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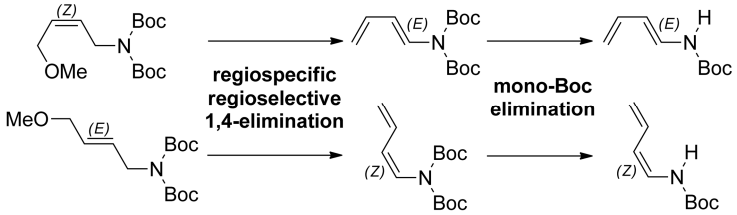

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Regioselective synthesis of secondary 1,3-dienamides by successive eliminations

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ABSTRACT

The regioselective synthesis of secondary 1,3-dienamides **3** (1-*N*-acylamino-1,3-dienes) is successfully demonstrated by regiospecific base-promoted 1,4-elimination (*Z*)- or (*E*)-*N*,*N*-di-Boc-4-methoxy-2-buten-1-ylamine **1** followed by mono-Boc elimination *in situ*.

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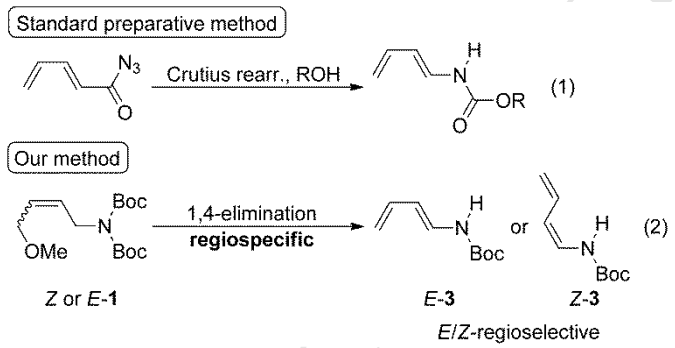
1. Introduction

Enamides (enecarbamates) constitute a class of valuable building blocks in organic synthesis for the synthesis of nitrogen-containing compounds.[1] Tertiary enamides, which is *N*-alkylated derivatives, are less nucleophilic.[2] Thus the synthetic application of tertiary enamides have been demonstrated in cycloaddition reactions.[3-5] In contrast, secondary enamides are reactive toward common electrophiles in the presence of Lewis or Brønsted acids. Especially, the *N*-acylamino substituent (NHCOR), as found in secondary enamides, can interact with the chiral Brønsted acids. Various asymmetric reactions using secondary enamides have been developed. The dienyl derivatives, secondary 1,3-dienamides (1-*N*-acylamino-1,3-dienes), have also attracted much attention from synthetic organic chemists because they function as reactive dienyl components, such as in Diels–Alder reactions to construct fused-ring compounds.[6-8] Their most standard preparative method is Curtius rearrangement of 2,4-dienoic acid azides followed by alcolysis under heated conditions (Scheme 1, eq. 1), which was originally developed by Overman et al. [9] This method usually affords the thermodynamically stable *E*-regioisomer as the main product. A number of synthetic methods of secondary 1,3-dienamides have been reported.[10,11] however, stereoselective and *E*/*Z*-stereo-controlled synthetic protocols have never been developed.

Our group has studied stereoselective and stereospecific base-promoted 1,4-elimination[12,13] affording *N*-Boc-1,3-dienamides;[14] however, this method was limited to preparing tertiary 1,3-dienamides.[15] Meanwhile, in our study on the regioselective cyclopropanation of 1,3-dienamides,[16] we obtained one example of the regioselective preparation of a secondary 1,3-dienamide **3** by the 1,4-elimination of *N*,*N*-di-Boc-4-methoxy-2-buten-1-ylamine **1** (Scheme 1, eq. 2). Therefore, we decided to further investigate the scope and limitations of this reaction. Herein, we report the regioselective synthesis of secondary 1,3-dienamides by base-promoted 1,4-elimination followed by mono-Boc elimination.

