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Stereoselective preparation of (1*Z*)- and (1*E*)-*N*-Boc-1-amino-1,3-dienes by stereospecific base-promoted 1,4-elimination

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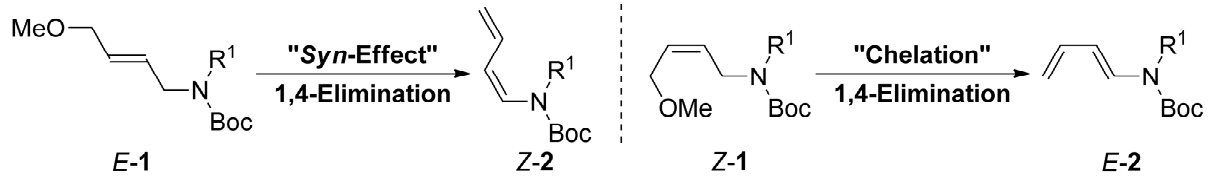

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Stereoselective preparation of (1*Z*)- and (1*E*)-*N*-Boc-1-amino-1,3-dienes by stereospecific base-promoted 1,4-elimination

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ABSTRACT

The base-promoted 1,4-elimination reaction of *N*-Boc-1-amino-4-methoxy-2-alkene **1** is shown to proceed with perfect stereoselectivity to afford the corresponding *N*-Boc-1-amino-1,3-diene **2** in good yields. The reaction is highly stereospecific. The substrate *E*-**1** gave 1*Z*-**2** by the "*Syn*-Effect" and *Z*-**1** gave 1*E*-**2** via formation of a chelated intermediate. Our method is widely applicable to the preparation of various types of *N*-Boc-1-amino-1,3-dienes **2**.

1. Introduction

1-Amino-1,3-dienes are useful building blocks in organic synthesis that function as reactive diene components in Diels–Alder reactions enabling the construction of nitrogen-containing fused-ring compounds.[1] Though *N*-acyl-1-amino-1,3-dienes (1,3-dienamides) are less reactive than the other 1-amino-1,3-dienes, they are sufficiently stable towards air and moisture and are easily handled in laboratory experiments. Traditional methods for the preparation of *N*-acyl-1-amino-1,3-dienes include *N*-acylation of conjugated imines followed by isomerization of the resulting *N*-acyliminium ions,[2] and Curtius rearrangements of 2,4-dienoic acids.[3] In natural product synthesis, copper catalyzed coupling of amides with dienyl iodides[4] (Buchwald protocol[5]) or palladium catalyzed cross-couplings of alkenyl stannanes with alkenyl iodides[6] have been used to construct *N*-acyl-1-amino-1,3-diene components. To date, a number of synthetic methods have been developed;[7–16] however, stereoselective and *E*/*Z*-stereo-controlled synthetic protocols are still limited.

In considering new methods for the preparation of *N*-acyl-1-amino-1,3-dienes, we have studied base-promoted 1,4-elimination reactions,[17] which enable the construction of various 1,3-dienes components[18] and have been used for the stereoselective preparation of *N*-Boc-1-amino-1,3-diene (1*E*,3*E*-**2**) through the 1,4-elimination of (*Z*)-*N*-Boc-4-substituted-4-methoxy-2-butene (*Z*-**1**)[17d] (Scheme 1, eq 1). The stereoselectivity may be rationalized as resulting from a concerted 1,4-elimination via formation of a chelate intermediate complex of sodium bis(trimethylsilyl)amide (NaHMDS) **A**, eventually leading to the 1*E*,3*E*-isomer. In that paper, we gave one example of a reaction starting from the *E*-isomer (*E*-**1**) in support the proposed intermediate **A** (eq 2). The reaction proceeded via an open-chain intermediate **B**, affording a mixture of 1*Z*,3*E*- and 1*Z*,3*Z*-isomers of **2**. A reasonable explanation for the 1*Z*-selectivity could not be advanced at that time. Recently, Inomata and Ukaji reported a "*Syn*-Effect" evident in the 1,4-elimination reactions of (*E*)-4-alkoxy-2-butenyl benzoates with potassium hydroxide, in the presence of a palladium(II) catalyst affording sterically unfavourable *Z*-dienes.[19,20] This work suggested that the 1*Z*-selectivity in our base-promoted 1,4-elimination reaction of *E*-**1** might also be explained by the "*Syn*-Effect" at work in the open-chain intermediate **B**. Therefore, we decided to further investigate the scope and limitations of our base-promoted 1,4-elimination of *N*-Boc-4-methoxy-2-butenes (**1**). Described herein is a stereoselective and stereospecific method for the synthesis of various *N*-Boc-1-amino-1,3-dienes (**2**) by 1,4-elimination reactions.

2. Results and discussion

We first selected (*Z*)-*tert*-butyl (4-methoxybut-2-en-1-yl)(phenyl)carbamate (*Z*-**1a**) as a substrate for the synthesis of *tert*-butyl buta-1,3-dien-1-yl(phenyl)carbamate (*E*-**2a**) by a base-promoted 1,4-elimination proceeding though the chelated intermediate **A**, as depicted in Scheme 1 (Table 1). The reactions were carried out under the various conditions to clarify the

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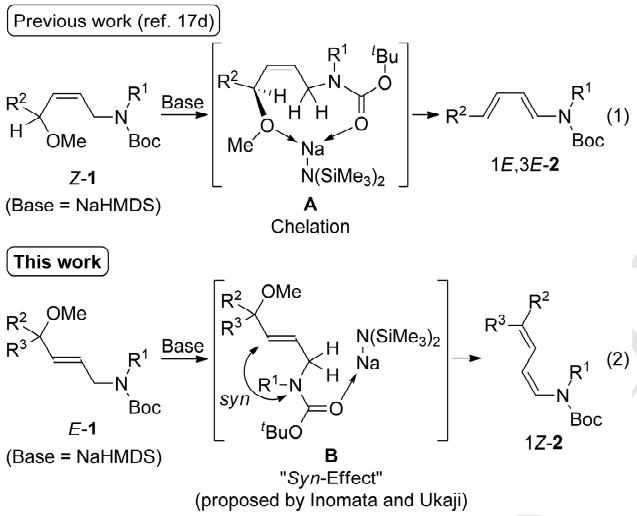
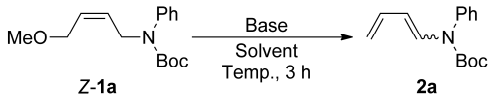
effects of base and solvent. Treatment of *Z*-**1a** with 1.5 equivalents of *n*-butyllithium (*n*-BuLi) in THF at 0 °C for 3 h afforded the desired 1,4-eliminated product (**2**) in 82% yield with excellent stereoselectivity (entry 1). The C_1–C_2 stereochemistry was assigned as *E* based on the ^{1}H NMR coupling constant ($J_{1\text{-H},2\text{-H}}$ = 14 Hz). When the reaction was carried out in diethyl ether (Et_2O), the yield was diminished (entry 2). Use of lithium diisopropylamide (LDA) in THF improved the yield to 94% with the same level of *E*-selectivity (entry 3). Reactions employing lithium bis(trimethylsilyl)amide (LiHMDS) were unsuccessful, resulting in the recovery of *Z*-**1a** at temperatures from 0 °C to room temperature (entries 4, 5). When the reactions were carried out with NaHMDS, **2a** was obtained in moderate yields (entries 6, 7), though the formation of undesirable side products at room temperature resulted in none of the substrate *Z*-**1a** being recovered (entry 7). When Et_2O was employed as the solvent, in hopes of minimizing side reactions (entry 8), the yield was improved to 79%, but the *E*-selectivity decreased (*E*/*Z* = 85/15). The use of potassium bis(trimethylsilyl)amide (KHMDS) gave **2a** in lowest *E*-selectivities (entries 9, 10). It seems that the greater Lewis acidity of Li^+, as compared to Na^+ or K^+, stabilizes the chelated intermediate **A**, and thereby improve the *E*-selectivity.



Scheme 1. Stereospecific formation of *N*-Boc-1-amino-1,3-dienes **2** by base-promoted 1,4-elimination of *Z*- or *E*-**1**

Next, we investigated the reaction of *E*-**1a** under similar conditions, which gave *Z*-**2a** by the "*Syn*-Effect" present in the open-chain intermediate **B**, as depicted in Scheme 1 (Table 2). The reaction of *E*-**1a** with *n*-BuLi at 0 °C afforded **2a** as a 30:70 mixture of *E*- and *Z*-**2a** (entries 1, 2). Use of LDA improved the *Z*-selectivity (entries 3, 4). The reaction with LiHMDS in THF did not proceed (entry 5); therefore, we attempted the reaction with the more-reactive NaHMDS, which resulted in the highly stereoselective formation of the desired **2a** in 71% yield (entry 6). The C_1–C_2 stereochemistry of **2a** was assigned as *Z* based on the ^{1}H NMR coupling constant ($J_{1\text{-H},2\text{-H}}$ = 9 Hz). When the reaction was carried out at room temperature, both the yield and *Z*-selectivity decreased and the formation of undesirable side products was observed (entry 7). The side reactions were minimized by using Et_2O as the primary solvent (entry 8), enabling the isolation of *Z*-**2a** in the yield and *Z*-selectivity comparable to entry 6. Similar results were obtained in the reaction with KHMDS. A complicated mixture was obtained in THF due to the extensive formation of side products (entry 9); however, the reaction in Et_2O afforded *Z*-**2a** in 79% yield with excellent *Z*-selectivity (entry 10).

