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RESEARCH ARTICLE - SPECIAL ISSUE - FUNCTIONAL MATERIALS - CHEMISTRY

Synthesis of 1,2-Diamino Acid Derivatives Utilizing Diastereoselective Tandem *N*-Alkylation/Homo- and Cross-Addition Reaction of α-Aldimino Thioesters

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Abstract Diastereoselective tandem *N*-alkylation/homo- and cross-addition reactions of α-aldimino thioesters were developed to give *anti*-1,2-diamine products in good to high yields. Furthermore, the synthesis of *anti*-3-amino β-lactam was also developed via *N*-alkylation/cross-addition/cyclization reaction.

Keywords 1, 2-Diamine · *N*-Alkylation · Umpolung reaction · β-Lactam

1 Introduction

1,2-Diamine skeletons are very important and widely found in natural products and pharmaceuticals [1–5]. They are also used as various ligands in organic synthesis [6–8]. Among them, 1,2-diamino acids derivatives are known as the biologically relevant and used for the chiral building blocks [9–23]. Although many synthetic methods for 1,2-diamino acids derivatives have been developed so far, there appears no report which can introduce substituents directly and freely on the imino nitrogen atom.

Since α-imino esters are known as reactive imines and often used as precursors to α-amino acids, various types of tandem C–C bond formation reaction using α-imino ester have been developed [24–59]. An umpolung of α-imino ester is difficult due to the electronegativity, and we have previously reported the *N*-alkylation of α-aldimino esters with aluminum reagents followed by homo-addition reaction to give the 1,2-diamines in high yields [41]. Recently we also reported 1,2-amino alcohol synthesis utilizing the reaction of the aluminum enolate formed from the *N*-alkylation with aldehydes as electrophiles to give the cross-addition products and extended to the application of a new flow system [53]. However, the control of stereoselectivity for the formation of diamines and amino alcohols has not been accomplished yet. Herein, we report the complete diastereoselective 1,2-diamine synthesis using the tandem *N*-alkylation/homo- and cross-addition reaction using α-aldimino thioesters and organozinc reagents.

Dedicated to Professor Teruaki Mukaiyama in celebration of his 90th birthday (Sotsuju).

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2 Experimental Methods

2.1 General Aspects

Infrared spectra were determined on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL ECX-400P, or a JEOL A-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL MS-700D spectrometer. Toluene was dried over calcium chloride, distilled, and stored over Molecular Sieves 4Å. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and stored over Molecular Sieves 4Å. Propionitrile (EtCN) was distilled from phosphorus pentoxide and then from calcium hydride, and stored over Molecular Sieves 4Å. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified with a Glass Contour Organic Solvent Purification System of Nikko Hansen Co., Ltd. Benzene was dried over calcium chloride, distilled, and stored over Molecular Sieves 4Å. Purification of prod-

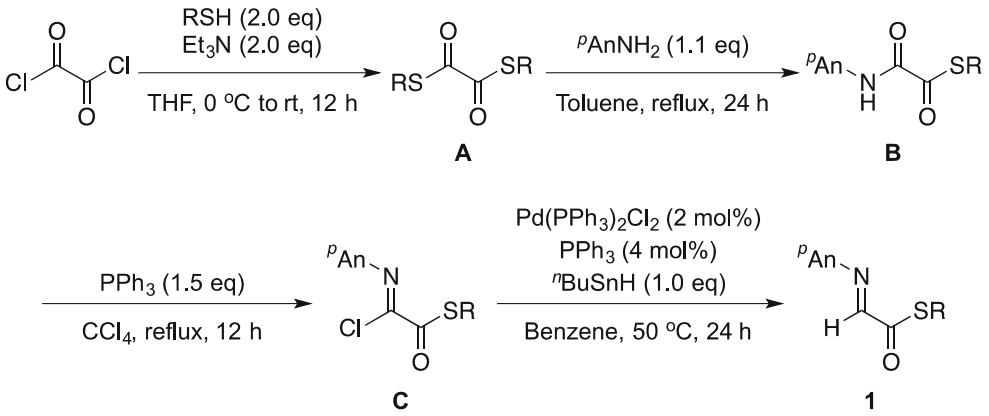


Fig. 1 Synthesis of α-aldimiothioesters 1a–e

ucts was performed by column chromatography on silica gel (Kanto Silica Gel 60 N) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254 or Wako Gel B-5F).

2.2 Synthesis of *S*, *S*-Dialkyl ethanebis(thioate) (A) (Fig. 1)

In a 100 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed RSH (80.0 mmol, 2.0 equiv) and Et_3N (80.0 mmol, 2.0 equiv) in THF (40.0 mL) at 0 °C, and to it was added oxalyl chloride (40.0 mmol) slowly. After the mixture was stirred for 12 h at 0 °C to room temperature, the reaction was quenched with dist. H_2O (5 mL), and the whole mixture was extracted with Et_2O (15 mL × 3). The combined extracts were washed with sat. NaClaq, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a curde oil **A**, which was used directly in the next step without further purification.

2.3 Synthesis of S-Alkyl (4-Methoxyphenyl) carbamothioate (B) (Fig. 1)

In a 200 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *p*-anisidine (42.0 mmol, 1.1 equiv) in toluene (80.0 mL) at room temperature, and to it was added the product **A** (40.0 mmol,) slowly. The whole mixture was heated at reflux for 24 h. After the reaction, the mixture was concentrated in vacuo to give a crude solid. The crude product was used directly in the next step without further purification.

2.4 Synthesis of *S*-Alkyl (*Z*)-2-Chloro-2-[(4-Methoxyphenyl)imino]ethanethioate (C) (Fig. 1)

In a 100 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed PPh_3 (6.72 mmol, 1.5 equiv) in CCl_4 (40.0 mL) at room temperature, and to it was added the compound **B** (4.48 mmol,) slowly. The whole mixture was heated at reflux for 12 h. After the reaction, the mixture was concentrated in vacuo and filtered with suction through a celite pad which was washed with *n*-hexane to give a crude oil. The crude product was used directly in the next step without further purification.

2.5 Synthesis of α-Aldimino Thioester (1) (Fig. 1)

In a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed imidoyl chloride (13.5 mmol), PPh_3 (142 mg, 0.54 mmol, 4 mol%), and $Pd(PPh_3)_2Cl_2$ (190 mg, 0.27 mmol, 2 mol%) in benzene (13.5 mL) at room temperature, and to it was added $^nBu_3SnH$ (3.63 mL, 13.5 mmol, 1.0 equiv) slowly. After the mixture was stirred for 24 h at 50 °C, the mixture was concentrated in vacuo and filtered with suction through a celite pad which was washed with *n*-hexane to give a crude oil. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 5/1 in the presence of 10 wt% K_2CO_3) to give the title compound **1**.

*2.5.1 S-Ethyl (E)-2-[(4-Methoxyphenyl)imino] ethanethioate (**1a**)*

Yield 31% (4 steps); yellow crystal; mp 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.4 Hz, 3H), 3.00 (q, J = 7.4 Hz, 2H), 3.84 (s, 3H), 6.91–6.95 (m, 2H), 7.33–7.37 (m, 2H), 7.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 22.6, 55.5, 114.6, 124.0, 140.5, 151.5, 160.7, 192.7; IR (neat): 3296, 2958, 2936, 2839, 2050, 2017, 1656, 1503, 1149, 1028, 836, 652 cm^{-1}; HRMS (EI): Calcd for $C_{11}H_{13}NO_2S(M)^+$ 223.0667, found 223.0676.