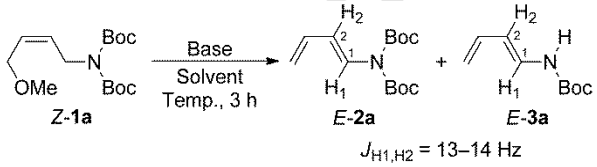


Scheme 1. Preparation of secondary 1,3-dienamides

2. Results and discussion

First, we prepared *Z*-**1a** as a substrate and investigated the base-promoted 1,4-elimination according to our previous result[14] (Table 1). Treatment of *Z*-**1a** with *n*-BuLi in THF or Et_2O at –78 °C did not afford the expected *N*,*N*-di-Boc-1,3-dienamide **2a** without the recovery of *Z*-**1a** (entries 1 and 2). The di-Boc group might be unstable toward strong nucleophiles such as *n*-BuLi. Thus, we used a non-nucleophilic base such as LDA. The desired product **2a** was obtained in 87% yield as a single regioisomer (entry 3). Interestingly, when the reaction was carried out at 0 °C, one of the *N*-Boc groups was eliminated to give the secondary 1,3-dienamide **3a** in 78% yield as a single regioisomer (entry 4). The C_1–C_2 stereochemistry of **2a** and **3a** was assigned as *E* based on the coupling constant of ^{1}H NMR between H_1 and H_2 (J = 13–14 Hz). Even if the reaction was performed on a larger scale, an acceptable yield was obtained (entry 5, 70%). The use of a larger amount of LDA (2.2 equiv.) did not improve the yield of *E*-**3a** (entry 6). When the reaction was performed with 1.0 equiv. of LDA, *E*-**3a** (52%) was obtained with a small amount of *E*-**2a** (5%) (entry 7). The use of analog bases, such as lithium 2,2,6,6-tetramethylpiperidide (LiTMP), lithium bis(trimethylsilyl)amide (LiHMDS), and sodium bis(trimethylsilyl)amide (NaHMDS) did not afford the 1,4-eliminated products **2a** and **3a**, with *Z*-**1a** being recovered (entries 8–10). The reaction promoted with potassium bis(trimethylsilyl)amide (KHMDS) afforded *E*-**2a** and *E*-**3a** in lower yields (entry 11). The use of 2.2 equiv. of KHMDS gave complicated products formed by undesirable side reactions (entry 12).

Table 1. Base-promoted 1,4-elimination of *Z*-**1a**[a]



Entry	Base (equiv.)[b]	Solvent	Temp. (°C)	*E*-**2a**[c] (%)	*E*-**3a**[c] (%)
1	*n*-BuLi (1.5)	THF	–78	0	0
2	*n*-BuLi (1.5)	Et_2O	–78	0	0
3	LDA (1.5)	THF	–78	87	0
4	LDA (1.5)	THF	0	0	78
5[d]	LDA (1.5)	THF	0	0	70
6	LDA (2.2)	THF	0	0	63
7[e]	LDA (1.0)	THF	0	5	52
8	LiTMP (1.5)	THF	0	0	0
9	LiHMDS (1.5)	THF	0	0	0
10[f]	NaHMDS (1.5)	THF	0	0	5
11[g]	KHMDS (1.5)	THF	0	11	30
12	KHMDS (2.2)	THF	0	messy	

[a] Unless otherwise noted, the reactions were performed using *Z*-**1a** (0.30 mmol) and ca. 0.7 M LDA solution (0.64 mL, 0.45 mmol) in THF (2.4 mL).

[b] LDA: ca. 0.7 M THF/*n*-hexane solution prepared from *n*-BuLi in *n*-hexane and diisopropylamine in THF; LiTMP: ca. 0.5 M THF/*n*-hexane solution prepared from *n*-BuLi in *n*-hexane and 2,2,6,6-tetramethylpiperidine in THF; LiHMDS and NaHMDS: 1.0 M THF solution (Aldrich); KHMDS: 0.5 M toluene solution (Aldrich).

[c] Isolated yield.

[d] *Z*-**1a**: 2.14 mmol scale.

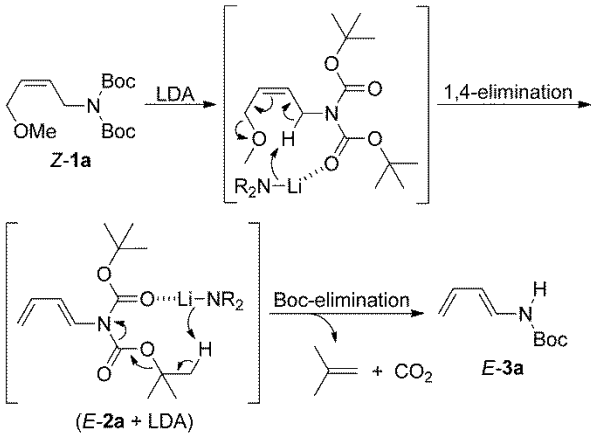
[e] Recovered *Z*-**1a** in 24% yield.

[f] Recovered *Z*-**1a** in 76% yield.

[g] Recovered *Z*-**1a** in 14% yield.

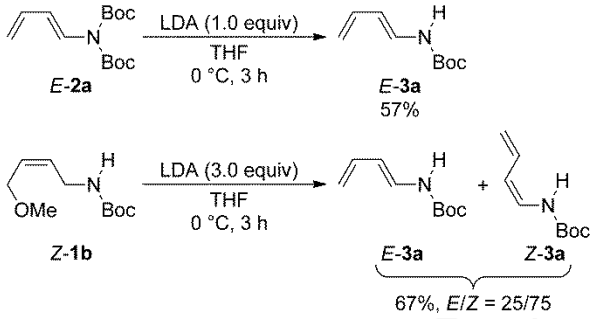
E-**3a** would be formed by the *E*-stereoselective 1,4-elimination of *Z*-**1a** followed by the base-promoted elimination of an *N*-Boc group, as in *E*-**2a** (Scheme 2). The coordination of excess LDA to one of the Boc-carbonyl oxygen (*E*-**2a** + LDA) accelerates the deprotonation of a *tert*-butyl proton. This mechanism required 2 equiv. of LDA for complete conversion;

however, the best yield of *E*-**3a** was obtained in the case of 1.5 equiv. of LDA (Table 1, entry 4). Although the exact reason is presently unclear, undesirable side reactions with LDA might occur to afford uncharacterized products.



Scheme 2. Proposed mechanism of the base-promoted 1,4-elimination.