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

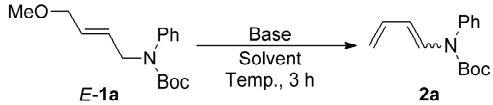


Z-**1a** **2a**

Entry	Base	Solvent	Temp. (°C)	**2a** (%)[a]	*E*/*Z*[b]
1	*n*-BuLi	THF	0	82	>98/2
2	*n*-BuLi	Et_2O	0	64	>98/2
3	LDA[c]	THF	0	94	>98/2
4	LiHMDS[d]	THF	0	4[g,h]	>98/2
5	LiHMDS[d]	THF	rt	25[g,i]	90/10
6	NaHMDS[d]	THF	0	58[j]	95/5
7	NaHMDS[d]	THF	rt	57[g,k]	95/5
8	NaHMDS[d]	Et_2O[f]	rt	79	85/15
9	KHMDS[e]	THF	0	31	81/19
10	KHMDS[e]	Et_2O	0	79	80/20

[a] Isolated yield unless otherwise noted. [b] Determined by ^{1}H NMR assay of the isolated product. [c] 1.0 M THF/hexanes solution (Aldrich). [d] 1.0 M THF solution (Aldrich). [e] 0.5 M toluene solution (TCI). [f] The resulting solvent is Et_2O/THF = 4/1. [g] Determined by ^{1}H NMR of the crude product using mesitylene as an internal standard. [h] 96% recovery of *Z*-**1a**. [i] 67% recovery of *Z*-**1a**. [j] 22% recovery of *Z*-**1a**. [k] 0% recovery of *Z*-**1a**

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



E-**1a** **2a**

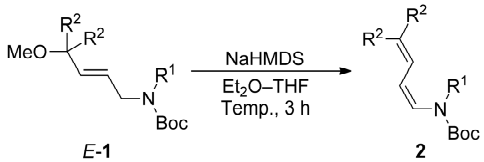
Entry	Base	Solvent	Temp. (°C)	**2a** (%)[a]	*E*/*Z*[b]
1	*n*-BuLi	THF	0	65	30/70
2	*n*-BuLi	Et_2O	0	52	30/70
3	LDA[c]	THF	0	56	16/84
4	LDA[d]	Et_2O	0	89	9/91
5	LiHMDS[e]	THF	0	4	3/97
6	NaHMDS[e]	THF	0	71	2/>98
7	NaHMDS[e]	THF	rt	45	9/91
8	NaHMDS[e]	Et_2O[g]	rt	69	2/>98
9	KHMDS[f]	THF	0	messy	–
10	KHMDS[f]	Et_2O	0	79	2/>98

[a] Isolated yield. [b] Determined by ^{1}H NMR assay of the isolated product. [c] 1.0 M THF/hexanes solution (Aldrich). [d] Prepared from *n*-BuLi and diisopropylamine in Et_2O at 0 °C. [e] 1.0 M THF solution (Aldrich). [f] 0.5 M toluene solution (TCI). [g] The resulting solvent is Et_2O/THF = 4/1.

To define the scope and limitations of the *Z*-stereoselective preparation of *N*-Boc-1,3-dienamides *Z*-**2** by 1,4-elimination, we prepared a series of *E*-**1** and used them in reactions with NaHMDS in Et_2O–THF at room temperature (Table 3). The reactions of the *N*-(4-methoxyphenyl) and *N*-[(*S*)-1-phenylethyl] derivatives (*E*-**1b** and *E*-**1c**) proceeded with the same levels of yield and *Z*-selectivity (entries 1, 2). Racemization of *Z*-**2c** was not observed by HPLC analysis using a chiral column, indicating that a methine proton in the *N*-[(*S*)-1-phenylethyl] substituent was not deprotonated. However, when the reaction of *N*-methyl derivative *E*-**1d** was carried out under the same conditions, the yield was lower (entry 3, 48%). The undesirable deprotonation of the *N*-methyl protons might proceed because of the decreased steric repulsion. Next, we attempted the reactions of 4,4-

disubstituted derivatives (*E*-**1e**–**1g**). The 4,4-dimethyl-*N*-(4-methoxyphenyl) derivative (*E*-**2e**) was obtained in moderate yield (entry 4, 62%); however, the *N*-[(*S*)-1-phenylethyl] derivative (*E*-**2f**) was not (entry 5, 23%). As the reactions of the 4,4-dimethyl derivatives proceeded rapidly, we performed the reactions with *E*-**1f** and *E*-**1g** at reflux, affording the desired products *Z*-**2f** and *Z*-**2g** in moderate yields (entries 6, 7). A slight decrease of *Z*-selectivity was observed in the case of the *N*-methyl derivative (*E*-**2g**, entry 7, *E*/*Z* = 7/93).

Table 3. Effects of 4- and *N*-substituents in base-promoted 1,4-elimination of *E*-**1**



E-**1** **2**

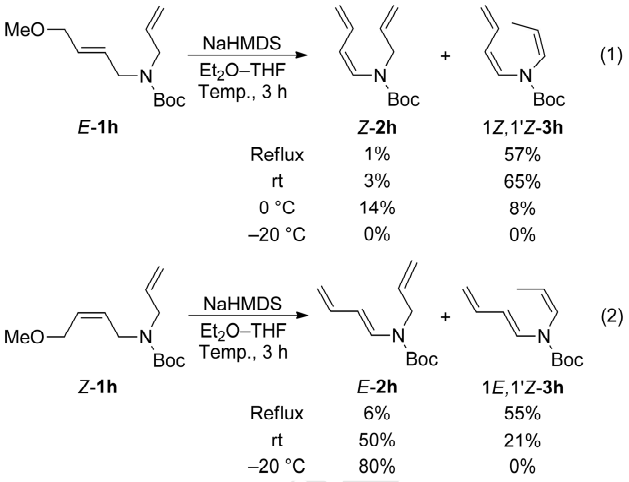
Entry	R^1	R^2		Temp. (°C)	**2** (%)[a]	*E*/*Z*[b]
1	*p*-MeO-Ph	H	**b**	rt	82	2/>98
2	(*S*)-CHMePh	H	**c**	rt	82	2/>98
3	Me	H	**d**	rt	48	2/>98
4	*p*-MeO-Ph	Me	**e**	rt	62	2/>98
5	(*S*)-CHMePh	Me	**f**	rt	23	2/>98
6	(*S*)-CHMePh	Me	**f**	Reflux	65	2/>98
7	Me	Me	**g**	Reflux	55	7/93

[a] Isolated yield. [b] Determined by ^{1}H NMR assay of the isolated product.

To demonstrate further synthetic transformations, we prepared the *N*-allyl derivatives **1h** as substrates and examined their reactions with 2.0 equivalents of NaHMDS in Et_2O–THF (Scheme 2). The 1,4-elimination of *E*-**1h** was initiated at approximately 0 °C, yielding *Z*-**2h** with isomerization of the *N*-allyl substituent into the *Z*-enamide as a result of deprotonation of allylic methylene proton (eq 1). The elimination–isomerization product 1*Z*,1'*Z*-**3h** was obtained in moderate yields at room temperature or above. None of the previously described reactions occurred at –20 °C. In contrast, the 1,4-elimination of *Z*-**1h** proceeded in good yield (80%) even at –20 °C (eq 2). At reflux, the elimination–isomerization product 1*E*,1'*Z*-**3h** was obtained as the major product. Though the reason is unclear at present, it is safe to say that *E*-**1** is less reactive than *Z*-**1** in the base-promoted 1,4-elimination because of the inaccessibility of the chelated intermediate **A** (Scheme 1), which enhances the rate of 1,4-elimination.

The high 1*Z*-stereoselectivity of *E*-**1** to *Z*-**2** in this 1,4-elimination can be explained by "*Syn*-Effect", as proposed by Inomata and Ukaji[19] (Figure 1). Interactions between the σ-orbital(s) of the allylic C–H σ-bond(s) and the antibonding (π*) orbital of the C=C double bond affords *s-cis* conformation in the transition state **B***, which leads to 1*Z*-alkenes by 1,4-elimination.

Finally, we prepared 4-butyl- and 4-phenyl-substituted derivatives *E*-**1i**, *E*-**1j** and used them in reactions to investigate the C_3–C_4 stereoselectivity of the 1,4-elimination (Scheme 3). The corresponding eliminated products (**2i** or **2j**) were obtained as a mixture of two isomers (~ 9/1) in similar yields. The stereochemistries of **2** were determined by their ^{1}H NMR coupling constants. The C_1–C_2 stereochemistries of both isomers were determined to be 1*Z* ($J_{1\text{-H},2\text{-H}}$ = 9–10 Hz). The C_3–C_4 stereochemistry was determined to be 3*E* for the major isomer ($J_{3\text{-H},4\text{-H}}$ = 15–16 Hz) and 3*Z* for the minor isomer ($J_{3\text{-H},4\text{-H}}$ = 12 Hz). The "*Syn*-Effect" did not control the C_3–C_4 stereochemistry, where the sterically favored *trans*-alkene was formed preferably.