2.5.2 *S-Methyl (E)-2-[(4-Methoxyphenyl)imino] ethanethioate (***1b***)*

Yield 7% (4 steps); yellow powder; mp 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.84 (s, 3H), 6.93–6.96 (m, 2H), 7.35–7.38 (m, 2H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 55.5, 114.6, 124.0, 140.4, 151.1, 160.7, 193.1; IR (neat): 2966, 2844, 1660, 1506, 1256, 1152, 1029, 844, 728, 661 cm^{-1}; HRMS (EI): Calcd for $C_{10}H_{11}NO_2S(M)^+$ 209.0511, found 209.0517.

2.5.3 *S-Hexyl (E)-2-[(4-Methoxyphenyl)imino] ethanethioate (***1c***)*

Yield 36% (4 steps); red crystal; mp 28-29 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3H), 1,29–1,32 (m, 4H), 1.42 (tt, J = 7.2, 7.2 Hz, 2H), 1.65 (tt, J = 7.2, 7.3 Hz, 2H), 2.99 (t, J = 7.3 Hz, 2H), 3.84 (s, 3H) 6.92–6.94 (m, 2H), 7.35–7.36 (m, 2H), 7.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 28.3, 28.6, 29.2, 31.3, 55.5, 114.6, 123.9, 140.5, 151.6, 160.7, 192.6; IR (neat): 2956, 2929, 2856, 1656, 1577, 1504, 1252, 1148, 1033, 835, 767, 673 cm$^{-1;}$ HRMS (EI): Calcd for $C_{15}H_{21}NO_2S(M)^+$ 279.1293, found 279.1283.

2.5.4 *S-Isobutyl (E)-2-[(4-Methoxyphenyl)imino] ethanethioate (***1d***)*

Yield 6% (4 steps); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, J = 6.9 Hz, 6H), 1.90 (tqq, J = 6.4, 6.9, 6.9 Hz, 1H), 2.92 (d, J = 6.4 Hz, 2H), 3.84 (s, 3H), 6.94 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 2H), 8.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 28.6, 36.5, 55.5, 114.5, 123.9, 140.5, 151.6, 160.6, 192.4; IR (neat): 2957, 2834, 1671, 1512, 1464, 1249, 1181, 1145, 1036, 819 cm^{-1}; HRMS (EI): Calcd for $C_{13}H_{17}NO_2S(M)^+$ 251.0980, found 251.0982.

2.5.5 *S-Cyclohexyl (E)-2-[(4-Methoxyphenyl)imino] ethanethioate (***1e***)*

Yield 6% (4 steps); yellow crystal; mp 26–27 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.39 (m, 1H), 1.44–1.55 (m, 4H), 1.61–1.64 (m, 1H), 1.75–1.76 (m, 2H), 1.96–2.00 (m, 2H), 3.61–3.70 (m, 1H), 3.84 (s, 3H), 6.93–6.94 (m, 2H), 7.34–7.36 (m, 2H), 7.96 (s, 1H);^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 25.8, 32.9, 41.5, 55.4, 114.5, 123.8, 140.5, 151.9, 160.6, 192.0; IR (neat): 2930, 2852, 1653, 1577, 1504, 1446, 1251, 1147, 1032, 834, 766, 674 cm^{-1}; HRMS (EI): Calcd for $C_{15}H_{19}NO_2S(M)^+$ 277.1137, found 277.1138.

2.5.6 *S-(Tert-butyl) (E)-2-[(4-Methoxyphenyl)imino] ethanethioate (***1f***)*

Yield 10% (4 steps); Yellow crystal; mp 90-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 3.84 (s, 3H), 6.92–6.94 (m, 2H), 7.30–7.34 (m, 2H), 7.86 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 47.5, 55.5, 114.6, 123.8, 140.6, 152.9, 160.5, 192.6; IR (neat) : 2999, 2963, 1650, 1587, 1507, 1252, 1147, 1046, 840, 686 cm^{-1}; HRMS (EI): Calcd for $C_{13}H_{17}NO_2S(M)^+$ 251.0980, found 251.0973.

2.6 General Procedure for the Tandem *N*-Alkylation/Homo-addition Reaction (Scheme 1)

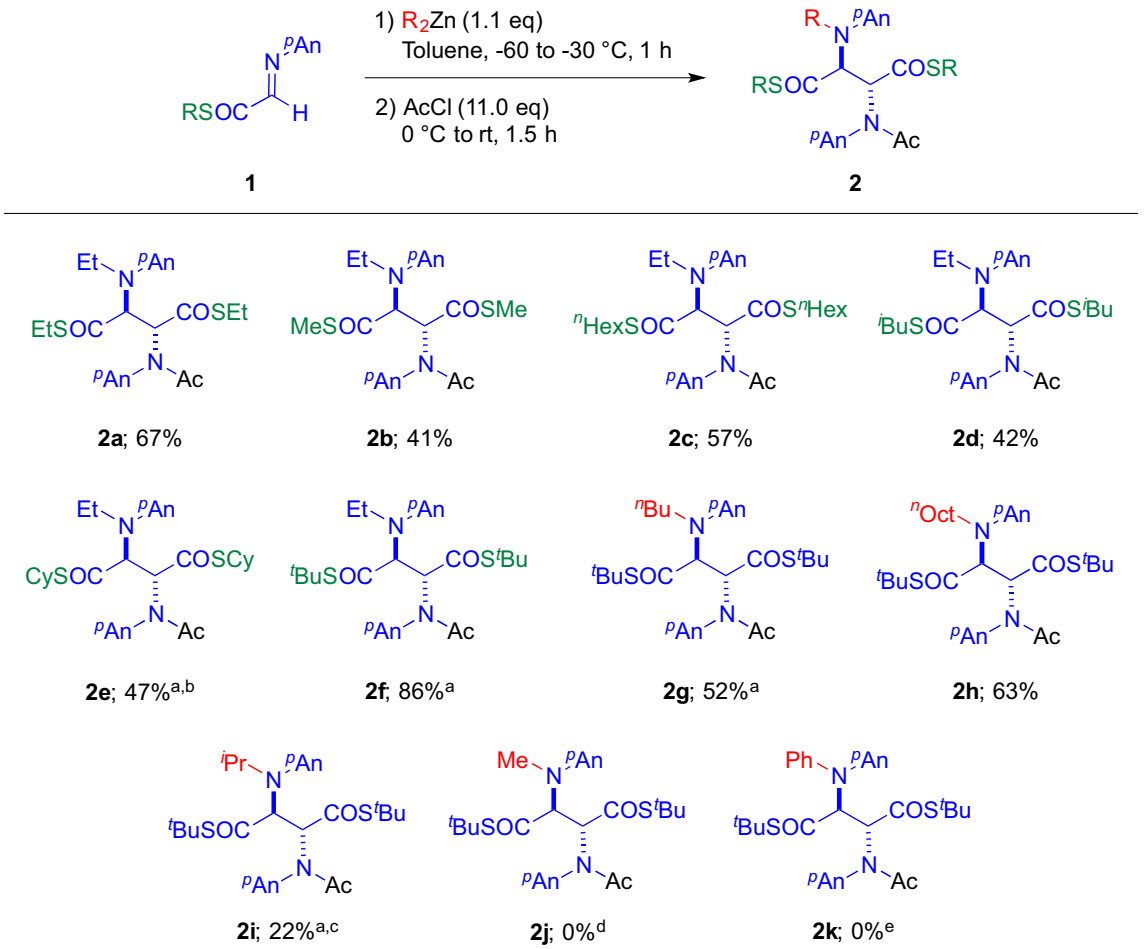
In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed α-aldimino thioester **1** (0.15 mmol), in toluene (1.5 mL) at −60 °C, and to it was added R_2Zn (0.17 mmol, 1.1 equiv), which was prepared according to the reported procedure [60,61], slowly. After the mixture was stirred for 1 h at −60 to −30 °C, to it was added AcCl (0.12 mL, 1.65 mmol, 11 equiv) and stirred for 1.5 h at 0 °C to room temperature. The mixture was quenched with $NaHCO_3$ aq (10.0 mL), and the whole mixture was extracted with ethyl acetate (5.0 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel on TLC (toluene/ethyl acetate = 7/1) to give the title compound **2**.

