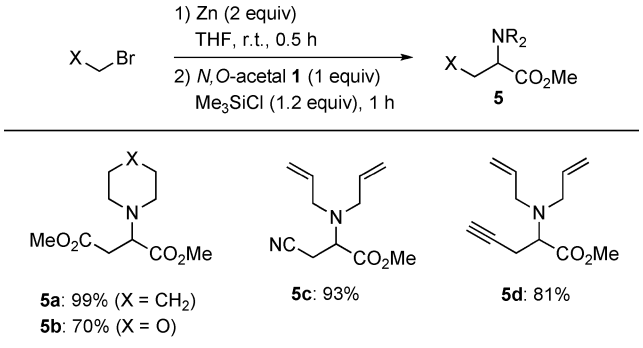
Table 4. Synthesis of amino acid derivatives **4** having an alkyl chain.[a]



[a] Isolated yield.

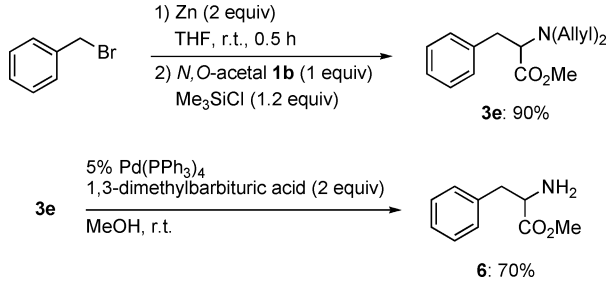
Moreover, as shown in Table 5, the reaction of N,O-acetals **1a**,**d** with methyl bromoacetate in the presence of metallic zinc and Me_3SiCl produced novel aspartic acid derivatives **5a**,**b** in 99 and 70% yield, respectively. When the reaction was performed with bromoacetonitrile and propargyl bromide, the corresponding amino acid derivatives **5c**,**d** were obtained in good yields.

Table 5. Synthesis of various amino acid derivatives.[a]



[a] Isolated yield.

Finally, to prepare an *N*-underivatized amino acid derivative, deprotection of the diallylamino group was performed (Scheme 2). It was demonstrated that a sequential procedure consisting of a Me_3SiCl-catalyzed coupling reaction of benzylzinc bromide with N,O-acetal **1b** having a diallylamino group and deprotection of the diallylamino group in product **3e** with the method described by Guibé or Tsukamoto[10] successfully produced *N*-unsubstituted phenylalanine derivative **6**.



Scheme 2. Synthesis of *N*-underivatized phenylalanine derivative **6**.

Conclusions

In summary, this study demonstrated the Me_3SiCl-promoted coupling reaction of aryl- and alkylzinc compounds, which were generated either by transmetalation of the corresponding organometallic reagents or by insertion of zinc metal into organic halides, with several N,O-acetals as a glycine cation equivalent, which led to the preparation of a variety of natural and non-natural amino acid derivatives involving standard amino acids, such as glycine, phenylalanine, aspartic acid, valine, and leucine.

Experimental Section

General Methods: Column chromatography was performed by using silica gel. THF and Et_2O were distilled from sodium–benzophenone and dried with 4Å MS. MeOH was distilled from Mg/I_2 and dried with 3Å MS. Secondary amines (piperidine, etc.) were commercially available and distilled prior to use. All reactions were carried out under a nitrogen atmosphere, unless otherwise noted. ^1H NMR spectra were measured at 500 (or 300) MHz by using tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured at 125 (or 75) MHz by using TMS or a center peak of chloroform (δ =77.0 ppm) as an internal standard. High-resolution mass spectra were measured by using NBA (3-nitrobenzylalcohol) as a matrix. Methyl 2-bromo-2-methoxyacetate was prepared according to the literature.[5a]

General Procedure for the Synthesis of N,O-Acetals 1a–d: To a freshly distilled THF (100 mL) was successively added the corresponding secondary amine (24 mmol), triethylamine (24 mmol), and methyl 2-bromo-2-methoxyacetate (20 mmol), and the solution was stirred at room temperature. After 2 h, the reaction was quenched by adding a saturated aqueous solution Na_2CO_3 (2.0 mL). The aqueous layer was extracted with $CHCl_3$, and the organic phase was combined, dried with anhydrous Na_2CO_3, filtered, and evaporated under reduced pressure. The crude product was distilled (Kugelrohr) to give the corresponding N,O-acetals.