Scheme 2. 1,4-Elimination of *N*-allyl derivatives **1h**

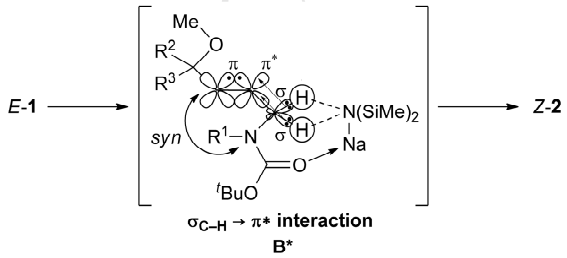
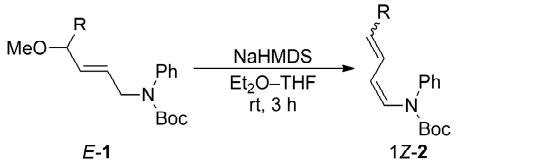


Figure 1. "*Syn*-Effect" in the base-promoted 1,4-elimination of *E*-**1**



Scheme 3. Study on C_3–C_4 stereoselectivity in the base-promoted 1,4-elimination of 4-substituted *E*-**1**

In summary, we have demonstrated a stereoselective and stereospecific base-promoted 1,4-elimination reaction of *N*-Boc-1-amino-4-methoxy-2-alkenes **1** to afford the corresponding *N*-Boc-1-amino-1,3-dienes **2**.[21] The reaction of *Z*-**1** affords 1*E*-**2** via formation of the chelated intermediate **A**. In contrast, the reaction of *E*-**1** affords 1*Z*-**2** by the "*Syn*-Effect" of the open-chain intermediate **B**. Both reactions proceed with perfect levels of *E*- or *Z*-selectivities. Our method is widely applicable to the preparation of various types of *N*-Boc-1-amino-1,3-dienes **2** which can act as useful building blocks in organic synthesis.[22]

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) and a 700 MHz spectrometer (^{1}H: 700 MHz, ^{13}C: 175 MHz). The splitting patterns are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad peak. Specific rotations were recorded on a JASCO Polarimeter P–1010. High-resolution mass spectra were measured on a Thermo

Fisher Scientific LC/FT-MS spectrometer. HPLC analyses were performed using a JASCO HPLC pump PU-2080 and a UV/VIS detector UV-2075. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate round-bottomed flasks with a magnetic stirring bar under an argon atmosphere. Lithium bis(trimethylsilyl)amide solution (LiHMDS: 1.0 M in THF), sodium bis(trimethylsilyl)amide solution (NaHMDS: 1.0 M in THF), and lithium diisopropylamide solution (LDA: 1.0 M in THF/hexanes) were purchased from Aldrich. Potassium bis(trimethylsilyl)amide solution (KHMDS: 0.5 M in toluene) 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. 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 *E*-2a by 1,4-Elimination of *Z*-1a

A solution of *Z*-**1a** (145 mg, 0.523 mmol) in THF (3.1 mL) was treated with a LDA solution (1.0 M in THF/hexanes, 0.79 mL, 0.79 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 3 h at the same temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate = 20/1 as the eluent) to give *E*-**2a** (120.1 mg, 94% yield) as a yellow oil.

*3.2.1. (E)-tert-Butyl buta-1,3-dien-1-yl(phenyl)carbamate (E-**2a**)*

Yellow oil. IR (KBr) 3064, 3001, 2973, 2936, 1703, 1644, 1594, 1495, 1477, 1454, 1425, 1391, 1368, 1347, 1320, 1284, 1251, 1155, 1071, 1049, 1031, 1017, 1000, 930, 896, 863, 764, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.39 (2H, m, Ph), 7.35 (1H, d, *J* = 14.2 Hz, 1-H), 7.34 (1H, tt, *J* = 7.6, 1.4 Hz, Ph), 7.15 (2H, ddd, *J* = 7.6, 1.4, 1.4 Hz, Ph), 6.31 (1H, ddd, *J* = 16.8, 10.8, 10.4 Hz, 3-H), 5.05 (1H, dd, *J* = 14.2, 10.8 Hz, 2-H), 4.83 (1H, dd, *J* = 16.8, 1.6 Hz, 4-H), 4.81 (1H, dd, *J* = 10.4, 1.6 Hz, 4-H), 1.42 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 138.5, 135.0, 133.0, 129.2, 128.6, 127.7, 113.0, 112.3, 81.7, 28.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{19}NO_2Na$: 268.1308. Found: 268.1307 (aq. HCO_2Na was added to improve sensitivity).

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

A solution of *E*-**1a** (140 mg, 0.505 mmol) in Et_2O (3.0 mL) was treated with a NaHMDS solution (1.0 M in THF, 0.76 mL, 0.76 mmol) at room temperature under an argon atmosphere and the mixture was stirred for 3 h. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate = 20/1 to 10/1 as the eluent) to give *Z*-**2a** (85.4 mg, 69% yield) as pale yellow crystals.

*3.3.1. (Z)-tert-Butyl buta-1,3-dien-1-yl(phenyl)carbamate (Z-**2a**)*

Pale yellow crystals. IR (KBr) 3085, 3009, 2981, 2969, 2932, 1700, 1644, 1592, 1496, 1454, 1434, 1393, 1369, 1333, 1304, 1283, 1254, 1165, 1113, 1073, 1044, 1019, 993, 905, 858, 823, 793, 768, 756, 733, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (2H, m, Ph), 7.28-7.20 (3H, m, Ph), 6.56 (1H, d, *J* = 9.2 Hz, 1-H), 5.57 (1H, ddd, *J* = 16.8, 11.6, 10.0 Hz, 3-H), 5.40 (1H, dd, *J* = 11.6, 9.2 Hz, 2-H), 4.98 (1H, dd, *J* = 16.8, 2.0 Hz, 4-H), 4.72 (1H, d, *J* = 10.0 Hz, 4-H), 1.45 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 141.6, 130.6, 128.9, 127.2, 127.0, 126.4, 116.9, 115.6, 81.6, 28.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{19}NO_2Na$: 268.1308. Found: 268.1311 (aq. HCO_2Na was added to improve sensitivity).

*3.3.2. (Z)-tert-Butyl buta-1,3-dien-1-yl(4-methoxyphenyl)carbamate (Z-**2b**)*

Colorless crystals. IR (KBr) 3087, 3046, 3000, 2973, 2937, 2842, 1692, 1642, 1605, 1586, 1512, 1477, 1457, 1432, 1393, 1370, 1322, 1300, 1249, 1162, 1113, 1044, 1033, 1024, 1007, 991, 917, 904, 851, 841, 823, 798, 765, 755, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (2H, ddd, *J* = 8.8, 2.8, 2.8 Hz, ArH), 6.89 (2H, ddd, *J* = 8.8, 2.8, 2.8 Hz, ArH), 6.59 (1H, d, *J* = 9.4 Hz, 1-H), 5.56 (1H, ddd, *J* = 16.5, 11.2, 10.4 Hz, 3-H), 5.33 (1H, dd, *J* = 11.2, 9.4 Hz, 2-H), 4.96 (1H, dd, *J* = 16.5, 2.2 Hz, 4-H), 4.71 (1H, d, *J* = 10.4 Hz, 4-H), 3.82 (3H, s, OCH_3), 1.45 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 153.4, 134.3, 130.7, 128.5, 127.0, 116.5, 114.2, 81.5, 55.4, 28.1; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{22}NO_3$: 276.1594. Found: 276.1588.

*3.3.3. (S,Z)-tert-Butyl buta-1,3-dien-1-yl(1-phenylethyl)carbamate (Z-**2c**)*

Colorless oil. $[\alpha]^{22}_{589}$ –6.7 (*c* 1.00, EtOH); 99% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/2-propanol = 99/1 as the eluent, flow rate = 0.50 mL/min, t_R = 8.9 min for (*R*)-*Z*-**2c** and 12.3 min for (*S*)-*Z*-**2c**]; IR (film) 3085, 3028, 2976, 2932, 1688, 1646, 1493, 1475, 1451, 1392, 1366, 1304, 1250, 1164, 1085, 1041, 1026, 985, 908, 862, 796, 783, 766, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (5H, m, Ph), 6.32 (1H, dddd, *J* = 17.2, 10.9, 10.2, 0.8 Hz, 3-H), 5.86 (1H, dddd, *J* = 10.9, 8.0, 0.8, 0.8 Hz, 2-H), 5.58-5.45 (2H, m, 1-H and NC*H*CH_3), 5.20 (1H, dddd, *J* = 17.2, 1.9, 0.8, 0.8 Hz, 4-H), 5.09 (1H, dddd, *J* = 10.2, 1.9, 1.9, 0.8 Hz, 4-H), 1.52 (3H, d, *J* = 7.2 Hz, NCHC*H*$_3$), 1.42 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 141.2, 131.8, 128.2, 127.7, 127.1, 127.0, 124.3, 117.9, 80.3, 54.4, 28.2, 17.4; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{23}NO_2Na$: 296.1621. Found: 296.1619 (aq. HCO_2Na was added to improve sensitivity).

*3.3.4. (Z)-tert-Butyl buta-1,3-dien-1-yl(methyl)carbamate (Z-**2d**)*

Colorless oil. IR (film) 3087, 2977, 2928, 2855, 1708, 1644, 1592, 1477, 1455, 1432, 1420, 1392, 1367, 1329, 1255, 1152, 1045, 1027, 995, 928, 895, 865, 839, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (1H, dddd, *J* = 16.8, 11.4, 10.1, 0.8 Hz, 3-H), 6.35 (1H, br, 1-H), 5.39 (1H, dd, *J* = 11.4, 10.2 Hz, 2-H), 5.15 (1H, dddd, *J* = 16.8, 2.0, 0.8, 0.8 Hz, 4-H), 5.06 (1H, ddd, *J* = 10.1, 2.0, 2.0 Hz, 4-H), 3.17 (3H, s, NCH_3), 1.48 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 131.4, 128.5, 116.7, 114.7, 80.9, 36.4, 28.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{17}NO_2Na$: 206.1152. Found: 206.1149 (aq. HCO_2Na was added to improve sensitivity).

*3.3.5. (Z)-tert-Butyl (4-methoxyphenyl)(4-methylpenta-1,3-dien-1-yl)carbamate (Z-**2e**)*

Yellow solid. IR (KBr) 3050, 2970, 2932, 2908, 2837, 1692, 1604, 1509, 1455, 1388, 1370, 1325, 1292, 1248, 1160, 1143, 1095, 1054, 1030, 1001, 982, 957, 854, 824, 791, 777, 766, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.8 Hz, ArH), 6.86 (2H, ddd, *J* = 8.8, 2.8, 2.8 Hz, ArH), 6.35 (1H, d, *J* = 9.0 Hz, 1-H), 5.61 (1H, dd, *J* = 11.4, 9.0 Hz, 2-H), 5.26 (1H, d, *J* = 11.4 Hz, 3-H), 3.80 (3H, s, OCH_3), 1.65 (3H, s, 4-CH_3), 1.54 (3H, s, 4-CH_3), 1.45 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ

157.6, 153.6, 135.3, 134.8, 128.0, 124.9, 118.9, 113.9, 113.2, 81.1, 55.4, 28.1, 26.3, 17.8; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{26}NO_3$: 304.1907. Found: 304.1900.