2.6.1 *S, S-Diethyl-2-[Ethyl(4-methoxyphenyl)amino]-3-[N-(4-Methoxyphenyl)acetamido]butanebis(thioate) (***2a***)*

Yield 67%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (dd, J = 7.1, 7.1 Hz, 3H), 1.19 (dd, J = 7.3, 7.3 Hz, 3H), 1.22 (dd, J = 7.3, 7.3 Hz, 3H), 1.79 (s, 3H), 2.78–2.96 (m, 4H), 3.13–3.38 (m, 2H), 3.74 (s, 3H), 3.82 (s, 3H), 4.60 (d, J = 11.0 Hz, 1H), 6.04 (d, J = 11.0 Hz, 1H), 6.76-7.11 (m, 8H);^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 14.4, 14.8, 23.2, 23.4, 23.7, 40.6, 55.4, 61.9, 70.7, 114.1, 114.5, 119.6, 130.8, 132.2, 140.7, 153.6, 159.5, 171.2, 195.2, 196.1; IR (neat): 2970, 2932, 1676, 1511, 1455, 1374, 1292, 1249, 1035, 729 cm^{-1}; HRMS (EI): Calcd for $C_{26}H_{34}N_2O_5S_2(M)^+$ 518.1909, found 518.1904.

2.6.2 *S, S-Dimethyl-2-[Ethyl(4-methoxyphenyl)amino]-3-[N-(4-Methoxyphenyl)acetamido]butanebis(thioate) (***2b***)*

Yield 41%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (dd, J = 7.1, 7.1 Hz, 3H), 1.79 (s, 3H), 2.26 (s, 3H), 2.28 (s, 3H), 3.12–3.27 (m, 2H), 3.74 (s, 3H), 3.83 (s, 3H),



Scheme 1 Scope of substrates and organozinc reagents. [a] Et_2O was used as a solvent. [b] (1) 2 h, (2) 11.5 h. [c] (2) 16 h. [d] (1) −60 °C to rt, 2.5 h, (2) 15 h. [e] (1) −60 °C to rt, 20 h, (2) 9.5 h

4.66 (d, J = 11.0 Hz, 1H), 6.01 (d, J = 11.0 Hz, 1H), 6.76–7.10 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 11.9, 13.1, 23.2, 40.8, 55.4, 62.2, 70.6, 114.2, 114.5, 119.6, 130.7, 132.3, 140.6, 153.7, 159.5, 171.3, 195.7, 196.3; IR (neat): 2970, 2931, 1679, 1511, 1373, 1292, 1249, 1034, 699, 647 cm^{-1}; HRMS (EI): Calcd for $C_{24}H_{30}N_2O_5S_2(M)^+$ 490.1596, found 490.1602.

2.6.3 *S, S-Dihexyl-2-[Ethyl(4-methoxyphenyl)amino]-3-[N-(4-Methoxyphenyl)acetamido]butanebis(thioate)* (**2c**)

Yield 50%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 6.9 Hz, 3H), 0.84 (t, J = 6.9 Hz, 3H), 1.03 (dd, J = 7.1, 7.1 Hz, 3H), 1.22–1.36 (m, 12H), 1.46–1.56 (m, 4H), 1.78 (s, 3H), 2.77–2.94 (m, 4H), 3.09–3.27 (m, 2H), 3.75 (s, 3H), 3.82 (s, 3H), 4.59 (d, J = 11.0 Hz, 1H), 6.06 (d, J = 11.0 Hz, 1H), 6.75–7.10 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 14.0, 22.4, 22.5, 23.2, 28.4, 28.5, 28.9, 29.2, 29.4, 31.3, 40.5, 55.4, 61.7, 70.8, 114.1, 114.5, 119.6, 130.8, 132.1, 140.7, 153.6, 159.5, 171.1, 194.9, 196.1; IR (neat): 2956, 2930, 2856, 1677, 1510, 1462, 1372, 1248, 1036, 756 cm^{-1}; HRMS (EI): Calcd for $C_{34}H_{50}N_2O_5S_2(M)^+$ 630.3161, found 630.3165.

2.6.4 *S, S-Diisobutyl-2-[Ethyl(4-methoxyphenyl)amino]-3-[N-(4-Methoxyphenyl)acetamido]butanebis(thioate)* (**2d**)

Yield 42%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91–0.94 (m, 12H), 1.03 (dd, J = 7.1, 7.1 Hz, 3H), 1.55–1.85 (m, 5H including a singlet at 1.78 ppm, 3H), 2.70–2.86 (m, 4H), 3.11–3.28 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.61 (d, J = 11.3 Hz, 1H), 6.07 (d, J = 11.3 Hz, 1H), 6.75–7.09 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 21.8, 23.2, 28.5, 29.7, 37.2, 37.5, 40.4, 55.4, 61.9, 71.0, 114.1, 114.5, 119.7, 130.8, 140.8, 153.7, 159.5, 171.1, 194.3, 196.0; IR (neat): 2952, 2923, 2868, 2836, 1686, 1666, 1546, 1511, 1249, 1044, 1023, 840, 699 cm^{-1}; HRMS (EI): Calcd for $C_{30}H_{42}N_2O_5S_2(M)^+$ 574.2535, found 574.2529.

*2.6.5 S, S-Dicyclohexyl-2-[Ethyl(4-methoxyphenyl) amino]-3-[N-(4-Methoxyphenyl)acetamido] butanebis(thioate) (***2e***)*

Yield 47%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (dd, J = 7.0, 7.0 Hz, 3H), 1.24–1.46 (m, 12H), 1.56–1.70 (m, 4H), 1.78 (s, 3H), 1.85–1.94 (m, 4H), 3.16 (dq, J = 7.0, 14.1 Hz, 1H), 3.23 (dq, J = 7.0, 14.1 Hz, 1H), 3.39–3.56 (m, 2H), 3.74 (s, 3H), 3.83 (s, 3H), 4.49 (d, J = 11.0 Hz, 1H), 6.08 (d, J = 11.0 Hz, 1H), 6.75–7.09 (m, 8H);^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 23.3, 25.5, 25.5, 25.8, 25.9, 26.0, 32.5, 32.6, 32.8, 33.3, 40.3, 42.5, 42.7, 55.4, 61.4, 70.9, 114.1, 114.5, 119.6, 130.9, 132.0, 140.8, 153.5, 159.5, 171.0, 194.5, 195.8; IR (neat): 2931, 2853, 1675, 1511, 1446, 1373, 1293, 1248, 1035, 999, 730 cm^{-1}; HRMS (EI): Calcd for $C_{34}H_{46}N_2O_5S_2(M)^+$ 626.2848, found 626.2876.

*2.6.6 S, S-Di-tert-butyl-2-[Ethyl(4-methoxyphenyl) amino]-3-[N-(4-Methoxyphenyl)acetamido] butanebis(thioate) (***2f***)*

Yield 86%; Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (dd, J = 6.8, 6.8 Hz, 3H), 1.40 (s, 9H), 1.43 (s, 9H), 1.78 (s, 3H), 3.15-3.32 (m, 2H), 3.74 (s, 3H), 3.83 (s, 3H), 4.39 (d, J = 11.3 Hz, 1H), 6.05 (d, J = 11.3 Hz, 1H), 6.75-7.12 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 23.2, 29.5, 29.8, 40.1, 48.4, 48.6, 55.3, 60.8, 70.9, 114.0, 114.4, 119.6, 131.0, 131.9, 140.8, 153.4, 159.4, 170.8, 195.1, 196.5; IR (neat): 2964, 2928, 1674, 1513, 1509, 1458, 1364, 1293, 1249, 1176, 1035, 731 cm^{-1}; HRMS (EI): Calcd for $C_{30}H_{42}N_2O_5S_2(M)^+$ 574.2535, found 574.2517.