1a:[5a] B.p. 71–72 °C/5 Torr (colorless oil). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.3–1.4 (m, 2 H, N-CH_2-CH_2-CH_2), 1.5–1.6 (m, 4 H, N-CH_2-CH_2), 2.5–2.8 (m, 4 H, N-CH_2), 3.39 (s, 3 H, O-CH_3), 3.77 (s, 3 H, CO_2-CH_3), 4.23 (s, 1 H, C-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2, 25.8, 48.4, 51.4, 55.5, 94.0, 168.7 ppm.

1b:[5a] B.p. 69–70 °C/5 Torr (colorless oil). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.2–3.3 (m, 4 H, N-CH_2-CH=CH_2), 3.36 (s, 3 H, O-CH_3), 3.76 (s, 3 H, CO_2-CH_3), 4.45 (s, 1 H, C-*H*), 5.1–5.2 (m, 4 H, N-CH_2-CH=CH_2), 5.7–5.8 (m, 2 H, N-CH_2-CH=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.8, 52.1, 55.5, 89.8, 117.5, 135.7, 169.7 ppm. MS (ESI): *m*/*z* = 222 [M + Na]. HRMS (ESI): calcd for $C_{10}H_{17}NNaO_3$ 222.1106; found 222.1095.

1c:[5a] B.p. 148–150 °C/5 Torr (brown oil). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.76 (t, *J* = 5.5 Hz, 2 H, CH-N-CH_2-CH_2-N-Ph), 2.92 (t, *J* = 5.5 Hz, 2 H, CH-N-CH_2-CH_2-N-Ph), 3.17 (t, *J* = 5.5 Hz, 4 H, CH-N-CH_2-CH_2-N-Ph), 3.42 (s, 3 H, O-CH_3), 3.78 (s, 3 H, CO_2-CH_3), 4.32 (s, 1 H, C-*H*), 6.83 (t, *J* = 7.5 Hz, 1 H, Ar-*H*), 6.91

(d, J = 7.5 Hz, 2 H, Ar-*H*), 7.23 (t, J = 7.5 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 47.3, 49.3, 51.6, 55.8, 93.2, 116.1, 119.7, 128.9, 151.2, 168.3 ppm.

1d:[5] B.p. 84–86 °C/5 Torr (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.6–2.8 (m, 4 H, N-CH_2-CH$_2$-O), 3.42 (s, 3 H, O-CH_3), 3.6–3.7 (m, 4 H, N-CH$_2$-CH_2-O), 3.79 (s, 3 H, CO$_2$-CH_3), 4.23 (s, 1 H, C-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.6, 51.7, 55.8, 66.9, 93.4, 168.2 ppm.

General Procedure for the Synthesis of Amino Acid Derivatives 2a–i: Aryl bromide (0.75 mmol) and *n*-butyllithium (1.6 M in hexane, 0.50 mL, 0.80 mmol) were successively mixed in Et_2O at room temperature by stirring. After 0.2 h, $ZnBr_2$ (0.75 mmol) was added, and the suspension was stirred for 0.5 h at room temperature. N,O-Acetal **1a** (0.50 mmol) and freshly distilled Me_3SiCl (0.60 mmol) were then added, and the mixture 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 of Na_2CO_3 (2 mL). The combined organic layer was dried with anhydrous Na_2CO_3 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt) to afford amino acid derivative **2**.

2a:[11] Yield: 108.3 mg, 93% (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.4–1.5 (m, 2 H, N-CH$_2$-CH$_2$-CH_2), 1.5–1.6 (m, 4 H, N-CH$_2$-CH_2), 2.3–2.4 (m, 4 H, N-CH_2), 3.67 (s, 3 H, CO$_2$-CH_3), 3.97 (s, 1 H, C-*H*), 7.2–7.3 (m, 3 H, Ar-*H*), 7.3–7.4 (m, 2 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2, 25.7, 51.8, 52.3, 128.0, 128.3, 128.7, 136.1, 172.2 ppm. MS (FA): *m*/*z* (%) = 234 (63) [M + H], 174 (100) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{14}H_{20}NO_2$ 234.1494; found 234.1504.