*3.3.6. (S,Z)-tert-Butyl (4-methylpenta-1,3-dien-1-yl)(1-phenylethyl)carbamate (Z-**2f**)*

Pale yellow oil. $[\alpha]^{22}_{589}$ +3.8 (*c* 1.00, EtOH); 98% ee [determined by HPLC analysis: Daicel Chiralpak AD–H column, *n*-hexane/2-propanol = 95/5 as the eluent, flow rate = 0.50 mL/min, t_R = 7.4 min for (*R*)-*Z*-**2f** and 7.9 min for (*S*)-*Z*-**2f**]; IR (film) 3032, 2976, 2929, 1686, 1608, 1494, 1477, 1451, 1389, 1365, 1304, 1250, 1207, 1164, 1085, 1042, 1025, 981, 930, 911, 862, 781, 763, 737, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.19 (5H, m, Ph), 6.03 (1H, dd, *J* = 11.3, 8.2 Hz, 2-H), 5.78 (1H, dq, *J* = 11.3, 1.2 Hz, 3-H), 5.60-5.30 (2H, br, 1-H and NC*H*CH_3), 1.77 (3H, s, 4-CH_3), 1.72 (3H, d, *J* = 1.2 Hz, 4-CH_3), 1.52 (3H, d, *J* = 7.2 Hz, NCHC*H*$_3$), 1.41 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 141.4, 136.4, 128.1, 127.04, 126.98, 123.7, 121.5, 120.2, 79.9, 54.2, 28.2, 26.3, 18.3, 17.5; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{28}NO_2$: 302.2115. Found: 302.2110.

*3.3.7. (Z)-tert-Butyl methyl(4-methylpenta-1,3-dien-1-yl)carbamate (Z-**2g**)*

Colorless oil. 1*Z*/1*E* = 93/7; IR (film) 3049, 2976, 2926, 1706, 1654, 1610, 1477, 1452, 1436, 1366, 1341, 1276, 1255, 1148, 1103, 1048, 1020, 982, 935, 869, 768, 757, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-6.92 (0.07H, br, 1-H), 6.16 (0.93H, br, 1-H), 5.99 (0.93H, dd, *J* = 11.4, 1.0 Hz, 3-H), 5.79 (0.07H, d, *J* = 10.4 Hz, 3-H), 5.58 (1H, dd, *J* = 11.4, 10.0 Hz, 2-H), 3.12 (2.79H, s, NCH_3), 3.06 (0.21H, s, NCH_3), 1.81 (2.79H, s, 4-CH_3), 1.78 (0.21H, d, *J* = 4.0 Hz, 4-CH_3), 1.74 (3H, s, 4-CH_3), 1.50 (0.63H, s, *t*-Bu), 1.47 (8.37H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, assigned only 1*Z*) δ 154.5, 135.4, 126.6, 119.4, 113.0, 80.4, 36.5, 28.3, 26.4, 18.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{21}NO_2Na$: 234.1465. Found: 234.1462.

*3.3.8. tert-Butyl (Z)-buta-1,3-dien-1-yl((Z)-prop-1'-en-1'-yl)carbamate (1Z,1'Z-**3h**)*

Colorless oil. IR (film) 3086, 3037, 2978, 2931, 2867, 1714, 1663, 1643, 1593, 1478, 1439, 1401, 1368, 1307, 1252, 1166, 1074, 1033, 994, 944, 901, 857, 811, 785, 761, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (1H, dddd, *J* = 17.2, 11.0, 10.6, 0.8 Hz, 3-H), 6.25 (1H, broad d, *J* = 8.8 Hz, 1-H), 6.15 (1H, dq, *J* = 8.3, 1.6 Hz, 1'-H), 5.50 (1H, dddd, *J* = 11.0, 8.8, 0.8, 0.8 Hz, 2-H), 5.26 (1H, dq, *J* = 8.3, 7.0 Hz, 2'-H), 5.15-5.07 (1H, m, 4-H), 5.04-4.98 (1H, m, 4-H), 1.53 (3H, dd, *J* = 7.0, 1.6 Hz, 3'-H), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 131.2, 127.7, 126.1, 118.9, 116.6, 81.4, 28.1, 13.0; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{20}NO_2$: 210.1489. Found: 210.1487.

*3.3.9. (E)-tert-Butyl allyl(buta-1,3-dien-1-yl)carbamate (E-**2h**)*

Colorless oil. IR (film) 3086, 3043, 2978, 2931, 1710, 1642, 1604, 1535, 1476, 1448, 1426, 1372, 1329, 1293, 1253, 1232, 1218, 1159, 1056, 996, 967, 930, 879, 857, 767, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-6.92 (1H, br, 1-H), 6.30 (1H, ddd, *J* = 16.6, 10.4, 10.4 Hz, 3-H), 5.78 (1H, ddt, *J* = 17.0, 10.6, 5.2 Hz, CH_2CH=CH_2), 5.53 (1H, dd, *J* = 14.0, 10.4 Hz, 2-H), 5.15 (1H, d, *J* = 10.6 Hz, CH_2CH=C*H*$_2$), 5.12 (1H, d, *J* = 17.0 Hz, CH_2CH=C*H*$_2$), 5.02 (1H, d, *J* = 16.6 Hz, 4-H), 4.87 (1H, d, *J* = 10.4 Hz, 4-H), 4.13 (2H, br, C*H*$_2$CH=CH_2), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2-152.1 (m), 135.5, 132.3, 131.0, 116.0, 112.4, 110.3, 81.6, 47.0-45.5 (m), 28.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{19}NO_2Na$: 232.1308. Found: 232.1307 (aq. HCO_2Na was added to improve sensitivity).

*3.3.10. tert-Butyl (E)-buta-1,3-dien-1-yl((Z)-prop-1'-en-1'-yl)carbamate (1E,1'Z-**3h**)*

Colorless oil. IR (film) 3085, 3039, 2978, 2931, 1712, 1663, 1643, 1603, 1478, 1455, 1434, 1421, 1398, 1368, 1314, 1302, 1253, 1157, 1080, 997, 937, 882, 854, 795, 768, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, d, *J* = 14.2 Hz, 1-H), 6.34 (1H, dddd, *J* = 17.2, 10.4, 10.4, 0.4 Hz, 3-H), 5.82 (1H, dq, *J* = 8.0, 1.8 Hz, 1'-H), 5.62 (1H, dq, *J* = 8.0, 7.0 Hz, 2'-H), 5.55 (1H, dddd, *J* = 14.2, 10.4, 0.8, 0.8 Hz, 2-H), 5.06-4.99 (1H, m, 4-H), 4.91-4.85 (1H, m, 4-H), 1.53 (3H, dd, *J* = 7.0, 1.8 Hz, 3'-H), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 135.2, 130.5, 125.9, 124.1, 112.9, 112.0, 81.5, 28.1, 12.5; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{19}NO_2Na$: 232.1308. Found: 232.1306.

*3.3.11. tert-Butyl (1Z)-octa-1,3-dien-1-yl(phenyl) carbamate (1Z-**2i**)*

Yellow oil. 1*Z*,3*E*/1*Z*,3*Z* = 87/13; IR (film) 3040, 2957, 2928, 2871, 1713, 1650, 1610, 1596, 1495, 1455, 1411, 1392, 1367, 1318, 1301, 1254, 1161, 1077, 1071, 1033, 1009, 997, 973, 926, 859, 832, 733, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (2H, m, Ph), 7.29-7.12 (3H, m, Ph), 6.49 (0.13H, d, *J* = 9.2 Hz, 1-H), 6.36 (0.87H, d, *J* = 8.6 Hz, 1-H), 5.70 (0.13H, ddd, *J* = 11.8, 9.2, 1.0 Hz, 2-H), 5.50 (0.87H, dt, *J* = 14.8, 6.6 Hz, 4-H), 5.43 (0.87H, dd, *J* = 11.2, 8.6 Hz, 2-H), 5.39-5.27 (1H, m, 3-H and 4-H), 5.19-5.10 (0.13H, m, 3-H), 2.11-2.02 (0.26H, m, 5-H), 1.80 (1.74H, dt, *J* = 6.6, 6.6 Hz, 5-H), 1.46 (9H, s, *t*-Bu), 1.32-1.23 (0.52H, m, 6-H and 7-H), 1.21-1.08 (3.48H, m, 6-H and 7-H), 0.87 (0.39H, t, *J* = 7.2 Hz, 8-H), 0.80 (2.61H, t, *J* = 7.2H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$, assigned only 1*Z*,3*E*) δ 153.3, 141.8, 135.0, 128.7, 127.0, 126.0, 124.9, 124.0, 116.9, 81.3, 32.1, 30.8, 28.1, 21.9, 13.8; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{28}NO_2$: 302.2115. Found: 302.2112.

*3.3.12. tert-Butyl phenyl((1Z)-4-phenylbuta-1,3-dien-1-yl)carbamate (1Z-**2j**)*

Yellow solid. 1*Z*,3*E*/1*Z*,3*Z* = 90/10; IR (KBr) 3059, 2979, 2931, 1706, 1636, 1594, 1492, 1454, 1391, 1367, 1324, 1305, 1285, 1254, 1161, 1090, 1073, 1012, 973, 937, 859, 846, 758, 741, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.20 (5H, m, ArH), 7.17 (2H, dddd, *J* = 7.2, 7.2, 1.4, 1.4 Hz, ArH), 7.11 (1H, tt, *J* = 7.2, 1.4 Hz, ArH), 6.94-6.88 (2H, m, ArH), 6.69 (0.9H, d, *J* = 9.2 Hz, 1-H), 6.64 (0.1H, d, *J* = 9.6 Hz, 1-H), 6.24 (0.9H, d, *J* = 15.5 Hz, 4-H), 6.09 (0.1H, d, *J* = 11.8 Hz, 4-H), 5.95-5.82 (0.1H, m, 3-H), 5.88 (0.9H, dd, *J* = 15.5, 11.8 Hz, 3-H), 5.56 (0.1H, dd, *J* = 11.8, 11.8 Hz, 2-H), 5.50 (0.9H, dd, *J* = 11.8, 9.2 Hz, 2-H), 1.47 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, assigned only 1*Z*,3*E*) δ 153.0, 141.5, 137.4, 131.1, 129.2, 128.3, 127.6, 127.04, 127.03, 126.8, 126.1, 123.0, 81.8, 28.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{23}NO_2Na$: 344.1621. Found: 344.1616.