*2.6.7 S, S-Di-tert-butyl-2-[Butyl(4-methoxyphenyl)amino]-3-[N-(4-Methoxyphenyl)acetamido]butanebis (thioate) (***2g***)*

Yield 52%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.3 Hz, 3H), 1.23–1.33 (m, 2H), 1.40 (s, 9H), 1.41–1.57 (m, 11H including a singlet at 1.44 ppm, 9H), 1.77 (s, 3H), 3.06–3.23 (m, 2H), 3.74 (s, 3H), 3.83 (s, 3H), 4.39 (d, J = 11.0 Hz, 1H), 6.04 (d, J = 11.0 Hz, 1H), 6.74–7.42 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 20.3, 23.2, 29.6, 29.7, 29.8, 46.2, 48.4, 48.6, 55.4, 61.0, 70.9, 114.0, 114.5, 120.1, 130.9, 132.0, 141.2, 153.6, 159.5, 170.8, 195.1, 196.2; IR (neat): 2960, 2868, 2837, 1675, 1511, 1459, 1363, 1293, 1249, 1176, 1035, 731 cm^{-1}; HRMS (EI): Calcd for $C_{32}H_{46}N_2O_5S_2(M)^+$ 602.2848, found 602.2865.

*2.6.8 S, S-Di-tert-butyl-2-[(4-Methoxyphenyl)(octyl) amino]-3-[N-(4-Methoxyphenyl)acetamido]butanebis (thioate) (***2h***)*

Yield 63%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (dd, J = 6.9, 6.9 Hz, 3H), 1.24–1.30 (m, 12H), 1.40 (s, 9H), 1.44 (s, 9H), 1.77 (s, 3H), 3.04–3.20 (m, 2H), 3.73 (s, 3H), 3.83 (s, 3H), 4.39 (d, J = 11.0 Hz, 1H), 6.04 (d, J = 11.0 Hz, 1H), 6.74–7.19 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 23.2, 27.1, 27.5, 29.2, 29.4, 29.6, 29.8, 31.8, 46.4, 48.4, 48.6, 55.4, 61.0, 70.9, 114.0, 114.4, 119.9, 130.9, 132.0, 141.2, 153.5, 159.5, 170.8, 195.0, 196.2; IR (neat): 2958, 2926, 2856, 1647, 1512, 1367, 1294, 1249, 1174, 1034, 834 cm^{-1}; HRMS (EI): Calcd for $C_{36}H_{54}N_2O_5S_2(M)^+$ 658.3474, found 658.3477.

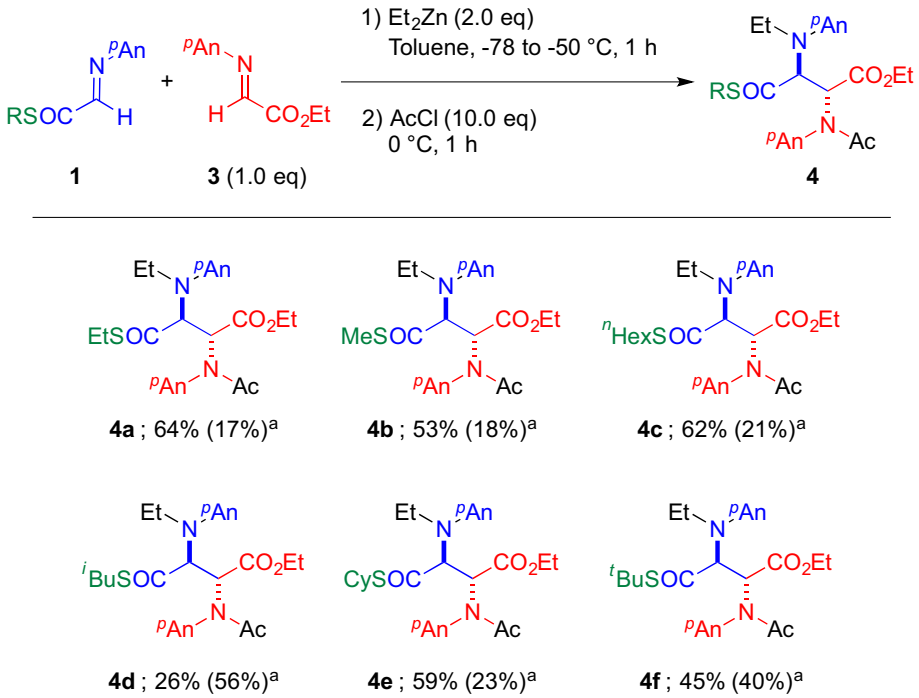
*2.6.9 S, S-Di-tert-butyl-2-[Isopropyl(4-methoxyphenyl) amino]-3-[N-(4-Methoxyphenyl)acetamido] butanebis(thioate) (***2i***)*

Yield 22%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.7 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H), 1.48 (s, 9H), 1.52 (s, 9H), 1.72 (s, 3H), 3.70 (qq, J = 6.7 Hz, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 4.34 (brs, 1H), 5.94 (brs, 1H), 6.73–6.88 (m, 4H), 7.08–7.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 19.6, 23.3, 27.5, 29.6, 48.4, 55.4, 69.2, 77.2, 114.3, 132.2, 159.4, 171.4, 197.3; IR (neat): 2964, 2928, 2838, 1678, 1512, 1366, 1291, 1248, 1176, 1033, 753 cm^{-1}; HRMS (EI): Calcd for $C_{31}H_{44}N_2O_5S_2(M)^+$ 588.2692, found 588.2672.

2.7 General Procedure for the Tandem *N* -Alkylation/ Cross-Addition Reaction (Scheme 2)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed α-aldimino thioester **1** (0.15 mmol), and α-aldimino ester **3** (31.1 mg, 0.15 mmol, 1.0 equiv) in toluene (3.0 mL) at −78 °C, and to it was added R_2Zn (0.30 mmol, 2.0 equiv), which was prepared according to the reported procedure [60,61], slowly. After the mixture was stirred for 1 h at −78 to −50 °C, to it was added AcCl (0.11 mL, 1.50 mmol, 10 equiv) and stirred for 1 h at 0 °C. The mixture was quenched with $NaHCO_3$ aq (10.0 mL), and the whole mixture was extracted with ethyl acetate (5.0 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel on TLC (toluene/ethyl acetate = 7/1) to give the title compound **4**.

Scheme 2 Scope of substrates for the tandem *N*-alkylation/cross-addition reaction. [a]Yields of the homo-addition product **2** in the parentheses



*2.7.1 Ethyl 3-[Ethyl(4-methoxyphenyl)amino]-4-(Ethylthio) -2-[N-(4-Methoxyphenyl)- acetamido]-4- Oxobutanoate (***4a***)*

Yield 64%; yellow oil;^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (dd, J = 7.1, 7.1 Hz, 3H), 1.18 (dd,J = 7.3, 7.3 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H), 1.78 (s, 3H), 2.80 (q, J = 7.5 Hz, 2H), 3.17 (dq, J = 7.1, 14.3 Hz, 1H), 3.21 (dq, J = 7.1, 14.3 Hz, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 4.02–4.17 (m, 2H), 4.55 (d,J = 11.0 Hz, 1H), 5.57 (d, J = 11.0 Hz, 1H), 6.75–7.48 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 13.9, 14.7, 23.0, 23.3, 40.5, 55.4, 58.6, 61.3, 70.9, 114.2, 114.4, 119.2, 131.1, 132.8, 140.9, 153.5, 159.4, 170.8, 171.6, 195.1; IR (neat): 2934, 2837, 1736, 1667, 1511, 1376, 1297, 1247, 1183, 1034, 839, 754 cm^{-1}; HRMS (EI): Calcd for $C_{26}H_{34}N_2O_6S$ $(M)^+$ 502.2138, found 502.2160.