2b: Yield: 110.0 mg, 89% (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.4–1.5 (m, 2 H, N-CH$_2$-CH$_2$-CH_2), 1.5–1.6 (m, 4 H, N-CH$_2$-CH_2), 2.3–2.4 (m, 7 H, N-CH_2, Ar-CH_3), 3.66 (s, 3 H, CO$_2$-CH_3), 3.93 (s, 1 H, C-*H*), 7.12 (d, J = 8.5 Hz, 2 H, Ar-*H*), 7.30 (d, J = 8.5 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 24.2, 25.7, 51.7, 52.3, 128.6, 129.0, 133.1, 137.8, 172.4 ppm. MS (FA): *m*/*z* (%) = 188 (80) [M + H], 248 (100) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{15}H_{22}NO_2$ 248.1651; found 248.1628.

2c: Yield: 106.5 mg, 81% (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.4–1.5 (m, 2 H, N-CH$_2$-CH$_2$-CH_2), 1.5–1.6 (m, 4 H, N-CH$_2$-CH_2), 2.3–2.4 (m, 4 H, N-CH_2), 3.67 (s, 3 H, O-CH_3), 3.79 (s, 3 H, CO$_2$-CH_3), 3.90 (s, 1 H, C-*H*), 6.85 (d, J = 8.5 Hz, 2 H, Ar-*H*), 7.34 (d, J = 8.5 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3, 25.6, 51.8, 52.3, 55.1, 113.7, 128.1, 129.8, 159.4, 172.5 ppm. MS (FA): *m*/*z* (%) = 264 (100) [M + H], 204 (85) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{15}H_{22}NO_3$ 264.1600; found 264.1589.

2d: Yield: 90.5 mg, 72% (yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.4–1.5 (m, 2 H, N-CH$_2$-CH$_2$-CH_2), 1.5–1.6 (m, 4 H, N-CH$_2$-CH_2), 2.3–2.4 (m, 4 H, N-CH_2), 3.68 (s, 3 H, CO$_2$-CH_3), 3.95 (s, 1 H, C-*H*), 7.00 (t, J = 8.5 Hz, 2 H, Ar-*H*), 7.40 (t, J = 8.5 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 25.7, 51.8, 52.2, 74.0, 115.2, 115.3, 130.3, 130.4, 131.9, 132.0, 161.5, 163.5, 172.1 ppm. MS (FA): *m*/*z* (%) = 252 (100) [M + H], 192 (82) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{14}H_{19}NO_2F$ 252.1400; found 252.1402.

2e: Yield: 93.5 mg, 71% (yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.18 (m, 4 H, N-CH_2-CH=CH$_2$), 3.71 (s, 3 H, CO$_2$-CH_3), 4.50 (s, 1 H, C-*H*), 5.1–5.2 (m, 4 H, N-CH$_2$-CH=CH_2), 5.8–5.9 (m, 2 H, N-CH$_2$-C*H*=CH$_2$), 7.00 (m, 2 H, Ar-*H*), 7.34 (m, 2 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.6, 53.0, 53.3, 66.9, 115.1, 115.3, 117.6, 130.2, 130.3, 131.8, 132.3, 135.3, 161.4, 163.3, 172.4 ppm. MS (FA): *m*/*z* (%) = 264 (80) [M + H], 192 (100) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{15}H_{19}NO_2F$ 264.1400; found 264.1410.

2f: Yield: 105.0 mg, 81% (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, Ar-CH_3), 3.16 (m, 2 H, N-CH_2-CH=CH$_2$), 3.30 (m, 2 H, N-CH_2-CH=CH$_2$), 3.69 (s, 3 H, CO$_2$-CH_3), 4.79 (s, 1 H, C-*H*), 5.0–5.2 (m, 4 H, N-CH$_2$-CH=CH_2), 5.7–5.8 (m, 2 H, N-CH$_2$-C*H*=CH$_2$), 7.14 (m, 3 H, Ar-*H*), 7.24 (m, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 51.3, 53.2, 64.5, 64.5, 117.2, 125.7, 127.8, 128.3, 130.7, 134.9, 135.9, 137.8, 172.9 ppm. MS (FA): *m*/*z* (%) = 260 (5) [M + H], 200 (100) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{16}H_{22}NO_2$ 260.1651; found 260.1668.