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18. For a review: Paolis, M. D.; Chataigner, I.; Maddaluno, J. In *Topics in Current Chemistry, Stereoselective Alkene Synthesis*; Wang, J., Ed.; Springer: Berlin, 2012, Vol. 327, pp. 87–146.
19. Nakano, T.; Soeta, T.; Endo, K.; Inomata, K.; Ukaji, Y. *J. Org. Chem.* **2013**, *78*, 12654–12661.
20. For a review and a recent work on "*Syn*-Effect": (a) Inomata, K. *J. Synth. Org. Chem., Jpn.* **2009**, *67*, 1172–1182; (b) Horii, S.; Ishimaru, I.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2011**, *40*, 521–523.
21. We prepared (*E*)- and (*Z*)-*N*-benzyloxycarbonyl (Cbz) derivatives and attempted the 1,4-elimination reactions to further expand scope and limitation. However, the reactions resulted in unsuccessful because of instability of the Cbz group under the reaction conditions.
22. The synthetic utilities of *N*-Boc-1-amino-1,3-dienes **2**: The 1*E*-isomer was applied to Diels–Alder reaction (ref. 17d). The 1*Z*-isomer was found to afford the corresponding vinylcyclopropylamine derivatives by copper-catalyzed cyclopropanation with α-aryl diazoesters. This work will be reported in due course. The preliminary result: Tayama, E.; Horikawa, K.; Iwamoto, H.; Hasegawa, E. *Tetrahedron Lett.* **2014**, *55*, 3041–3044.

Supplementary Material

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

Stereoselective preparation of (1*Z*)- and (1*E*)-*N*-Boc-1-amino-1,3-dienes by stereospecific base-promoted 1,4-elimination

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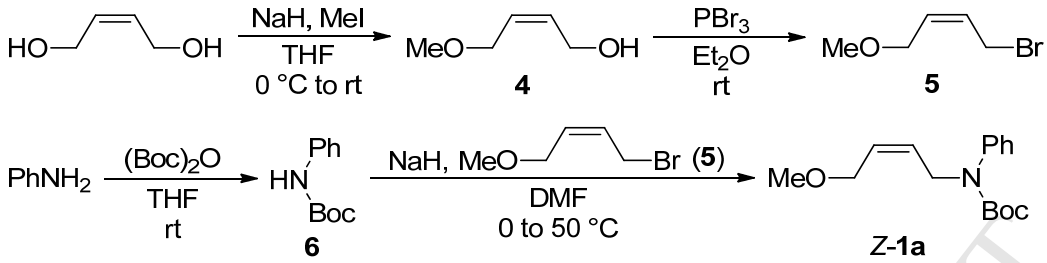
Supplementary data

Contents:

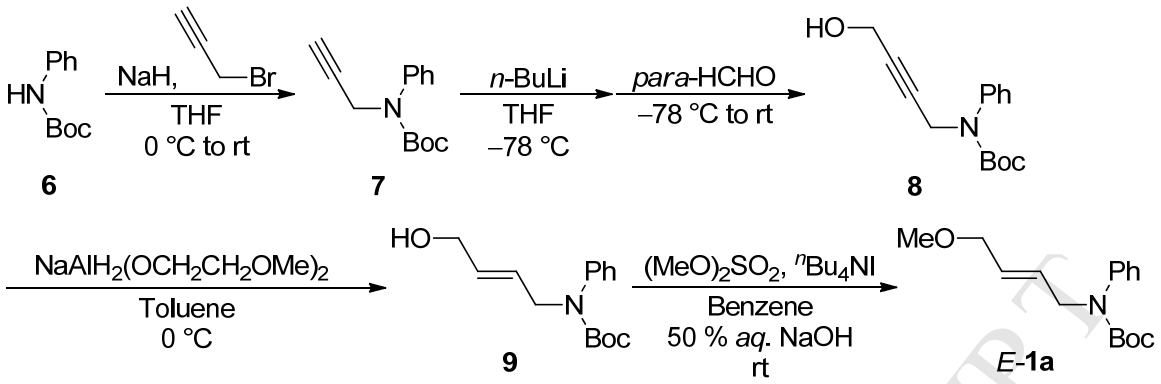
Preparation of substrates 1

(*Z*)-*tert*-Butyl (4-methoxybut-2-en-1-yl)(phenyl)carbamate (*Z*-1a)



(Step 1-1) Sodium hydride (60 wt.% in oil, 0.26 g, 6.5 mmol) was added to a solution of (*Z*)-2-buten-1,4-diol (1.7 mL, 21 mmol) in THF (20 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 30 min at room temperature and cooled to 0 °C. The resulting mixture was treated with iodomethane (0.31 mL, 5.0 mmol) and stirred for 10 min at the same temperature. After stirring for 17 h at room temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1/2 as the eluent) to give (*Z*)-4-methoxybut-2-en-1-ol (**4**) (378 mg, 74% yield) as a pale yellow oil. (Step 1-2) A solution of **4** (378 mg, 3.70 mmol) in diethyl ether (6.3 mL) was treated with phosphorus tribromide (0.36 mL, 3.8 mmol) at room temperature. After stirring for 1 h at the same temperature, the resulting mixture was diluted with water at 0 °C and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and water. The organic layer was dried over sodium sulfate and concentrated to give (*Z*)-1-bromo-4-methoxybut-2-ene (**5**) (426 mg, 70% yield) as a pale yellow oil. (Step 2-1) A solution of aniline (0.911 mL, 10.0 mmol) and di-*tert*-butyl dicarbonate (2.34 mL, 10.2 mmol) in THF (5.0 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated to obtain crude *tert*-butyl phenylcarbamate (**6**) (2.11 g, quant.) as colorless crystals. (Step 2-2) A solution of **6** (742 mg, 3.84 mmol) and **5** (547 mg, 3.31 mmol) in DMF (10.9 mL) was treated with sodium hydride (60 wt.% in oil, 0.20 g, 5.0 mmol) at 0 °C under an argon atmosphere. The resulting mixture was stirred for 1 h at 50 °C and quenched with saturated aqueous ammonium chloride at 0 °C. Extractive workup and purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 5/1 as the eluent) afforded *Z*-**1a** (822 mg, 90% yield) as a yellow oil; IR (film) 3063, 2977, 2929, 2817, 1698, 1597, 1496, 1475, 1455, 1384, 1333, 1296, 1279, 1254, 1221, 1169, 1144, 1115, 1041, 1015, 953, 911, 864, 806, 759, 719, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (2H, m, Ph), 7.22-7.07 (3H, m, Ph), 5.76-5.57 (2H, m, CH=CH), 4.29 (2H, d, J = 6.4 Hz, CH_2), 3.87 (2H, d, J = 6.0 Hz, CH_2), 3.21 (3H, s, OCH_3), 1.43 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 142.4, 129.1, 128.6, 128.5, 126.7, 125.9, 80.3, 67.8, 57.8, 47.2, 28.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{23}NO_3Na$: 300.1570. Found: 300.1563 (aq. HCO_2Na was added to improve sensitivity).

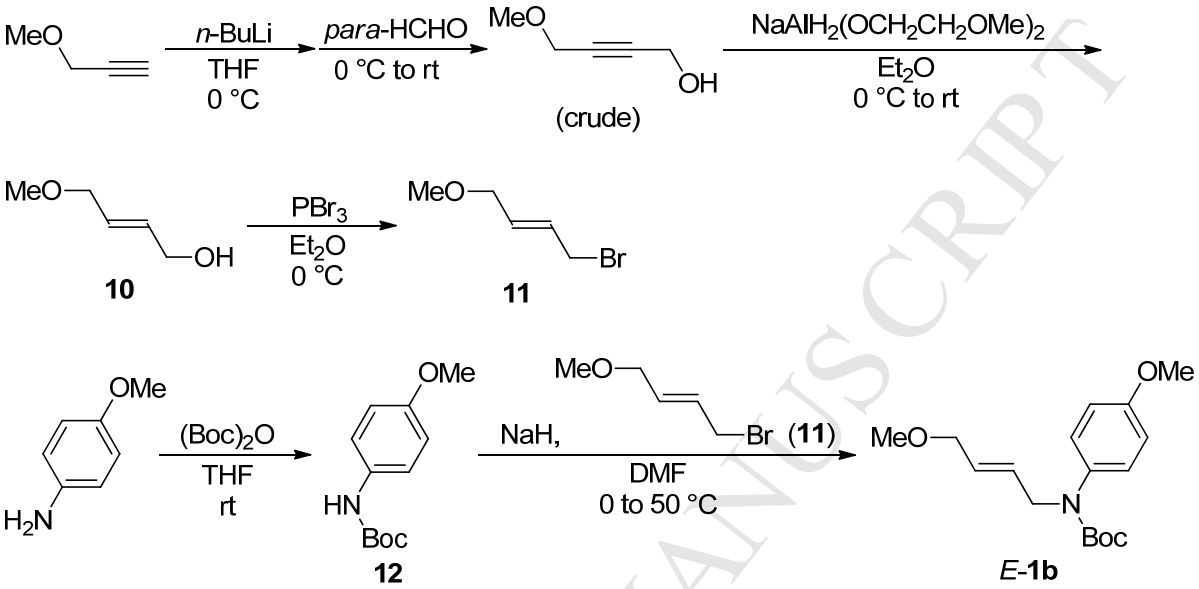
(*E*)-*tert*-Butyl (4-methoxybut-2-en-1-yl)(phenyl)carbamate (*E*-1a)