*2.7.2 Ethyl 3-[Ethyl(4-methoxyphenyl)amino]-2-[N-(4-Methoxyphenyl)acetamido]-4- (Methylthio)-4- Oxobutanoate (***4b***)*

Yield 53%; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (dd,J = 7.0, 7.0 Hz, 3H), 1.18 (dd, J = 7.1, 7.1 Hz, 3H), 1.78 (s, 3H), 2.21 (s, 3H), 3.16 (dq, J = 7.1, 14.0 Hz, 1H), 3.21 (dq, J = 7.1, 14.0 Hz, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 4.03–4.17 (m, 2H), 4.59 (d, J = 11.0 Hz, 1H), 5.56 (d,J = 11.0 Hz, 1H), 6.61–7.44 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6, 12.9, 13.9, 23.0, 40.6, 55.4, 58.7, 61.3, 70.8, 114.2, 114.4, 119.2, 131.0, 132.9, 140.8, 153.5, 159.4, 170.7, 171.7, 195.6; IR (neat): 2980, 2933, 2837, 1735, 1668, 1511, 1376, 1297, 1248, 1183, 1034, 839, 734 cm^{-1}; HRMS (EI): Calcd for $C_{25}H_{32}N_2O_6S$ $(M)^+$ 488.1981, found 488.1991.

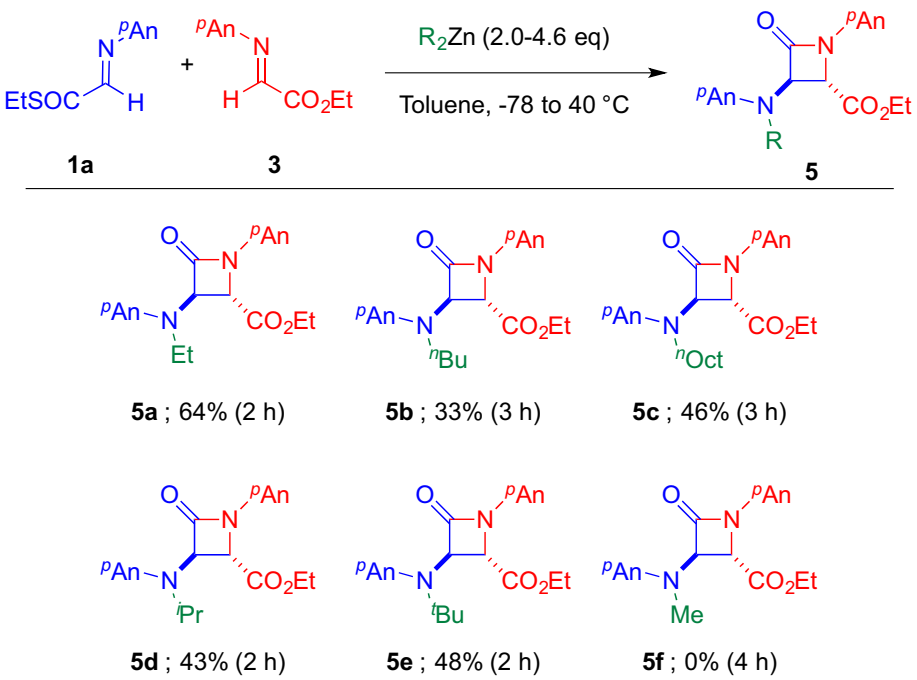
*2.7.3 Ethyl 3-[Ethyl(4-methoxyphenyl)amino]-4- (Hexylthio)-2-[N-(4-Methoxyphenyl)- acetamido] -4-Oxobutanoate (***4c***)*

Yield 62%; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3H), 1.00 (dd,J = 6.8, 6.8 Hz, 3H), 1.19 (dd, J = 7.0, 7.0 Hz, 3H), 1,25–1.33 (m, 6H), 1.45–1.51 (m, 2H), 1.78 (s, 3H), 2.77 (dt, J = 6.9, 13.7 Hz, 1H), 2.80 (dt, J = 6.9, 13.7 Hz, 1H), 3.14 (dq, J = 6.8, 14.0 Hz, 1H), 3.20 (dq, J = 6.8, 14.0 Hz, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 4.03–4.18 (m, 2H), 4.52 (d, J = 11.0 Hz, 1H), 5.58 (d, J = 11.0 Hz, 1H), 6.76–7.48 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0, 14.0, 22.5, 23.0, 28.4, 28.9, 29.3, 31.3, 40.5, 55.4, 55.4, 58.6, 61.3, 71.1, 114.2, 114.4, 119.3, 131.1, 132.9, 141.0, 153.5, 159.5, 170.9, 171.7, 195.0; IR (neat): 2957, 2932, 2857, 1736, 1670, 1511, 1377, 1297, 1248, 1225, 1183, 1036, 839, 754 cm^{-1}; HRMS (EI): Calcd for $C_{30}H_{42}N_2O_6S(M)^+$ 558.2764, found 558.2753.

*2.7.4 Ethyl 3-[Ethyl(4-methoxyphenyl)amino]-4- (Isobutylthio)-2-[N-(4-Methoxyphenyl)- acetamido] -4-Oxobutanoate (***4d***)*

Yield 26%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (dd, J = 6.6, 6.6 Hz, 6H), 0.99 (dd, J = 6.9, 6.9 Hz, 3H), 1.19 (dd,J = 7.1, 7.1 Hz, 3H), 1.68–1.76 (m, 1H), 1.77

Scheme 3 Scope of zinc reagents for β-lactams



(s, 3H), 2.69 (dd, J = 6.7, 13.2 Hz, 1H), 2.73 (dd,J = 6.7, 13.2 Hz, 1H), 3.09–3.24 (m, 2H), 3.75 (s, 3H), 3.82 (s, 3H), 4.02–4.19 (m, 2H), 4.53 (d, J = 11.2 Hz, 1H), 5.58 (d,J = 11.2 Hz, 1H), 6.76–7.42 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 14.0, 21.8, 21.8, 23.1, 28.5, 37.3, 40.3, 55.4, 58.5, 61.4, 71.3, 114.2, 114.4, 119.3, 131.2, 132.7, 141.0, 153.5, 159.4, 171.0, 171.7, 194.7; IR (neat): 2961, 2837, 1736, 1667, 1511, 1464, 1378, 1297, 1248, 1183, 1034, 839 cm^{-1}; HRMS (EI): Calcd for $C_{28}H_{38}N_2O_6S$ $(M)^+$ 530.2451, found 530.2451.

2.7.5 *Ethyl 4-(Cyclohexylthio)-3-[Ethyl(4-methoxyphenyl) amino]-2-[N-(4-Methoxyphenyl)- acetamido]-4-Oxobutanoate (***4e***)*

Yield 59%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (dd,J = 6.9, 6.9 Hz, 3H), 1.19 (dd, J = 7.1, 7.1 Hz, 3H), 1.29–1.46 (m, 5H), 1.54–1.67 (m, 3H), 1.78 (s, 3H), 1.79–1.84 (m, 2H), 3.10–3.25 (m, 2H), 3.42–3.48 (m, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 4.01–4.18 (m, 2H), 4.44 (d, J = 11.5 Hz, 1H), 5.59 (d,J = 11.5 Hz, 1H), 6.53–7.54 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 13.9, 23.0, 25.4, 25.7, 25.8, 32.6, 33.2, 40.2, 42.4, 55.4, 58.2, 61.3, 71.2, 114.1, 114.4, 119.3, 131.3, 132.6, 140.9, 153.4, 159.4, 171.1, 171.6, 194.4; IR (neat): 2933, 2854, 1735, 1668, 1511, 1376, 1297, 1248, 1225, 1182, 1108, 1035, 993, 837 cm^{-1}; HRMS (EI): Calcd for $C_{30}H_{40}N_2O_6S$ $(M)^+$ 556.2607, found 556.2595.