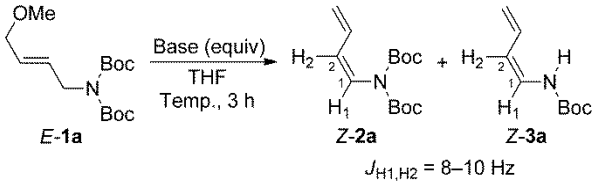
To clarify the mechanism of this stereoselective formation of the secondary 1,3-dienamide *E*-**3a**, we treated *E*-**2a** with LDA to remove one of the Boc groups (Scheme 3). The reaction proceeded to afford *E*-**3a** in 57% yield without isomerization to *Z*-**3a**. Next, we prepared the mono-*N*-Boc substrate *Z*-**1b** and examined the reaction with 3.0 equiv. of LDA. The 1,4-eliminated product **3a** was obtained as an *E*/*Z* = 25/75 mixture in 67% combined yield.



Scheme 3. Experimental studies on the base promoted 1,4-elimination.

With the results in hand, we next investigated the reaction of the *E*-counterpart (*E*-**1a**) to prepare another regioisomer *Z*-**2a** or *Z*-**3a** by the regiospecific and stereoselective 1,4-elimination (Table 2). When the reaction was carried out under the same conditions depicted in Table 1, it afforded *Z*-**2a** in 45% and *Z*-**3a** in 34% yield (entry 1). The C_1–C_2 stereochemistry of **2a** and **3a** was assigned as *Z* based on the coupling constant of ^{1}H NMR between H_1 and H_2 ($J_{H1,H2}$ = 8–10 Hz). One of the Boc groups, as in *Z*-**2a**, may be eliminated more easily than from *E*-**2a** to form *Z*-**3a** at –78 °C. Complete conversion to the secondary 1,3-dienamide *Z*-**3a** was not accomplished at –78 °C even with the use of 2.2 equiv. of LDA (entry 2). The elimination proceeded smoothly at 0 °C, and the desired product *Z*-**3a** was obtained in 71% yield (entry 3). The yield was acceptable if the reaction was performed on a larger scale (entry 4, 64%). Similarly to the reaction of *Z*-**1a** (Table 1, entry 6), the use of 2.2 equiv. of LDA did not improve the yield of *Z*-**3a** (entry 5) and the stereoisomer *E*-**3a** was isolated in 8% yield as a side product by careful chromatographic purification. The reaction with KHMDS was unsuccessful (entry 6). Elimination of one of the Boc groups, as in *E*-**1a**, proceeded to afford (*E*)-*tert*-butyl (4-methoxybut-2-en-1-yl)carbamate (*E*-**1b**) in 37% yield.

Table 2. Base-promoted 1,4-elimination of *E*-**1a**[a]



Entry	Base (equiv.)[b]	Temp. (°C)	*Z*-**2a** (%)[c]	*Z*-**3a** (%)[c]
1	LDA (1.5)	–78	45	34
2	LDA (2.2)	–78	30	44
3	LDA (1.5)	0	0	71
4[d]	LDA (1.5)	0	0	64
5	LDA (2.2)	0	0	56[e]
6	KHMDS (1.5)	0	0	29[f]

[a] Unless otherwise noted, the reactions were performed using *E*-**1a** (0.30 mmol) and ca. 0.7 M LDA solution (0.64 mL, 0.45 mmol) in THF (2.4 mL).

[b] LDA: ca. 0.7 M THF/*n*-hexane solution (prepared), KHMDS: 0.5 M toluene solution (Aldrich).

[c] Isolated yield.

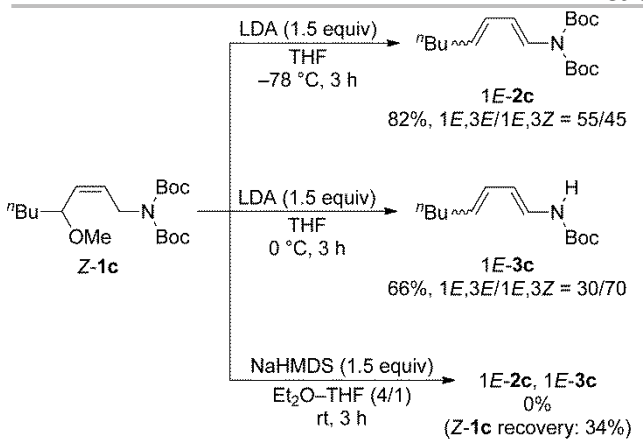
[d] *E*-**1a**: 2.18 mmol scale.

[e] *E*-**3a** was obtained in 8 % yield.

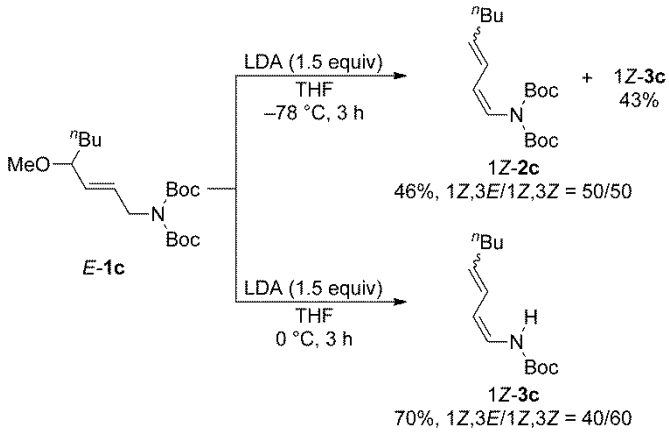
[f] (*E*)-*tert*-Butyl (4-methoxybut-2-en-1-yl)carbamate (*E*-**1b**) was obtained in 37 % yield.