2g: Yield: 89.7 mg, 75% (red oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.4–1.5 (m, 2 H, N-CH$_2$-CH$_2$-CH_2), 1.5–1.6 (m, 4 H, N-CH$_2$-CH_2), 2.4–2.5 (m, 4 H, N-CH_2), 3.74 (s, 3 H, CO$_2$-CH_3), 4.36 (s, 1 H, C-*H*), 6.94 (t, J = 4.0 Hz, 1 H, Ar-*H*), 7.02 (d, J = 4.0 Hz, 1 H, Ar-*H*), 7.28 (d, J = 4.0 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 25.8, 51.9, 52.0, 69.4, 126.1, 126.2, 127.0, 139.0, 171.1 ppm. MS (FA): *m*/*z* (%) = 240 (42) [M + H], 180 (100) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{12}H_{18}NO_2S$ 240.1058; found 240.1051.

2h: Yield: 106.8 mg, 85% (brown oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.2–3.3 (m, 4 H, N-CH_2-CH=CH$_2$), 3.76 (s, 3 H, CO$_2$-CH_3), 4.86 (s, 1 H, C-*H*), 5.1–5.3 (m, 4 H, N-CH$_2$-CH=CH_2), 5.8–5.9 (m, 2 H, N-CH$_2$-C*H*=CH$_2$), 6.94 (m, 2 H, Ar-*H*), 7.26 (m, 1 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.6, 53.2, 62.2, 117.5, 125.7, 126.3, 126.4, 135.6, 139.9, 171.3 ppm. MS (FA): *m*/*z* (%) = 252 (100) [M + H], 192 (75) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{13}H_{18}NO_2S$ 252.1058; found 252.1059.

2i: Yield: 49.6 mg, 32% (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (t, J = 5.0 Hz, 4 H, CH-N-CH_2-CH$_2$-N-Ph), 3.20 (t, J = 5.0 Hz, 4 H, CH-N-CH$_2$-CH_2-N-Ph), 3.70 (s, 3 H, CO$_2$-CH_3), 4.05 (s, 1 H, C-*H*), 6.82 (t, J = 7.0 Hz, 1 H, Ar-*H*), 6.88 (d, J = 7.0 Hz, 2 H, Ar-*H*), 7.22 (t, J = 7.0 Hz, 2 H, Ar-*H*), 7.34 (m, 3 H, Ar-*H*), 7.45 (m, 2 H, Ar-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.9, 51.1, 52.0, 74.1, 116.0, 119.7, 127.1, 128.6, 128.8, 129.0, 135.5, 151.1, 171.8 ppm. MS (FA): *m*/*z* (%) = 311 (100) [M + H], 251 (93) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{19}H_{23}N_2O_2$ 311.1760; found 311.1744.

General Procedure for Phenylalanine Derivatives 3: Freshly distilled THF (3 mL) and benzyl bromide (0.75 mmol) were successively added to a glass vessel (20 mL) containing Zn dust (1.0 mmol) under a nitrogen atmosphere, and the suspension was stirred at room temperature for 0.5 h. N,O-Acetal (0.50 mmol) and Me_3SiCl (0.6 mmol) were then added, and the mixture was stirred at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried with anhydrous Na_2CO_3 and the solvent removed. The product was isolated by flash chromatography (hexane/AcOEt) and characterized by using spectroscopic techniques.

3a:[12] Yield: 118.7 mg, 96% (yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.2–1.3 (m, 2 H, N-CH$_2$-CH$_2$-CH_2), 1.3–1.5 (m, 4 H, N-CH$_2$-CH_2), 2.3–2.5 (m, 4 H, N-CH_2), 2.76 (m, 1 H, Ar-CH_2-CH), 2.88 (m, 1 H, Ar-CH_2-CH), 3.23 (m, 1 H, C-*H*), 3.41 (s, 3 H, CO$_2$-CH_3), 7.0–7.2 (m, 5 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.4, 26.3, 35.6, 50.7, 50.9, 70.3, 126.2, 128.1, 129.0, 138.3, 171.7 ppm. MS (FA): *m*/*z* (%) = 248 (95) [M + H], 188 (100) [M – CO$_2$Me]. HRMS (FAB): calcd. for $C_{15}H_{22}NO_2$ 248.1651; found 248.1637.