(Step 1) A solution of **6** (1.08 g, 5.59 mmol) in THF (28 mL) was treated with sodium hydride (60 wt.% in oil, 0.29 g, 7.3 mmol) at 0 °C and stirred for 10 min under an argon atmosphere. 3-Bromo-1-propyne (0.51 mL, 6.8 mmol) was added to the mixture at the same temperature and the mixture was stirred for 12 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C 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 (hexane/ethyl acetate = 20/1 to 10/1 as the eluent) gave *N*-*tert*-butoxycarbonyl-*N*-(prop-2-ynyl)aniline (**7**) (1.09 g, 84% yield) as a yellow oil. (Step 2) A solution of **7** (933 mg, 4.03 mmol) in THF (19 mL) was treated with a 1.64 M *n*-butyllithium hexane solution (2.57 mL, 4.21 mmol) at –78 °C under an argon atmosphere and stirred for 10 min at the same temperature. Paraformaldehyde (270 mg, 9.0 mmol) was added to the solution and the mixture was stirred for 15 min at –78 °C and for 2 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) to obtain *tert*-butyl (4-hydroxybut-2-yn-1-yl)(phenyl)carbamate (**8**) (918 mg, 87% yield) as a yellow oil. (Step 3) A 1.0 M sodium bis(2-methoxyethoxy)aluminum hydride toluene solution (4.3 mL, 4.3 mmol) was added to a solution of **8** (913 mg, 3.49 mmol) in toluene (17 mL) at 0 °C under an argon atmosphere and the mixture was stirred for 1 h at the same temperature. The resulting mixture was quenched with water at 0 °C and treated with a 1 M aqueous potassium hydrogen sulfate to dissolve inorganic salts. The mixture was extracted with ethyl acetate and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried over sodium sulfate and concentrated to obtain (*E*)-*tert*-butyl (4-hydroxybut-2-en-1-yl)(phenyl)carbamate (**9**) (1.14 g) as a yellow viscous oil. (Step 4) A mixture of **9** (587 mg), tetrabutylammonium iodide (166 mg, 0.45 mmol), and 50 wt.% aqueous sodium hydroxide solution (2.3 mL) in benzene (24 mL) was treated with dimethyl sulfate (0.25 mL, 2.6 mmol) and stirred for 46 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride 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 (hexane/ethyl acetate = 6/1 to 4/1 as the eluent) gave *E*-**1a** (454 mg, 91% yield from **8**) as a pale yellow oil; IR (film) 3063, 2977, 2929, 2822, 1697, 1597, 1496, 1473, 1455, 1384, 1366, 1301, 1278, 1252, 1168, 1124, 1092, 1049, 1011, 972, 945, 909, 864, 760, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (2H, m, Ph), 7.20 (2H, broad d, J = 7.6 Hz, Ph),

7.16 (1H, tt, J = 7.6, 1.2 Hz, Ph), 5.80 (1H, dtt, J = 15.4, 5.8, 1.2 Hz, CH=CH), 5.64 (1H, dtt, J = 15.4, 5.8, 1.2 Hz, CH=CH), 4.23 (2H, ddt, J = 5.8, 1.2, 1.2 Hz, CH_2), 3.89 (2H, ddt, J = 5.8, 1.2, 1.2 Hz, CH_2), 3.27 (3H, s, OCH_3), 1.44 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 142.7, 129.2, 128.7, 128.5, 126.4, 125.7, 80.3, 72.3, 57.7, 51.7, 28.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{23}NO_3Na$: 300.1570. Found: 300.1566 (aq. HCO_2Na was added to improve sensitivity).

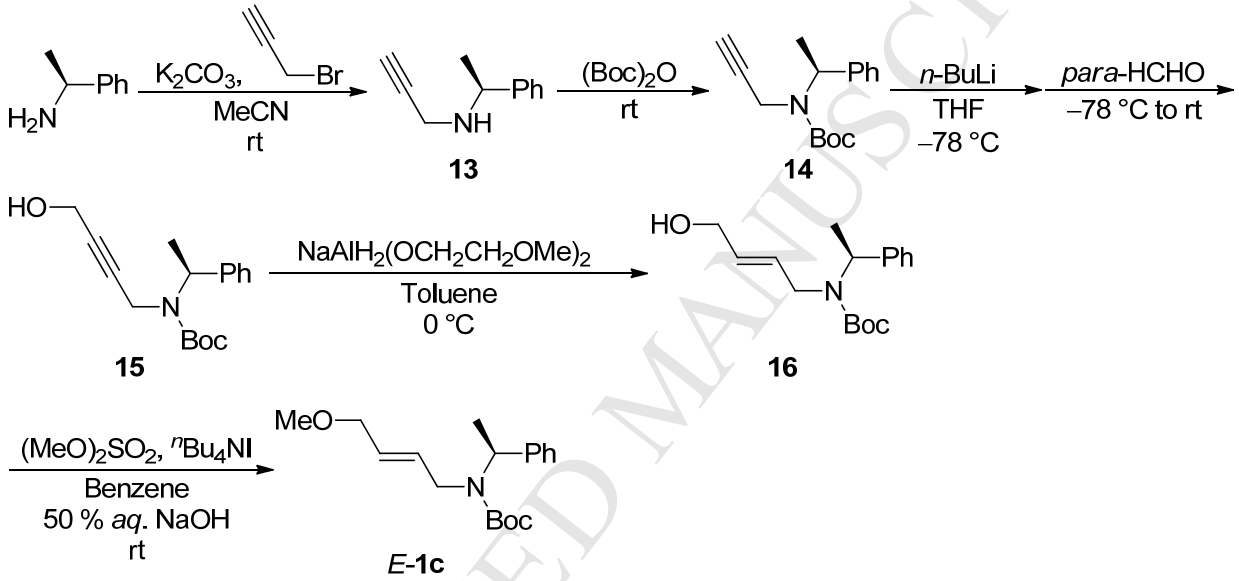
(*E*)-*tert*-Butyl (4-methoxybut-2-en-1-yl)(4-methoxyphenyl)carbamate (*E*-1b)



(Step 1-1) A solution of methyl propargyl ether (1.69 mL, 20.0 mmol) in THF (60 mL) was treated with a 1.64 M *n*-butyllithium hexane solution (12.8 mL, 21.0 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 30 min at the same temperature. Paraformaldehyde (0.90 g, 30 mmol) was added to the solution in one portion at 0 °C and the mixture was stirred for 12 h at room temperature. The resulting mixture was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic solution was dried over sodium sulfate and concentrated. The residue was dissolved in diethyl ether (75 mL) and treated with sodium bis(2-methoxyethoxy)aluminum hydride toluene solution (65 wt.%, 9.0 mL, 30 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at 0 °C and 1 h at room temperature. The resulting mixture was quenched with saturated aqueous potassium sodium tartrate at 0 °C and stirred for 1 h at room temperature. The mixture was extracted with ethyl acetate and the combined extracts were dried over sodium sulfate. Evaporation of the solvent and purification of the residue by bulb to bulb distillation under vacuum (2 hPa, 80 to 90 °C) afforded (*E*)-4-methoxybut-2-en-1-ol (**10**) (1.48 g, 72% yield) as a colorless oil. (Step 1-2) A solution of **10** (802 mg, 7.85 mmol) in ether (16 mL) was treated with phosphorus tribromide (0.74 mL, 7.9 mmol) at 0 °C. After stirring for 30 min at the same temperature, the resulting mixture was diluted with water at 0 °C and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and water. The organic layer was dried over sodium sulfate and concentrated to give (*E*)-1-bromo-4-methoxybut-2-ene (**11**) (776 mg, 60% yield) as a pale yellow oil. (Step 2-1) A solution of *p*-anisidine (1.27 g, 10.3 mmol) and di-*tert*-butyl dicarbonate (2.34 mL, 10.2 mmol) in THF (5.0 mL) was stirred for 40 h at room temperature. The resulting mixture was concentrated to obtain crude *tert*-butyl (4-methoxyphenyl)carbamate (**12**) (2.33 g, quant.) as colorless crystals. (Step 2-2) A solution of **12** (216 mg, 0.967 mmol) and **11** (156 mg, 0.95 mmol) in DMF (5 mL) was treated with sodium hydride

(60 wt.% in oil, 57 mg, 1.4 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at 50 °C and quenched with saturated aqueous ammonium chloride at 0 °C. Extractive workup and purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 5/1 as the eluent) afforded *E*-**1b** (209 mg, 72% yield) as a yellow oil; IR (film) 2976, 2931, 2836, 1702, 1692, 1610, 1585, 1512, 1452, 1443, 1390, 1366, 1313, 1293, 1248, 1168, 1145, 1124, 1106, 1036, 1004, 973, 945, 910, 864, 834, 768, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (2H, br, ArH), 6.83 (2H, ddd, *J* = 9.2, 2.8, 2.8 Hz, ArH), 5.78 (1H, dtt, *J* = 16.0, 5.8, 1.2 Hz, CH=CH), 5.62 (1H, dt, *J* = 16.0, 5.8 Hz, CH=CH), 4.17 (2H, dd, *J* = 5.8, 1.2 Hz, CH_2), 3.89 (2H, dd, *J* = 5.8, 1.2 Hz, CH_2), 3.79 (3H, s, $ArOCH_3$), 3.28 (3H, s, 4-OCH_3), 1.42 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 154.8, 135.6, 129.3, 128.8, 127.9, 113.8, 80.1, 72.4, 57.7, 55.3, 52.0, 28.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{25}NO_4Na$: 330.1676. Found: 330.1660 (aq. HCO_2Na was added to improve sensitivity).