To investigate the scope and limitations of this method, we prepared the 4-substituted (*n*-butyl) substrate *Z*-**1c** and investigated the reactions (Scheme 4). Under the same conditions described above, the corresponding secondary 1,3-dienamides, di-Boc derivative 1*E*-**2c** or mono-Boc derivative 1*E*-**3c**, were obtained as a mixture of 1*E*,3*E* and 1*E*,3*Z* regioisomers, respectively. We attempted the reaction with NaHMDS in Et_2O–THF (4/1), and those conditions afforded tertiary 1*E*,3*E*-1,3-dienamide via the formation of the chelated intermediate as reported by our group.[14b,17] However, the reaction was unsuccessful with the recovery of *Z*-**1c** (34%). Elimination of one Boc group, as in *Z*-**1c**, proceeded in 20% yield. Similarly, the reaction of *E*-**1c** gave the secondary 1,3-dienamides 1*Z*-**2c** or 1*Z*-**3c** as a mixture of 1*Z*,3*E* and 1*Z*,3*Z* regioisomers by the '*syn*-effect', as proposed by Inomata and Ukaji[18] (Scheme 5).

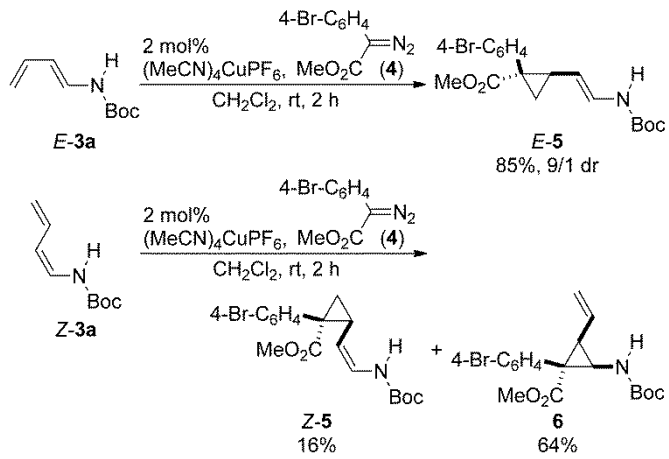
To demonstrate the sequential, regiospecific, and regioselective synthetic transformations, we performed the copper(I)-catalyzed cyclopropanation of *E*-**3a** and *Z*-**3a** with α-aryl diazoesters **4** according to our previous report[16] (Scheme 6). The reaction of *E*-**3a** proceeded at the C_3–C_4 double bond to give the corresponding cyclopropyl enamide *E*-**5** exclusively. On the other hand, when *Z*-**3a** was subjected to the same conditions, the reaction preferentially proceeded at the C_1–C_2 double bond to afford vinylcyclopropylamine derivative **6** as the main product.



Scheme 4. 1,4-Elimination of the 4-butyl derivative *Z*-**1c**.



Scheme 5. 1,4-Elimination of the 4-butyl derivative *E*-**1c**.



Scheme 6. Regiospecific and regioselective cyclopropanation of **3a**

In summary, the regioselective synthesis of secondary 1,3-dienamides **3** (1-*N*-acylamino-1,3-dienes) was reported. The reaction proceeds via the regioselective base-promoted 1,4-elimination of (*Z*)- or (*E*)-*N*,*N*-di-Boc-4-methoxy-2-buten-1-ylamine **1** followed by mono-Boc elimination.[19] Further sequential synthetic transformations were demonstrated by the Cu-catalyzed regiospecific 3,4- or 1,2-regioselective cyclopropanation of **3**.

3. Experimental

3.1. General

Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian 400 MHz spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz). The splitting patterns are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad peak. High-resolution mass spectra were measured on a Thermo Fisher Scientific LC/FT-MS spectrometer. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate round-bottomed flasks with a magnetic stirring bar under an argon atmosphere. *n*-Butyllithium was purchased from Wako Pure Chemical Industries, Ltd. Diisopropylamine was were purchased from Aldrich (purified by redistillation, 99.95%) and used without purification. Lithium bis(trimethylsilyl)amide solution (LiHMDS: 1.0 M in THF), sodium bis(trimethylsilyl)amide solution (NaHMDS: 1.0 M in THF), and potassium bis(trimethylsilyl) amide solution (KHMDS: 0.5 M in toluene) and were purchased from Aldrich. Tetrakis(acetonitrile)copper(I) hexafluorophosphate [$(MeCN)_4CuPF_6$] was purchased from Tokyo Chemical Industry (TCI) Co., Ltd. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purchased from KANTO Chemical Co., Inc., Japan as an anhydrous solvent. Dichloromethane was distilled from calcium hydride prior to use. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60 F_{254}) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan).