3b: Yield: 80.3 mg, 61% (yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, Ar-CH_3), 2.6–2.7 (m, 4 H, N-CH_2-CH$_2$-O), 2.91

(m, 1 H, Ar-CH_2-CH), 3.01 (m, 1 H, Ar-CH_2-CH), 3.38 (m, 1 H, C-*H*), 3.60 (s, 3 H, CO_2-CH_3), 3.6–3.8 (m, 4 H, N-CH_2-CH_2-O), 6.9–7.0 (m, 3 H, Ar-*H*), 7.16 (t, *J* = 8.0 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 35.2, 50.2, 51.0, 67.2, 69.9, 126.0, 127.2, 128.2, 129.8, 137.6, 137.8, 171.5 ppm. MS (FA): *m*/*z* (%) = 264 (100) [M + H], 204 (96) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{15}H_{22}NO_3$ 264.1600; found 264.1610.

3c: Yield: 125.3 mg, 79% (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.94 (m, 1 H, Ar-CH_2-CH), 3.05 (m, 3 H, Ar-CH_2-CH, N-CH_2-CH=CH_2), 3.34 (m, 2 H, N-CH_2-CH=CH_2), 3.65 (s, 3 H, CH-CO_2-CH_3), 3.72 (t, *J* = 7.5 Hz, 1 H, C-*H*), 3.90 (s, 3 H, Ar-CO_2-CH_3), 5.0–5.2 (m, 4 H, N-CH_2-CH=CH_2), 5.6–5.7 (m, 2 H, N-CH_2-C*H*=CH_2), 7.23 (d, *J* = 8.0 Hz, 2 H, Ar-*H*), 7.93 (d, *J* = 8.0 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.6, 51.1, 51.9, 53.3, 63.2, 117.2, 128.1, 129.3, 129.4, 136.0, 144.1, 167.0, 172.6 ppm. MS (FA): *m*/*z* (%) = 318 (100) [M + H], 258 (98) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{18}H_{24}NO_4$ 318.1705; found 318.1718.

3d: Yield: 128.5 mg, 76% (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.81 (m, 1 H, Ar-CH_2-CH), 2.97 (m, 1 H, Ar-CH_2-CH), 3.02 (m, 2 H, N-CH_2-CH=CH_2), 3.33 (m, 2 H, N-CH_2-CH=CH_2), 3.65 (s, 3 H, CO_2-CH_3), 3.69 (t, *J* = 7.5 Hz, 1 H, C-*H*), 5.0–5.2 (m, 4 H, N-CH_2-CH=CH_2), 5.6–5.7 (m, 2 H, N-CH_2-C*H*=CH_2), 7.03 (d, *J* = 8.0 Hz, 2 H, Ar-*H*), 7.37 (d, *J* = 8.0 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.1, 51.1, 53.4, 63.4, 117.2, 120.0, 131.0, 131.1, 136.1, 137.5, 172.7 ppm. MS (FA): *m*/*z* (%) = 338 (35) [M + H], 278 (100) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{16}H_{22}BrNO_2$ 338.0756; found 338.0736.

3e: Yield: 116.6 mg, 90% (yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.86 (m, 1 H, Ar-CH_2-CH), 3.0–3.1 (m, 3 H, Ar-CH_2-CH, N-CH_2-CH=CH_2), 3.34 (m, 2 H, N-CH_2-CH=CH_2), 3.62 (s, 3 H, CO_2-CH_3), 3.69 (t, *J* = 7.5 Hz, 1 H, C-*H*), 5.0–5.2 (m, 4 H, N-CH_2-CH=CH_2), 5.6–5.7 (m, 2 H, N-CH_2-C*H*=CH_2), 7.1–7.2 (m, 3 H, Ar-*H*), 7.2–7.3 (m, 2 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.7, 50.9, 53.4, 63.8, 117.0, 126.1, 128.0, 129.2, 136.2, 138.4, 172.9 ppm. MS (FA): *m*/*z* (%) = 260 (93) [M + H], 200 (100) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{16}H_{22}NO_2$ 260.1651; found 260.1656.