2.7.6 *Ethyl 4-(Tert-butylthio)-3-[Ethyl(4-methoxyphenyl) amino]-2-[N-(4-Methoxyphenyl)- acetamido] -4-Oxobutanoate (***4f***)*

Yield 45%; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (dd, J = 6.9, 6.9, 3H), 1.17 (dd, J = 7.3, 7.3 Hz, 3H), 1.40 (s, 9H), 1.78 (s, 3H), 3.17 (dq, J = 6.9, 7.0 Hz, 1H), 3.24 (dq, J = 6.9, 7.0 Hz, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 4.03 (dq, J = 7.3, 10.8 Hz, 1H), 4.12 (dq, J = 7.3, 10.8 Hz, 1H), 4.44 (d, J = 11.3 Hz, 1H), 5.53 (d,J = 11.3 Hz, 1H), 6.60–7.58 (m, 8H); ^{13}C NMR (125 MHz, CDCl3) δ 13.0, 13.9, 23.0, 29.7, 40.1, 48.4, 55.4, 58.2, 61.3, 70.9, 114.2, 114.5, 118.9, 131.2, 132.9, 141.0, 153.3, 159.4, 171.2, 171.6, 195.2; IR (neat): 2965, 2934, 2870 1735, 1668, 1511, 1463, 1377, 1296, 1248, 1183, 1036, 986, 840, 755 cm^{-1}; HRMS (EI): Calcd for $C_{28}H_{38}N_2O_6S$ $(M)^+$ 530.2451, found 530.2432.

2.8 General Procedure for the Tandem *N*-Alkylation/Cross-Addition/Cyclization Leading to β-Lactam. (Scheme 3)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed α-aldimino thioester **1** (0.15 mmol), and α-aldimino ester **3** (31.1 mg, 0.15 mmol, 1.0 equiv) in toluene (2.0 mL) at −78 °C, and to it was added R_2Zn (0.30 mmol, 2.0 equiv), which was prepared according to the reported procedure [60,61], slowly. After the mixture was stirred for 1 h

at −78 to −30 °C, the reaction was warmed up to 40 °C and stirred for 1 h. The mixture was quenched with $NaHCO_3$ aq (10.0 mL), and the whole mixture was extracted with ethyl acetate (5.0 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel on TLC (*n*-hexane/ethyl acetate = 2/1) to give the title compound **5**.

2.8.1 *Ethyl 3-[Ethyl(4-methoxyphenyl)amino]-1-(4-Methoxyphenyl)-4-Oxoazetidine-2-Carboxylate (***5a***)*

Yield 64%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (dd, J = 7.0, 7.0 Hz, 3H), 1.25 (dd, J = 7.0, 7.0 Hz, 3H), 3.31 (dq, J = 7.0, 14.0 Hz, 1H), 3.37 (dq, J = 7.0, 14.0 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 4.20–4.33 (m, 2H), 4.46 (d, J = 2.3 Hz, 1H), 4.90 (d, J = 2.3 Hz, 1H), 6.81–6.89 (m, 4H), 6.93–6.96 (m, 2H), 7.26–7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.1, 44.9, 55.4, 57.7, 61.8, 75.4, 114.3, 114.5, 118.2, 121.0, 130.5, 140.2, 154.9, 156.6, 163.9, 169.9; IR (neat): 2976, 2937, 2837, 1755, 1653, 1512, 1462, 1399, 1248, 1195, 1135, 1032, 912, 832, 732 cm^{-1}; HRMS (EI): Calcd for $C_{22}H_{26}N_2O_5(M)^+$ 398.1842, found 398.1846.

2.8.2 *Ethyl 3-[Butyl(4-methoxyphenyl)amino]-1-(4-Methoxyphenyl)-4-Oxoazetidine-2-Carboxylate (***5b***)*

Yield 33%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (dd, J = 7.3, 7.3 Hz, 3H), 1.24 (dd, J = 7.1, 7.1 Hz, 3H), 1,27–1,37 (m, 2H), 1.39–1.62 (m, 2H), 3.16–3.30 (m, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 4.17–4.32 (m, 2H), 4.46 (d, J = 2.2 Hz, 1H), 4.87 (d, J = 2.2 Hz, 1H), 6.77–6.88 (m, 4H), 6.93–6.97 (m, 2H), 7.24–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.1, 20.2, 30.3, 50.4, 55.5, 57.6, 61.7, 76.1, 114.4, 114.5, 118.2, 118.3, 121.4, 130.6, 140.6, 155.0, 156.6, 164.0, 170.0; IR (neat): 2957, 2872, 1758, 1512, 1465, 1397, 1298, 1247, 1188, 1137, 1034, 829 cm^{-1}; HRMS (EI): Calcd for $C_{24}H_{30}N_2O_5(M)^+$ 426.2155, found 426.2162.

2.8.3 *Ethyl 1-(4-Methoxyphenyl)-3-[(4-Methoxyphenyl)(octyl)amino]-4-Oxoazetidine-2- Carboxylate (***5c***)*

Yield 46%; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (dd, J = 6.7, 6.7 Hz, 3H), 1.17–1.41 (m, 13H), 1.43–1.60 (m, 2H), 3.17–3.29 (m, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 4.19–4.32 (m, 2H), 4.46 (d, J = 2.8 Hz, 1H), 4.87 (d, J = 2.8 Hz, 1H), 6.80–6.89 (m, 4H), 6.93–6.95 (m, 2H), 7.26–7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.1, 22.6, 27.0, 28.1, 29.2, 29.3, 31.7, 50.6, 55.5, 57.7, 61.7, 63.0, 76.0, 114.4, 114.5, 118.3, 121.3, 130.6, 140.6, 154.9, 156.6, 164.0, 169.9; IR (neat): 2928, 2854, 1760, 1512, 1465, 1398, 1298, 1247, 1183, 1114, 1035, 830 cm^{-1}; HRMS (EI): Calcd for $C_{28}H_{38}N_2O_5(M)^+$ 482.2781, found 482.2792.

2.8.4 *Ethyl 3-[Isopropyl(4-methoxyphenyl)amino]-1-(4-Methoxyphenyl)-4-Oxoazetidine-2-Carboxylate (***5d***)*

Yield 43%; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, J = 6.6 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H), 1.26 (dd, J = 7.0, 7.0 Hz, 3H), 3.59 (qq, J = 6.6, 6.6 Hz, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 4.21–4.31 (m, 2H), 4.36 (d, J = 2.4 Hz, 1H), 4.76 (d, J = 2.4 Hz, 1H), 6.77–6.87 (m, 4H), 7.08–7.11 (m, 2H), 7.20–7.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.0, 22.2, 52.5, 55.3, 55.5, 58.0, 61.6, 73.7, 114.2, 114.3, 118.2, 127.0, 130.8, 138.5, 156.5, 156.5, 165.9, 170.1; IR (neat): 2966, 2931, 2854, 2837, 1757, 1513, 1464, 1390, 1298, 1247, 1192, 1114, 1034, 830 cm^{-1}; HRMS (EI): Calcd for $C_{23}H_{28}N_2O_5(M)^+$ 412.1998, found 412.1990.