3.2. Preparation of ca. 0.7 M LDA THF/*n*-hexane solution

A dried 100 mL storage flasks with stopcock-equipped septum-inlet (Aldrich) is charged with diisopropylamine (2.86 mL, 20.4 mmol) in THF (15 mL) under an argon atmosphere. A 1.61 M *n*-butyllithium hexane solution (12.7 mL, 20.4 mmol) was added to the solution of at –78 °C. The mixture was stirred for 15 min at the same temperature and allowed to warm to 0 °C slowly. The resulting pale yellow solution was titrated[20] and stored in refrigerator.

3.3. Representative procedure for preparation of *E*-2a by 1,4-elimination of *Z*-1a

A solution of *Z*-**1a** (90 mg, 0.30 mmol) in THF (2.4 mL) was treated with a ca. 0.7 M LDA THF/*n*-hexane solution (0.64 mL, 0.45 mmol) at –78 °C under an argon atmosphere and stirred for 3 h at the same temperature. The resulting mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extractes were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate = 30/1 as the eluent) to afford *E*-**2a** (70 mg, 87% yield) as a colorless oil.

3.4. Representative procedure for preparation of *Z*-3a by 1,4-elimination of *E*-1a

A solution of *E*-**1a** (90 mg, 0.30 mmol) in THF (2.4 mL) was treated with a ca. 0.7 M LDA THF/*n*-hexane solution (0.64 mL, 0.45 mmol) at 0 °C under an argon atmosphere. After stirring for 3 h at the same temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride. Extractive workup and purification of the residue by chromatography on silica gel (*n*-hexane/ethyl acetate = 20/1 as the eluent) gave *Z*-**3a** (36 mg, 71% yield) as a white solid.

3.4.1. (E)-N,N-Di-(tert-butoxycarbonyl)buta-1,3-dien-1-ylamine (E-2a)

Colorless oil; IR (film) 3088, 2980, 2934, 1755, 1724, 1650, 1604, 1478, 1457, 1420, 1394, 1369, 1329, 1292, 1259, 1230,

1165, 1135, 1101, 1035, 997, 929, 900, 856, 815, 784, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (1H, dd, *J* = 14.2, 0.6 Hz, 1-H), 6.29 (1H, dddd, *J* = 16.8, 10.4, 10.4, 0.6 Hz, 3-H), 6.00 (1H, dddd, *J* = 14.2, 10.4, 0.6, 0.6 Hz, 2-H), 5.12 (1H, ddd, *J* = 16.8, 0.6, 0.6 Hz, 4-H), 5.00 (1H, ddd, *J* = 10.4, 0.6, 0.6 Hz, 4-H), 1.53 (18H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 134.5, 127.3, 117.6, 115.2, 83.3, 27.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{23}NO_4Na$: 292.1519. Found: 292.1514.

*3.4.2. (E)-tert-Butyl buta-1,3-dien-1-ylcarbamate (E-**3a**)*

White solid; Mp 67–68 °C (lit.[9c-9d] 67–68 °C); IR (KBr) 3357, 3085, 3037, 2982, 2935, 1698, 1658, 1608, 1503, 1460, 1445, 1409, 1391, 1368, 1294, 1280, 1252, 1232, 1158, 1051, 1023, 994, 949, 932, 877, 861, 773, 766, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.33 (1H, br d, *J* = 10.8 Hz, NH), 6.63 (1H, dd, *J* = 13.0, 10.8 Hz, 1-H), 6.26 (1H, ddd, *J* = 17.0, 11.0, 10.4 Hz, 3-H), 5.70 (1H, dd, *J* = 13.0, 11.0 Hz, 2-H), 4.91 (1H, d, *J* = 17.0 Hz, 4-H), 4.76 (1H, d, *J* = 10.4 Hz, 4-H), 1.42 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 134.7, 127.4, 112.5, 111.0, 80.7, 28.1; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_9H_{16}NO_2$: 170.1176. Found: 170.1172.

*3.4.1. (Z)-N,N-Di-(tert-butoxycarbonyl)buta-1,3-dien-1-ylamine (Z-**2a**)*

Colorless oil; IR (film) 3088, 3047, 2980, 2934, 1793, 1751, 1718, 1648, 1595, 1478, 1458, 1433, 1393, 1369, 1340, 1283, 1246, 1152, 1117, 1035, 995, 911, 883, 852, 824, 790, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (1H, ddd, *J* = 16.9, 10.4, 10.4 Hz, 3-H), 5.87 (1H, dd, *J* = 8.0, 1.0 Hz, 1-H), 5.81 (1H, dd, *J* = 10.4, 8.0 Hz, 2-H), 5.23 (1H, dd, *J* = 16.9, 1.2 Hz, 4-H), 5.12 (1H, ddd, *J* = 10.4, 1.2, 1.0 Hz, 4-H), 1.41 (18H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 130.0, 125.9, 124.3, 119.3, 82.6, 27.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{23}NO_4Na$: 292.1519. Found: 292.1512.