General Procedure for the Synthesis of Amino Acid Derivatives 4: Alkyl bromide (1.0 mmol) and Mg turnings (2.0 mmol) were successively mixed in THF (2 mL) at room temperature with vigorous stirring. After 0.5 h, $ZnBr_2$ (1.0 mmol) was added, and the suspension was stirred 0.5 h at room temperature. N,O-Acetal **1** (0.50 mmol) and freshly distilled Me_3SiCl (0.60 mmol) were then added, and the mixture 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 of Na_2CO_3 (2 mL). The combined organic layer was dried with anhydrous Na_2CO_3 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt) to afford derivative **4**. In case of **4a**, *n*BuLi (1.5 mmol) was used instead of the corresponding Grignard reagent.

4a:[13] Yield: 89.5 mg, 84% (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.0 Hz, 3 H, CH-CH_2-CH_2-CH_2-CH_3), 1.1–1.7 (m, 12 H, CH-CH_2-CH_2-CH_2-CH_3, N-CH_2-CH_2-CH_2), 2.4–2.5 (m, 4 H, N-CH_2), 3.08 (t, *J* = 7.0 Hz, 1 H, C-*H*), 3.64 (s, 3 H, CO_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.5, 24.5, 26.3, 28.4, 29.1, 50.7, 50.8, 68.4, 172.9 ppm. MS (FA): *m*/*z* (%) = 214 (100) [M + H], 154 (65) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{12}H_{24}NO_2$ 214.1807; found 214.1814.

4b: Yield: 65.7 mg, 66% (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 [d, *J* = 6.0 Hz, 3 H, CH-CH-(CH_3)$_2$], 0.91 [d, *J* = 6.0 Hz, 3 H, CH-CH-(CH_3)$_2$], 1.3–1.5 (m, 6 H, N-CH_2-CH_2-CH_2), 2.00 [dd, *J* = 6.0, 10.5 Hz, 1 H, CH-C*H*-(CH_3)$_2$], 2.33 (m, 2 H, N-CH_2), 2.48 (m, 2 H, N-CH_2), 2.65 [d, *J* = 10.5 Hz, 1 H, C*H*-CH-(CH_3)$_2$], 3.65 (s, 3 H, CO_2-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.1, 19.7, 24.7, 26.5, 26.6, 50.3, 50.7, 75.1, 172.2 ppm. MS (FA): *m*/*z* (%) = 200 (100) [M + H], 139 (75) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{11}H_{22}NO_2$ 200.1651; found 200.1641.

4c: Yield: 81.0 mg, 76% (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 [d, *J* = 6.0 Hz, 3 H, CH-CH_2-CH-(CH_3)$_2$], 0.87 [d, *J* = 6.0 Hz, 3 H, CH-CH_2-CH-(CH_3)$_2$], 1.37 (m, 2 H, N-CH_2-CH_2-CH_2), 1.4–1.6 [m, 7 H, CH-CH_2-C*H*-(CH_3)$_2$, N-CH_2-CH_2-CH_2], 2.42 (m, 2 H, N-CH_2), 2.52 (m, 2 H, N-CH_2), 3.17 [m, 1 H, C*H*-CH_2-CH-(CH_3)$_2$], 3.64 (s, 3 H, CO_2-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 22.6, 24.6, 25.1, 26.4, 38.2, 50.7, 50.8, 66.3, 173.0 ppm. MS (FA): *m*/*z* (%) = 214 (100) [M + H], 153 (75) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{12}H_{24}NO_2$ 214.1807; found 214.1815.

General Procedure for Amino Acids 5: Freshly distilled THF (3 mL) and the corresponding alkyl bromide (0.75 mmol) were successively added to a glass vessel (20 mL) containing Zn dust (1.0 mmol) under a nitrogen atmosphere, and the suspension was stirred at room temperature for 0.5 h. N,O-Acetal (0.50 mmol) and Me_3SiCl (0.6 mmol) were then added, and the mixture was stirred at room temperature. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 (2 mL) and extracted with $CHCl_3$. The organic layer was dried with anhydrous Na_2CO_3, and the solvent was removed under reduced pressure. The product was isolated by flash chromatography (hexane/AcOEt) and characterized by using spectroscopic techniques.