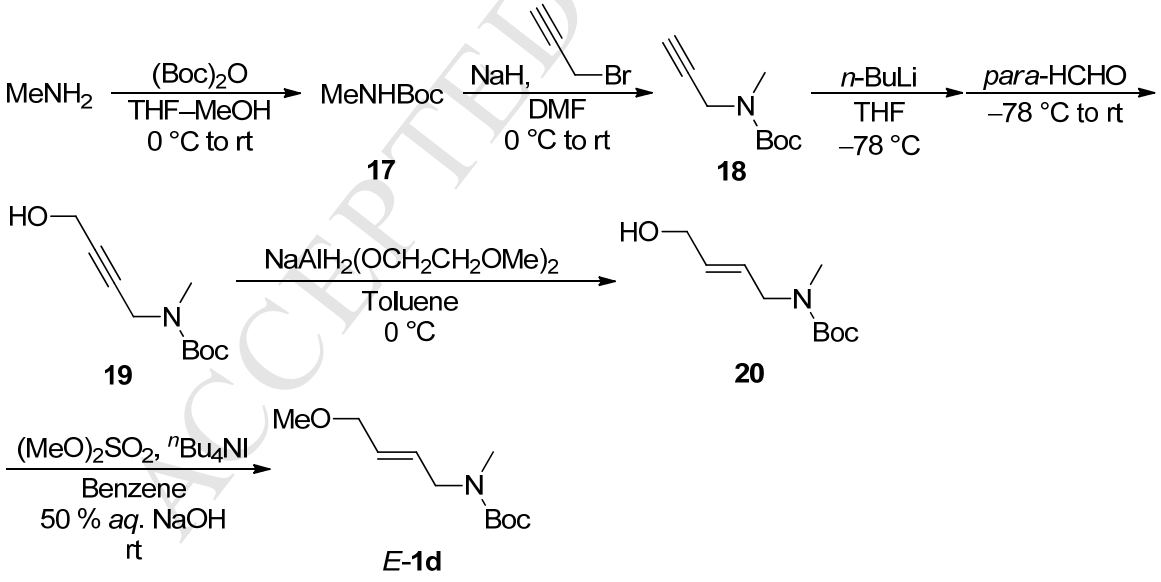
(*S*,*E*)-*tert*-Butyl (4-methoxybut-2-en-1-yl)(1-phenylethyl)carbamate (*E*-1c)



(Step 1) A mixture of (*S*)-1-phenylethylamine (0.90 g, 7.4 mmol), 3-bromo-1-propyne (0.53 mL, 7.0 mmol), and potassium carbonate (1.21 g, 8.75 mmol) in acetonitrile (14 mL) was stirred for 17 h at room temperature. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol = 25/1 to 10/1 as the eluent) to obtain (*S*)-*N*-(1-phenylethyl)-*N*-(prop-2-yn-1-yl)amine (**13**) (0.67 g, 60% yield) as a pale yellow oil. (Step 2) A mixture of **13** (0.67 g, 4.2 mmol) and di-*tert*-butyl dicarbonate (0.98 mL, 4.3 mmol) was stirred for 15 h at room temperature. The volatiles were removed under reduced pressure to obtain crude (*S*)-*N*-*tert*-butoxycarbonyl-*N*-(1-phenylethyl)-*N*-(prop-2-yn-1-yl)amine (**14**) (1.22 g, quant.) as a colorless oil. (Step 3) A solution of **14** (1.27 g, 4.90 mmol) in THF (30 mL) was treated with a 1.64 M *n*-butyllithium hexane solution (3.81 mL, 6.25 mmol) at –78 °C under an argon atmosphere and stirred for 10 min at the same temperature. Paraformaldehyde (357 mg, 11.9 mmol) was added to the solution and the mixture was stirred for 15 min at –78 °C and for 22 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) to obtain (*S*)-*tert*-butyl (4-hydroxybut-2-yn-1-yl)(1-phenylethyl)carbamate (**15**) (846 mg, 60% yield) as a yellow oil. (Step 4) A 1.0 M sodium bis(2-

methoxyethoxy)aluminum hydride toluene solution (3.4 mL, 3.4 mmol) was added to a solution of **15** (806 mg, 2.79 mmol) in toluene (14 mL) at 0 °C under an argon atmosphere and the mixture was stirred for 1 h at the same temperature. The resulting mixture was quenched with water at 0 °C and treated with a 1 M aqueous potassium hydrogen sulfate to dissolve inorganic salts. The mixture was extracted with ethyl acetate and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) to obtain (*S*,*E*)-*tert*-butyl (4-hydroxybut-2-en-1-yl)(1-phenylethyl)carbamate (**16**) (765 mg, 94% yield) as a yellow viscous oil. (Step 5) A mixture of **16** (760 mg, 2.61 mmol), tetrabutylammonium iodide (48 mg, 0.13 mmol), and 50 wt.% aqueous sodium hydroxide solution (2.7 mL) in benzene (13 mL) was treated with dimethyl sulfate (0.30 mL, 3.2 mmol) and stirred for 15 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride 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 (hexane/ethyl acetate = 5/1 as the eluent) gave *E*-**1c** (688 mg, 86% yield) as a pale yellow oil; $[\alpha]^{22}_{589}$ –82.8 (*c* 1.00, EtOH); IR (film) 3061, 3029, 2976, 2930, 2821, 1689, 1495, 1450, 1402, 1365, 1327, 1294, 1275, 1252, 1167, 1135, 1042, 1026, 973, 911, 865, 771, 735, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (5H, m, Ph), 5.70-5.20 (3H, br, CH=CH and NC*H*CH_3), 3.81 (2H, d, *J* = 5.6 Hz, CH_2), 3.72 (1H, br, CH_2), 3.45 (1H, br, CH_2), 3.26 (3H, s, OCH_3), 1.51 (3H, d, *J* = 6.8 Hz, NCHC*H*$_3$), 1.44 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 141.9, 131.0, 128.2, 127.8, 127.0, 79.7, 72.5, 57.7, 53.4, 44.8, 28.4, 17.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{27}NO_3Na$: 328.1883. Found: 328.1876 (aq. HCO_2Na was added to improve sensitivity).

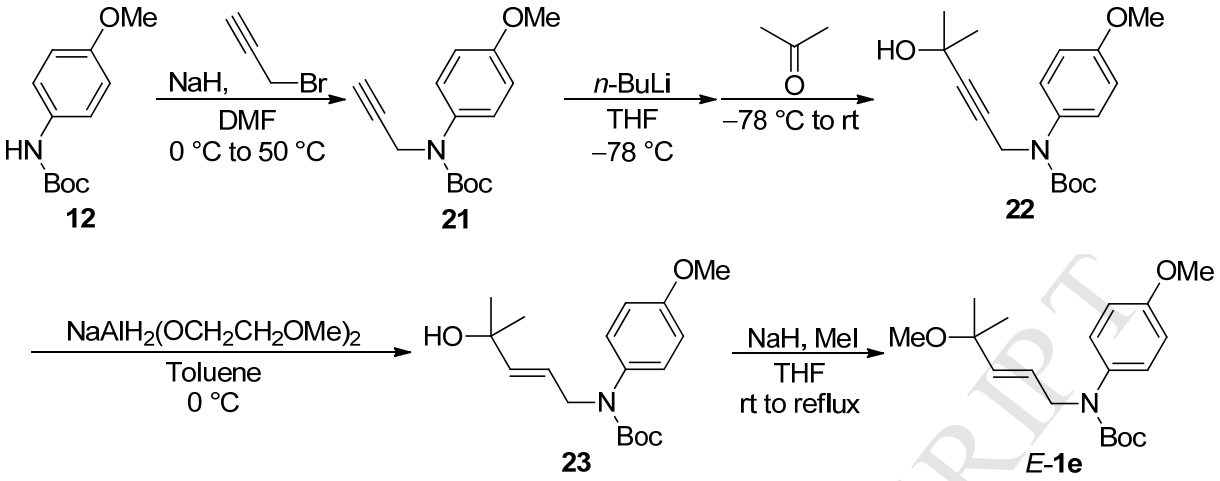
(*E*)-*tert*-Butyl (4-methoxybut-2-en-1-yl)(methyl)carbamate (*E*-1d)



(Step 1) A solution of 40 wt.% methylamine methanol solution (2.0 mL, 20 mmol) was diluted with THF (3 mL) and treated with di-*tert*-butyl dicarbonate (2.3 mL, 10 mmol) at 0 °C. The solution was stirred for 3 h at room temperature and concentrated to obtain crude *tert*-butyl methylcarbamate (**17**) (0.77 g, 59% yield) as a colorless oil. (Step 2) A solution of **17** (0.77 g, 5.9 mmol) in DMF (13 mL) was treated with sodium hydride (60 wt.% in oil, 0.29 g, 7.3 mmol) at 0 °C under an argon atmosphere. After stirring for 15 min at room temperature, 3-bromo-1-propyne (0.65 mL, 8.6 mmol) was added to the mixture at 0 °C. The mixture was