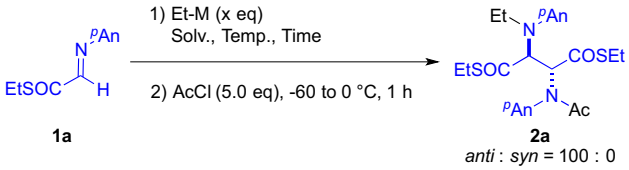
2.8.5 *Ethyl 3-[Tert-butyl(4-methoxyphenyl)amino]-1-(4-Methoxyphenyl)-4-Oxoazetidine-2- Carboxylate (***5e***)*

Yield 48%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.28 (dd,J = 7.1, 7.1 Hz, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 4.21 (d, J = 2.8 Hz, 1H), 4.22–4.34 (m, 2H), 4.95 (d, J = 2.8 Hz, 1H), 6.75–6.80 (m, 4H), 7.09–7.12 (m, 2H), 7.23–7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 29.9, 55.2, 55.4, 58.6, 61.5, 72.6, 113.8, 114.2, 114.4, 118.2, 130.8, 132.9, 135.8, 156.3, 158.1, 166.9, 170.4; IR (neat): 2973, 2836, 1750, 1513, 1465, 1393, 1247, 1192, 1138, 1032, 830 cm^{-1}; HRMS (EI): Calcd for $C_{24}H_{30}N_2O_5(M)^+$ 426.2155, found 426.2162.

3 Results and Discussion

Homo-addition reaction of α-aldimino thioester **1a** was examined, and the results are shown in Table 1. The reaction of α-aldimino thioester **1a** with an organometallic reagent was carried out, and after the reaction the product was treated with acetyl chloride to give the desired 1,2-diamine product **2a** as an *N*-acetylated form. When diethyl aluminum chloride and ethyl Grignard reagent were used, the addition product **2a** was not obtained at all due to the formation of by-products (entries 1 and 2). When the reaction was carried out using Et_2Zn, the desired addition product **2a** was obtained in 71% yield with *anti*-selectively (entry 3). Regarding the amount of Et_2Zn, when the amount of nucleophile was increased, the yield of the product decreased, while use of a reduced equivalent of nucleophile also led to a decrease in the yield (entries 4–6). Regarding the solvent, we found that reaction

Table 1 Optimization of the reaction conditions



Entry	Et-M (x eq)	Solv.	Temp. (°C)	Time (h)	Yield (%)
1	Et_2AlCl (1.0)	Toluene	−90 to −60	1	0
2	EtMgBr (1.0)	Toluene	−90 to −60	1	0
3	Et_2Zn (1.0)	Toluene	−90 to −60	1	71
4	Et_2Zn (1.5)	Toluene	−90 to −60	1	59
5	Et_2Zn (0.75)	Toluene	−90 to −45	2	40
6	Et_2Zn (0.5)	Toluene	−90 to −40	1.5	0
7	Et_2Zn (1.0)	Toluene	−78 to −60	0.5	71
8	Et_2Zn (1.0)	CH_2Cl_2	−78 to −60	0.5	67
9	Et_2Zn (1.0)	EtCN	−78 to −60	0.5	12
10	Et_2Zn (1.0)	THF	−78 to −60	0.5	0
11	Et_2Zn (1.1)	Et_2O	−60 to −30	1.5	21

in CH_2Cl_2 gave a similar result to that in toluene, while use of EtCN, THF and Et_2O was not effective (entries 8–11).

Next, we investigated the scope of substrates under the optimized conditions, and the results are summarized in Scheme 1. When substrates having a primary or secondary alkylthioester moiety were used, homo-addition products **2a-e** were obtained in moderate to good yields with *anti*-selectively. Interestingly, α-imino ester having a ^{t}Bu-thio group was the most effective in this reaction to provide the desired product **2f** in the highest 86% yield. The scope of organozinc reagents was also examined. When dialkylzinc reagents having a primary alkyl group such as Et, ^{n}Bu and ^{n}Oct were used, the desired products **2f**, **g, h** were obtained in good to high yields, while with secondary alkyl group such as an ^{i}Pr group, decrease in the yield of the addition products **2i** was observed (22%). We also found that the introduction of Me and Ph groups to the imino nitrogen was not successful in this reaction (**2j**, **k**).

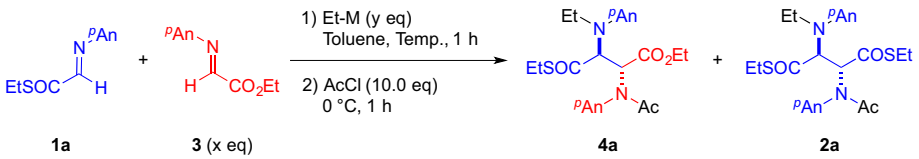
As a preliminary experiment, we found that when the reaction of α-aldimino ester**3** with Et_2Zn was carried out, *C*-ethylated product was obtained instead of *N*-ethylated one. This result indicates that *N*-alkylation/homo-addition reaction of α-aldimino thioester may extend to a cross-addition version with the α-aldimino ester. Thus, we next investigated the selective tandem *N*-alkylation/cross-addition reaction.

When the tandem *N*-alkylation/cross-addition reaction of α-aldimino thioester **1a** with Et_2Zn (2.0 eq) was carried out in toluene at −90 to −60 °C for 1 h in the presence of α-aldimino ester **3** (1.0 eq), the desired cross-addition product **4a** was obtained in 58% yield with *anti*-selectively [62] along with 17% of the homo-addition product **2a** (Table 2, entry 1). This promising result let us to optimize the cross-addition reaction, and the results are summarized in Table 2. Regarding the reaction temperature (entries 1–7), we found that the cross-addition product *anti*-**4a** was obtained in 64% yield when the reaction was performed at −78 to −50 °C (entry 3). The examination of the amount of the electrophile indicated that an increase of the imino ester **3** was not effective (entris 8–10). Although other nucleophiles such as Et_2AlCl, $EtAlCl_2$, EtMgBr, EtZnI and Et_2Mg were examined, the yields of the cross-addition product **4a** were not improved (entries 11–17).

The scope of substrates was next examined (Scheme 2). The reaction proceeded to give the corresponding addition products **4** in moderate to good yields even with not only primary alkyl thioesters but also secondary and tertiary alkyl thioesters as well.

To extend the utility of this tandem reaction, we focused on the formation of 3-amino-β-lactam via the reaction carried out at room temperature (Table 2, entry 7). 3-Amino-β-lactam is an important structure found in antibiotics and a useful skeleton because of the ability to transform its functional groups [63,64]. Thus, we also investigated the synthesis of 3-amino-β-lactam utilizing *N*-alkylation/addition reaction. After optimization of the reaction conditions, the desired β-lactam **5a** was obtained in 64% yield when the reaction was performed at −78 to 40 °C. The scope of zinc reagents was examined under the optimized conditions, and the results are shown in Scheme 3. Although the use of dimethylzinc did not provide the desired compound **5f** presumably due to its low reactivity, other primary, secondary and tertiary alkyl groups such as ^{n}Bu, ^{n}Oct, ^{i}Pr and ^{t}Bu could be introduced at the nitrogen atom to afford the corresponding *anti*-β-lactams **5b–e** in moderate to good yields.