*3.4.2. (Z)-tert-Butyl buta-1,3-dien-1-ylcarbamate (Z-**3a**)*

White solid; Mp 96–98 °C; IR (KBr) 3276, 3162, 3086, 3006, 2979, 2935, 1705, 1678, 1655, 1605, 1517, 1458, 1392, 1363, 1314, 1272, 1252, 1165, 1117, 1044, 1022, 996, 939, 921, 890, 857, 788, 777, 758, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (8/2 mixture of rotamers) δ 7.42 (0.2H, br, NH), 6.80-6.15 (1.8H, br m, 3-H and NH), 6.62 (1H, br d, *J* = 10.0 Hz, 1-H), 5.28 (1H, dd, *J* = 10.4, 10.0 Hz, 2-H), 5.15 (1H, d, *J* = 16.8 Hz, 4-H), 5.01 (1H, d, *J* = 10.4 Hz, 4-H), 1.48 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 129.0, 123.1, 115.4, 107.8, 80.8, 28.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_9H_{15}NO_2Na$: 192.0995. Found: 192.0994.

*3.4.3. (E)-tert-Butyl (4-methoxybut-2-en-1-yl)carbamate (E-**1b**)*

Colorless oil; IR (film) 3340, 2977, 2930, 2824, 1708, 1694, 1531, 1519, 1504, 1470, 1454, 1391, 1366, 1338, 1270, 1250, 1173, 1126, 1053, 1014, 972, 943, 912, 863, 786, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 5.74 (1H, dt, *J* = 15.6, 4.4 Hz, 2- or 3-H), 5.69 (1H, dt, *J* = 15.6, 4.4 Hz, 2- or 3-H), 4.65 (1H, br, NH), 3.90 (2H, dt, *J* = 4.4, 1.2 Hz, 1- or 4-H), 3.75 (2H, br, 1- or 4-H), 3.33 (3H, s, OCH_3), 1.45 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 130.0, 127.9, 79.3, 72.4, 57.9, 41.9, 28.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{19}NO_3Na$: 224.1257. Found: 224.1253.

*3.4.4. (1E)-N,N-Di-(tert-butoxycarbonyl)octa-1,3-dien-1-ylamine (1E-**2c**)*

Colorless oil; 1*E*,3*E*/1*E*,3*Z* = 55/45; IR (film) 3077, 2979, 2931, 2872, 1755, 1723, 1650, 1624, 1611, 1478, 1458, 1393, 1369, 1346, 1259, 1226, 1168, 1134, 1108, 1035, 977, 929, 900, 857, 816, 785, 761 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.61 (0.45H, d, *J* = 13.6 Hz, 1-$H_{1E,3Z}$), 6.48 (0.55H, d, *J* = 14.3 Hz, 1-$H_{1E,3E}$), 6.14-5.94 (1.45H, m, 2-$H_{1E,3Z}$ and 3-H), 5.84 (0.55H, dd, *J* = 14.3, 10.6 Hz, 2-$H_{1E,3E}$), 5.61 (0.55H, dt, *J* = 15.2, 7.2 Hz, 4-$H_{1E,3E}$), 5.36 (0.45H, dt, *J* = 10.4, 7.8 Hz, 4-$H_{1E,3Z}$), 2.11-1.99 (2H, m, 5-H), 1.48 (8.1H, s, *t*-$Bu_{1E,3Z}$), 1.47 (9.9H, s, *t*-$Bu_{1E,3E}$), 1.38-1.21 (4H, m, 6- and 7-H), 0.87 (1.65H, t, *J* = 7.2 Hz, 8-$H_{1E,3E}$), 0.86 (1.35H, t, *J* = 7.2 Hz, 8-$H_{1E,3Z}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.7, 150.5, 132.9, 130.1, 127.4, 126.6, 125.9, 124.9, 117.3, 111.7, 83.4, 83.2, 31.8, 31.2, 31.0, 27.4, 27.3, 26.7, 21.64, 21.62, 13.8, 13.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{31}NO_4Na$: 348.2145. Found: 348.2137.

*3.4.5. tert-Butyl (1E)-octa-1,3-dien-1-ylcarbamate (1E-**3c**)*

Colorless oil; 1*E*,3*E*/1*E*,3*Z* = 30/70; IR (film) 3303, 3135, 3066, 2960, 2929, 2872, 1727, 1703, 1657, 1633, 1621, 1513, 1504, 1455, 1403, 1392, 1367, 1286, 1254, 1233, 1163, 1080, 1047, 1020, 976, 936, 902, 866, 787, 764 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) 6.57 (0.7H, d, *J* = 13.6 Hz, 1-$H_{1E,3Z}$), 6.49 (0.3H, d, *J* = 14.2 Hz, 1-$H_{1E,3E}$), 6.02-5.82 (1.7H, m, 2-$H_{1E,3Z}$ and 3-H), 5.66 (0.3H, dd, *J* = 14.2, 10.8 Hz, 2-$H_{1E,3E}$), 5.43 (0.3H, dt, *J* = 14.8, 7.0 Hz, 4-$H_{1E,3E}$), 5.19 (0.7H, dt, *J* = 10.0, 7.6 Hz, 4-$H_{1E,3Z}$), 2.11 (1.4H, dt, *J* = 7.6, 6.7 Hz, 5-$H_{1E,3Z}$), 2.05 (0.6H, dt, *J* = 7.0, 7.0 Hz, 5-$H_{1E,3E}$), 1.47 (9H, s, *t*-Bu), 1.40-1.27 (4H, m, 6- and 7-H), 0.97-0.85 (3H, m, 8-H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.5, 155.4, 131.0, 129.6, 128.6, 128.3, 127.9, 126.5, 112.6, 108.0, 81.3, 81.2, 33.7, 33.3, 33.2, 28.8, 28.5, 23.5, 23.4, 14.53, 14.49; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{24}NO_2$: 226.1802. Found: 226.1800.