5a:[14] Yield: 113.4 mg, 99% (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.3–1.4 (m, 2 H, N-CH_2-CH_2-CH_2), 1.4–1.5 (m, 4 H, N-CH_2-CH_2), 2.3–2.4 (m, 2 H, N-CH_2), 2.5–2.6 (m, 3 H, CH_2-CO_2-CH_3, N-CH_2), 2.78 (m, 1 H, CH-CH_2-CO_2-CH_3), 3.63 (s, 3 H, CO_2-CH_3), 3.6–3.7 (m, 1 H, C-*H*), 3.74 (s, 3 H, CO_2-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 26.3, 34.0, 50.8, 51.2, 51.6, 64.1, 171.2, 171.9 ppm. MS (FA): *m*/*z* (%) = 230 (100) [M + H], 170 (100) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{11}H_{20}NO_4$ 230.1392; found 230.1414.

5b:[15] Yield: 80.9 mg, 70% (yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.51 (m, 2 H, N-CH_2-CH_2-O), 2.62 (m, 1 H, CH-CH_2-CO_2-CH_3), 2.66 (m, 2 H, N-CH_2-CH_2-O), 2.86 (m, 1 H, CH-CH_2-CO_2-CH_3), 3.6–3.7 (m, 4 H, N-CH_2-CH_2-O), 3.67 (s, 3 H, CO_2-CH_3), 3.72 (m, 1 H, C-*H*), 3.75 (s, 3 H, CO_2-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.9, 49.8, 49.9, 51.4, 51.7, 63.6, 67.2, 170.8, 171.5 ppm. MS (FA): *m*/*z* (%) = 232 (100) [M + H], 172 (98) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{10}H_{18}NO_5$ 232.1185; found 232.1214.

5c: Yield: 96.8 mg, 93% (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.62 (m, 2 H, CH-CH_2-CN), 3.04 (m, 2 H, N-CH_2-CH=CH_2), 3.23 (m, 2 H, N-CH_2-CH=CH_2), 3.71 (s, 3 H, CO_2-CH_3), 3.81 (m, 1 H, C-*H*), 5.1–5.3 (m, 4 H, N-CH_2-CH=CH_2), 5.7–5.8 (m, 2 H, N-CH_2-C*H*=CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2, 51.8, 53.6, 57.9, 117.5, 118.0, 135.3, 170.6 ppm. MS (FA): *m*/*z* (%) = 209 (100) [M + H], 149 (98) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{11}H_{17}N_2O_2$ 209.1290; found 209.1270.

5d: Yield: 83.9 mg, 81% (yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.94 (s, 1 H, CC*H*), 2.43 (m, 1 H, CH_2-CCH), 2.60 (m, 1 H, CH_2-CCH), 3.03 (m, 2 H, N-CH_2-CH=CH_2), 3.24 (m, 2 H, N-CH_2-CH=CH_2), 3.65 (m, 1 H, C-*H*), 3.69 (s, 3 H, CO_2-CH_3), 5.0–5.2 (m, 4 H, N-CH_2-CH=CH_2), 5.7–5.8 (m, 2 H, N-CH_2-C*H*=CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7, 51.3, 53.6, 61.0, 69.8,

80.9, 117.3, 136.0, 171.9 ppm. MS (FA): *m/z* (%) = 208 (100) [M + H], 168 (86) [M – CO_2Me]. HRMS (FAB): calcd. for $C_{12}H_{18}NO_2$ 208.1338; found 208.1341.

6:[16] Glycine derivative **3e** (0.50 mmol), 1,3-dimethylbarbituric acid (1.0 mmol), and $Pd(PPh_3)_4$ (0.025 mmol) were successively mixed together in MeOH (5 mL) at room temperature by stirring. After 3 h, the reaction was quenched with 1 N HCl (3 mL). The aqueous layer was washed by $CHCl_3$ (3 × 5 mL). A saturated aqueous solution of Na_2CO_3 (10.0 mL) was then added to the resulting $CHCl_3$ solution. The separated organic layer was dried with sodium carbonate and evaporated under reduced pressure to afford product **6**, which was almost pure. Yield: 62.7 mg, 70% (colorless oil). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (br., 2 H, NH_2), 2.8–3.0 (m, 2 H, Ar-CH_2-), 3.69 (s, 3 H, CO_2-CH_3), 3.70 (m, 1 H, C-*H*), 7.1–7.3 (m, 5 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.0, 51.8, 55.7, 126.7, 128.4, 129.1, 137.1, 175.2 ppm. MS (FA): *m/z* (%) = 180 (48) [M + H], 120 (100) [M – CO_2Me].

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