Table 2 Optimization of *N*-alkylation/cross-addition reaction



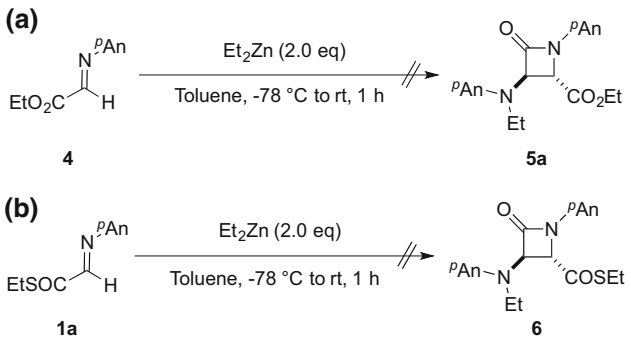
1a **3** (x eq) **4a** **2a**

Entry	x eq	Et-M (y eq)	Temp. (°C)	**4a** (%)	*anti* : *syn*	**2a** (%)
1	1.0	Et_2Zn (2.0)	−90 to −60	58	100 : 0	17
2	1.0	Et_2Zn (2.0)	−100 to −70	55	100 : 0	28
3	1.0	Et_2Zn (2.0)	−78 to −50	64	100 : 0	17
4	1.0	Et_2Zn (2.0)	−60 to −30	52	100 : 0	Trace
5[a]	1.0	Et_2Zn (2.0)	−78	63	100 : 0	16
6[a]	1.0	Et_2Zn (2.0)	−50	58	100 : 0	30
7[b]	1.0	Et_2Zn (2.0)	rt	7	100 : 0	0
8	1.5	Et_2Zn (2.0)	−60 to −50	51	100 : 0	44
9	2.0	Et_2Zn (2.0)	−60 to −50	52	100 : 0	20
10	3.0	Et_2Zn (2.0)	−60 to −50	54	100 : 0	Trace
11	1.0	Et_2AlCl (2.0)	−78 to −50	34	28 : 72	Trace
12	1.0	$EtAlCl_2$ (2.0)	−78 to −50	43	48 : 52	Trace
13	1.0	Et_2AlCl (1.0) + $EtAlCl_2$ (1.0)	−78 to −50	36	26 : 74	Trace
14	1.0	EtMgBr (1.0)	−78 to −50	0	–	0
15[c]	1.0	EtMgBr (1.0)	−78 to −50	0	–	0
16	1.0	EtZnI (2.0)	−78 to −50	0	–	0
17	1.0	Et_2Mg (2.0)	−78 to −50	Trace	–	Trace

[a] Reaction time was 15 min
[b] β-Lactam **5** was obtained in 20%
[c] THF was used as a solvent

To ascertain whether the β-lactam was formed from cross-addition product, the reaction of the α-aldimino ester **4** with diethylzinc was carried out (Scheme 4a). However, the desired β-lactam was not obtained at all. On the other hand, the β-lactam formation derived from the homo-addition product of α-aldimino thioester **1a** was also examined but the desired product was not obtained, either (Scheme 4b). This result may be attributed to the coordination to the zinc atom of the alkylthio group, which interrupts the cyclization of the homo-addition intermediate due to the affinity of sulfur and zinc.

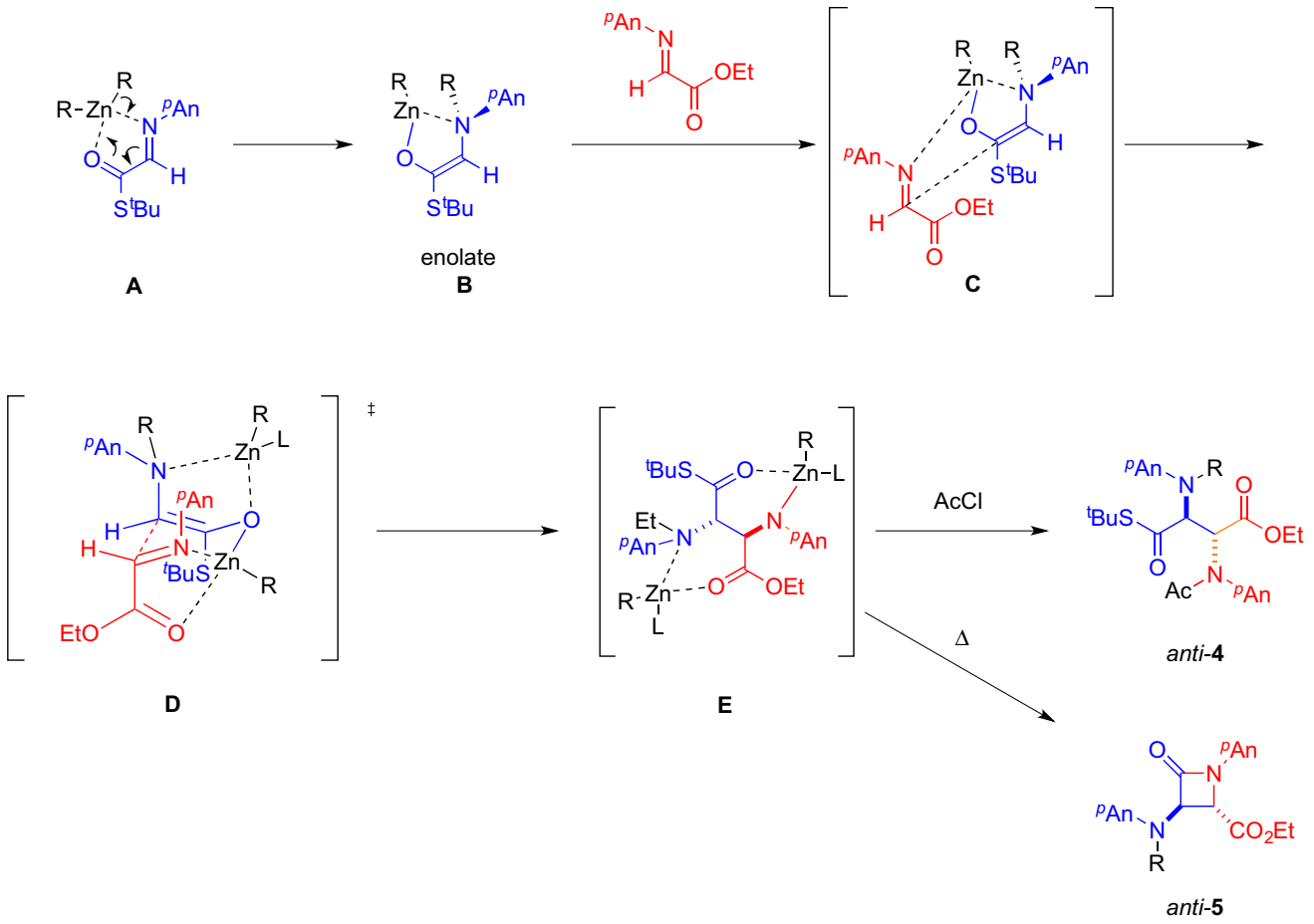
From these results, the reaction mechanism is proposed as shown in Scheme 5. First, R_2Zn coordinates to the nitrogen atom and the carbonyl oxygen to activate the α-aldimino thioester to form the 5-membered intermediate **A**. We speculate that it would be easier for a thioester to coordinate with dialkylzinc reagent than for a simple ester, since a thioester has a similar electronic property to that of a ketone. After the *N*-alkylation the reaction proceeds to form the zinc enolate **B**, which next coordinates to the imino nitrogen of the α-aldimino ester. Thus, the nucleophilic addition to α-aldimino ester proceeds to provide the *anti*-1,2-diamine product via a 6-membered chair-like transition state **C**. Finally, the *anti*-1,2-diamine product or *anti*-β-lactam product is obtained with an acetyl protection or via cyclization upon heating.



Scheme 4 β-Lactam syntheses from homo-addition product

4 Summary

In conclusion, *anti*-selective 1,2-diamine synthesis was developed utilizing the tandem *N*-alkylation/homo-addition reaction of α-aldimino thioesters with dialkylzinc in good to



Scheme 5 Proposed reaction mechanism

high yields. We also found the tandem *N*-alkylation/cross-addition reaction of α-aldimino thioesters in the presence of another imino ester gave the 1,2-diamine products in good yields. Moreover, the highly diastereoselective 3-amino-β-lactam synthesis was accomplished via a reaction conducted at 40 °C.

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