*3.4.6. (1Z)-N,N-Di-(tert-butoxycarbonyl)octa-1,3-dien-1-ylamine (1Z-**2c**)*

Colorless oil; 1*Z*,3*E*/1*Z*,3*Z* = 50/50; IR (film) 2978, 2931, 2872, 1790, 1749, 1721, 1656, 1614, 1601, 1479, 1456, 1393, 1368, 1339, 1283, 1246, 1151, 1110, 1035, 975, 926, 885, 853, 824, 769 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.36-6.23 (1H, m, 3-H), 6.14 (0.5H, d, *J* = 8.1, 1.0 Hz, 1-$H_{1Z,3Z}$), 6.05 (0.5H, ddd, *J* = 11.4, 8.1, 1.2 Hz, 2-$H_{1Z,3Z}$), 6.02 (0.5H, d, *J* = 8.0 Hz, 1-$H_{1Z,3E}$), 5.76 (0.5H, dd, *J* = 11.0, 8.0 Hz, 2-$H_{1Z,3E}$), 5.54 (0.5H, dt, *J* = 14.8, 7.2 Hz, 4-$H_{1Z,3E}$), 5.40 (0.5H, dtd, *J* = 10.8, 7.5, 1.0 Hz, 4-$H_{1Z,3Z}$), 1.96 (1H, dtd, *J* = 7.5, 7.1, 1.2 Hz, 5-$H_{1Z,3Z}$), 1.90 (1H, dt, *J* = 7.2, 6.6 Hz, 5-$H_{1Z,3E}$), 1.394 (9H, s, *t*-Bu), 1.388 (9H, s, *t*-Bu), 1.25-1.10 (4H, m, 6- and 7-H), 0.80 (3H, t, *J* = 7.0 Hz, 8-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.9, 150.8, 137.1, 134.5, 124.4, 124.0, 123.3, 122.3, 121.4, 119.2, 82.3, 82.2, 31.9, 31.1, 30.7, 27.4, 26.8, 21.62, 21.61, 13.7; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{32}NO_4$: 326.2326. Found: 326.2315.

*3.4.7. tert-Butyl (1Z)-octa-1,3-dien-1-ylcarbamate (1Z-**3c**)*

Colorless oil; 1*Z*,3*E*/1*Z*,3*Z* = 40/60; IR (film) 3458, 3313, 3269, 3149, 3096, 2958, 2929, 2872, 1703, 1655, 1611, 1503, 1483, 1430, 1366, 1245, 1160, 1062, 1014, 971, 926, 863, 785, 758 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.34 (0.4H, ddd, *J* = 15.3, 11.2, 1.0 Hz, 3-$H_{1Z,3E}$), 6.31 (0.6H, d, *J* = 9.8 Hz, 1-$H_{1Z,3Z}$), 6.23 (0.6H, ddd, *J* = 11.1, 11.1, 1.2 Hz, 3-$H_{1Z,3Z}$), 6.16 (0.4H, d, *J* = 9.5 Hz, 1-$H_{1Z,3E}$), 5.56 (0.4H, dt, *J* = 15.3, 7.3 Hz, 4-$H_{1Z,3E}$), 5.43 (0.6H, dd, *J* = 11.1, 9.8 Hz, 2-$H_{1Z,3Z}$), 5.34 (0.6H, dt, *J* = 11.1, 7.6 Hz, 4-$H_{1Z,3Z}$), 5.18 (0.4H, dd, *J* = 11.2, 9.5 Hz, 2-$H_{1Z,3E}$), 2.19-2.06 (2H, m, 5-H), 1.48 (9H, s, *t*-Bu), 1.43-1.27 (4H, m, 6- and 7-H), 0.913 (1.2H, t, *J* = 7.0 Hz, 8-$H_{1Z,3E}$), 0.909 (1.8H, t, *J* = 7.2 Hz, 8-$H_{1Z,3Z}$); ^{13}C NMR (100 MHz, CD_3OD) δ 155.7, 155.6, 133.7, 131.1, 125.2, 123.8, 123.1, 122.0, 110.2, 105.0, 81.5, 81.3, 33.7, 33.1, 33.0, 28.8, 28.3, 23.50, 23.46, 14.5; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{23}NO_2Na$: 248.1621. Found: 248.1617.

3.5. Representative procedure for cyclopropanation of Z-3a

A solution of *Z*-**3a** (50 mg, 0.30 mmol) and **4** (66 mg, 0.26 mmol) in dichloromethane (2.6 mL) was added to tetrakis(acetonitrile)copper(I) hexafluorophosphate (2.2 mg, 0.006 mmol) in a flask at room temperature under an argon atmosphere. After stirring for 2 h at the same temperature, the resulting mixture was quenched with saturated sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (*n*-hexane/ethyl acetate = 10/1 as the eluent) afforded *Z*-**5** (15 mg, 16% yield) as a white solid and **6** (66 mg, 64% yield) as a white solid.

*3.5.1. Methyl 1-(4-bromophenyl)-2-((E)-2-((tert-butoxycarbonyl)amino)vinyl)cyclopropanecarboxylate (E-**5**)*

White solid; Mp 62–64 °C; *rel*-(1*S*,2*R*)/(1*R*,2*R*) = 9/1; IR (KBr) 3346, 2978, 2951, 1720, 1671, 1513, 1491, 1453, 1434, 1392, 1368, 1252, 1157, 1091, 1070, 1048, 1023, 1011, 946, 859, 818, 767, 732, 715 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.20 (0.1H, br d, *J* = 10.8 Hz, NH), 8.05 (0.9H, br d, *J* = 11.4 Hz, NH), 7.48 (2H, d, *J* = 7.2 Hz, ArH), 7.34 (0.2H, d, *J* = 7.2 Hz, ArH), 7.23 (1.8H, d, *J* = 7.2 Hz, ArH), 6.75 (0.1H, dd, *J* = 13.8, 10.8 Hz, CH=C*H*N), 6.60 (0.9H, dd, *J* = 13.6, 11.4 Hz, CH=C*H*N), 5.15 (0.1H, dd, *J* = 13.8, 9.2 Hz, C*H*=CHN), 4.18 (0.9H, dd, *J* = 13.6, 9.8 Hz, C*H*=CHN), 3.57 (3H, s, OCH_3), 2.53-2.38 (0.9H, m, 2-H), 2.30-2.19 (0.1H, m, 2-H), 1.85 (0.9H, dd, *J* = 9.0, 4.6 Hz, 3-H), 1.74 (0.1H, dd, *J* = 6.8, 4.8 Hz, 3-H), 1.52-1.31 (1H, m, 3-H), 1.43 (0.9H, s, *t*-Bu), 1.39 (8.1H, s, *t*-Bu); ^{13}C NMR (100 MHz, acetone-d_6) [assined only *rel*-(1*S*,2*R*)] δ 174.0, 153.5, 136.8, 134.8, 131.8, 127.3, 121.5, 107.3, 80.0, 52.7, 34.9, 28.6, 28.5, 22.0; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{22}BrNO_4Na$: 418.0624. Found: 418.0618.

*3.5.2. rel-(1S,2R)-Methyl 1-(4-bromophenyl)-2-((Z)-2-((tert-butoxycarbonyl)amino)vinyl)cyclopropanecarboxylate (Z-**5**)*

White solid; Mp 102–105 °C; IR (film) 3338, 2977, 2929, 2853, 1722, 1668, 1504, 1488, 1455, 1435, 1393, 1367, 1341, 1325, 1256, 1159, 1118, 1088, 1070, 1054, 1011, 988, 952, 864, 825, 772, 755, 736, 716 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.41 (1H, br d, *J* = 10.0 Hz, NH), 7.49 (2H, ddd, *J* = 8.6, 2.2, 2.2 Hz, ArH), 7.23 (2H, ddd, *J* = 8.6, 2.2, 2.2 Hz, ArH), 6.41 (1H, dd, *J* = 10.0, 10.0 Hz, CH=C*H*N), 3.55 (3H, s, OCH_3), 3.53 (1H, dd, *J* = 10.0, 9.6 Hz, C*H*=CHN), 2.71 (1H, dddd, *J* = 9.6, 9.0, 6.6, 1.0 Hz, 2-H), 1.90 (1H, dd, *J* = 9.0, 4.2 Hz, 3-H), 1.44 (9H, s, *t*-Bu), 1.35 (1H, dd, *J* = 6.6, 4.2 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 152.6, 134.3, 133.1, 131.3, 124.8, 121.5, 105.0, 80.9, 52.7, 29.7, 28.2, 25.2, 22.8; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{22}BrNO_4Na$: 418.0624. Found: 418.0613.

*3.5.3. rel-(1R,2S,3S)-Methyl 1-(4-bromophenyl)-2-((tert-butoxycarbonyl)amino)-3-vinylcyclopropanecarboxylate (**6**)*

White solid; Mp 139–142 °C; IR (KBr) 3362, 3274, 2976, 1731, 1715, 1688, 1667, 1635, 1530, 1491, 1456, 1434, 1393, 1366, 1315, 1237, 1162, 1102, 1071, 1048, 1028, 1012, 968, 922, 890, 845, 786, 774, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (2H, d, *J* = 8.2 Hz, ArH), 7.15 (2H, d, *J* = 8.2 Hz, ArH), 5.48 (1H, dd, *J* = 16.9, 1.2 Hz, CH=CH_2), 5.27 (1H, dd, *J* = 10.4, 1.2 Hz, CH=CH_2), 5.08 (1H, ddd, *J* = 16.9, 10.4, 10.0 Hz, C*H*=CH_2), 4.39 (1H, br d, *J* = 5.2 Hz, NH), 3.75 (1H, dd, *J* = 9.0, 5.2 Hz, 2-H), 3.60 (3H, s, OCH_3), 2.85 (1H, dd, *J* = 10.0, 9.0 Hz, 3-H), 1.45 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 156.0, 134.3, 131.5, 130.6, 130.0, 122.0, 120.7, 80.4, 52.7, 40.7, 37.3, 32.9, 28.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{22}BrNO_4Na$: 418.0624. Found: 418.0605.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at xxx.