stirred for 2.5 h at room temperature and quenched with saturated aqueous ammonium chloride at 0 °C. Extractive workup and purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 10/1 as the eluent) afforded *tert*-butyl methyl(prop-2-yn-1-yl)carbamate (**18**) (0.56 g, 56% yield) as a yellow oil. (Step 3) A solution of **18** (0.56 g, 3.3 mmol) in THF (17 mL) was treated with a 1.64 M *n*-butyllithium hexane solution (2.00 mL, 3.30 mmol) at –78 °C under an argon atmosphere and stirred for 10 min at the same temperature. Paraformaldehyde (0.20 g, 6.7 mmol) was added to the solution and the mixture was stirred for 15 min at –78 °C and for 2 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 as the eluent) to obtain *tert*-butyl (4-hydroxybut-2-yn-1-yl)(methyl)carbamate (**19**) (0.58 g, 88% yield) as a brown oil. (Step 4) A 1.0 M sodium bis(2-methoxyethoxy)aluminum hydride toluene solution (3.5 mL, 3.5 mmol) was added to a solution of **19** (0.58 g, 2.9 mmol) in toluene (15 mL) at 0 °C under an argon atmosphere and the mixture was stirred for 1 h at the same temperature. The resulting mixture was quenched with water at 0 °C and treated with a 1 M aqueous potassium hydrogen sulfate to dissolve inorganic salts. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine. The organic layer was dried over sodium sulfate and concentrated to obtain (*E*)-*tert*-butyl (4-hydroxybut-2-en-1-yl)(methyl)carbamate (**20**) (346 mg, 59% yield) as a brown oil. (Step 5) A mixture of **20** (346 mg, 1.72 mmol), tetrabutylammonium iodide (32 mg, 0.087 mmol), and 50 wt.% aqueous sodium hydroxide solution (1.8 mL) in benzene (8.6 mL) was treated with dimethyl sulfate (0.20 mL, 2.1 mmol) and stirred for 13 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride 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 (hexane/ethyl acetate = 5/1 as the eluent) gave *E*-**1d** (342 mg, 92% yield) as a colorless oil; IR (film) 2977, 2929, 2823, 1693, 1480, 1454, 1421, 1392, 1366, 1301, 1247, 1176, 1150, 1121, 1044, 975, 912, 878, 771 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 5.73-5.60 (2H, m, CH=CH), 3.95-3.91 (2H, m, CH_2), 3.85-3.81 (2H, m, CH_2), 3.32 (3H, s, OCH_3), 2.83 (3H, s, NCH_3), 1.46 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, CD_3OD) δ 157.6, 130.4-129.8 (m), 129.6, 81.2, 73.5, 58.4-58.0 (m), 51.8-50.5 (m), 34.4, 28.8; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{11}H_{21}NO_3Na$: 238.1414. Found: 238.1407.

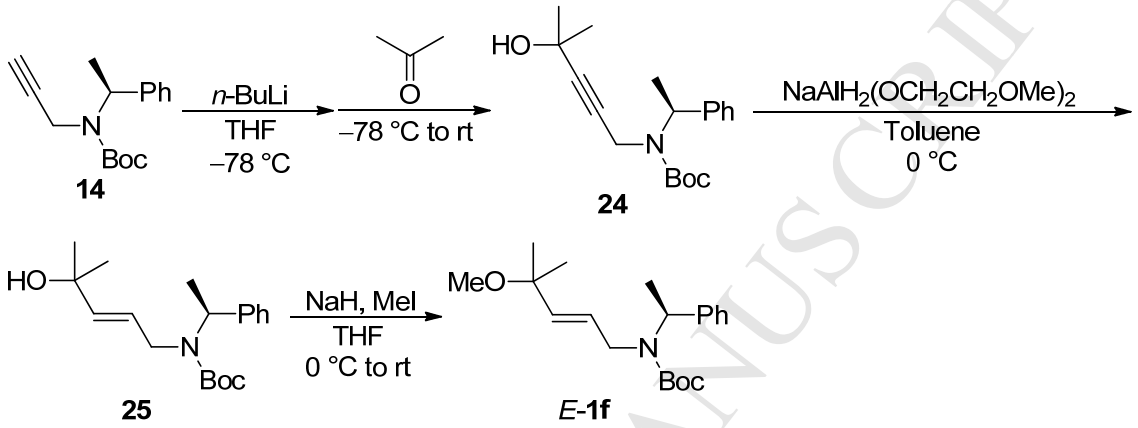
(*E*)-*tert*-Butyl (4-methoxy-4-methylpent-2-en-1-yl)(4-methoxyphenyl)carbamate (*E*-1e)



(Step 1) A solution of **12** (1.13 g, 5.06 mmol) in DMF (25 mL) was treated with sodium hydride (60 wt.% in oil, 0.24 g, 6.0 mmol) at 0 °C under an argon atmosphere and stirred for 30 min. 3-Bromo-1-propyne (0.52 mL, 6.9 mmol) was added to the mixture at the same temperature and the mixture was stirred for 1 h at 50 °C. The resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C 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 (hexane/ethyl acetate = 5/1 as the eluent) gave *tert*-butyl (4-methoxyphenyl)(prop-2-yn-1-yl)carbamate (**21**) (1.22 g, 92% yield) as a yellow oil. (Step 2) A solution of **21** (1.13 g, 4.32 mmol) in THF (22 mL) was treated with a 1.64 M *n*-butyllithium hexane solution (2.64 mL, 4.33 mmol) at –78 °C under an argon atmosphere and stirred for 10 min at the same temperature. Acetone (0.64 mL, 8.7 mmol) was added to the solution and the mixture was stirred for 15 min at –78 °C and for 2 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) to obtain *tert*-butyl (4-hydroxy-4-methylpent-2-yn-1-yl)(4-methoxyphenyl)carbamate (**22**) (971 mg, 70% yield) as a yellow oil. (Step 3) A 1.0 M sodium bis(2-methoxyethoxy)aluminum hydride toluene solution (3.7 mL, 3.7 mmol) was added to a solution of **22** (971 mg, 3.04 mmol) in toluene (15 mL) at 0 °C under an argon atmosphere and the mixture was stirred for 1 h at the same temperature. The resulting mixture was quenched with water at 0 °C and treated with a 1 M aqueous potassium hydrogen sulfate to dissolve inorganic salts. The mixture was extracted with ethyl acetate and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) to obtain (*E*)-*tert*-butyl (4-hydroxy-4-methylpent-2-en-1-yl)(4-methoxyphenyl)carbamate (**23**) (858 mg, 88% yield) as a yellow viscous oil. (Step 4) A solution of **23** (852 mg, 2.65 mmol) in THF (13 mL) was treated with sodium hydride (60 wt.% in oil, 0.16 g, 4.0 mmol) at 0 °C under an argon atmosphere and stirred for 10 min. The mixture was treated with iodomethane (0.25 mL, 4.0 mmol) at the same temperature and refluxed for 2 h. The resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C 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 (hexane/ethyl acetate = 5/1 as the eluent) gave *E*-**1e** (741 mg, 83% yield) as a yellow oil; IR (film) 2975, 2933, 2835, 2824, 1702, 1610, 1585, 1513, 1455, 1443, 1390, 1365, 1294, 1248, 1171, 1106, 1073, 1036, 1005, 975, 935, 869, 834, 767, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (2H, br, ArH), 6.82 (2H, ddd, *J* = 8.8, 2.8, 2.8 Hz, ArH), 5.62 (1H, dt, *J* = 15.8, 6.0 Hz, CH=CH), 5.48 (1H, d, *J* = 15.8 Hz, CH=CH), 4.18 (2H, dd, *J* = 6.0, 1.2 Hz, CH_2), 3.78 (3H, s, $ArOCH_3$), 3.05 (3H, s, 4-OCH_3), 1.43 (9H, s, *t*-Bu), 1.22 (6H, s, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 154.7, 138.1, 135.4, 128.0, 125.6, 113.8, 80.0, 74.5, 55.3, 52.0, 50.2, 28.3, 25.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{29}NO_4Na$: 358.1989. Found: 358.1983 (aq. HCO_2Na was added to improve sensitivity).

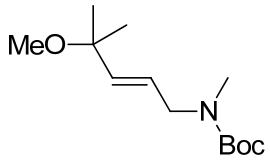
(*S*,*E*)-*tert*-Butyl (4-methoxybut-2-en-1-yl)(1-phenylethyl)carbamate (*E*-1f)



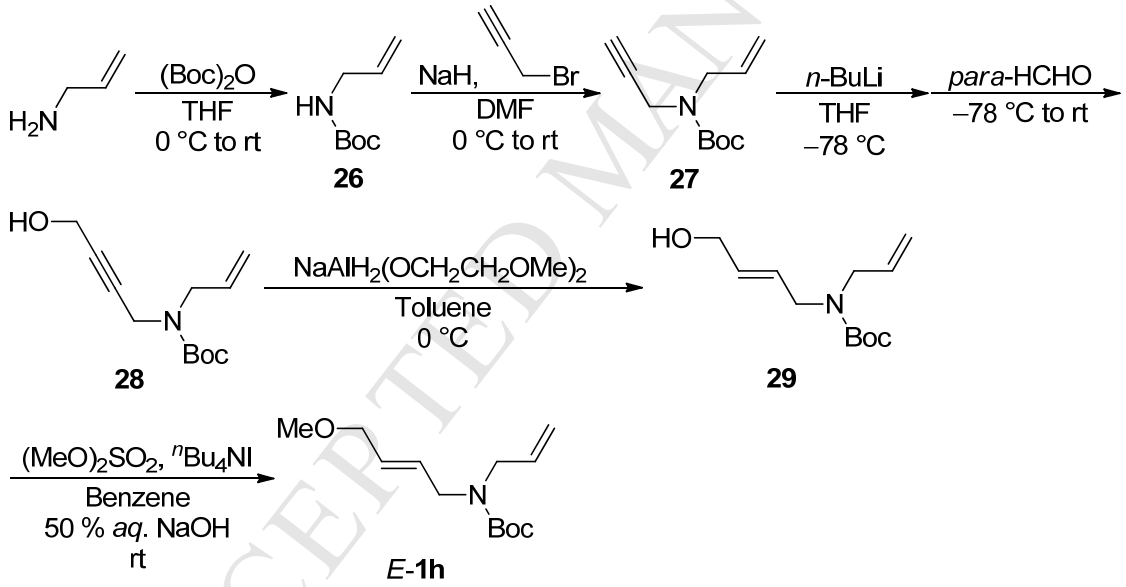
(Step 1) A solution of **14** (1.13 mg, 4.36 mmol) in THF (27 mL) was treated with a 1.64 M *n*-butyllithium hexane solution (3.41 mL, 5.59 mmol) at –78 °C under an argon atmosphere and stirred for 10 min at the same temperature. Acetone (0.78 mL, 10.6 mmol) was added to the solution and the mixture was stirred for 15 min at –78 °C and for 4 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) to obtain (*S*)-*tert*-butyl (4-hydroxy-4-methylpent-2-yn-1-yl)(1-phenylethyl)carbamate (**24**) (1.03 g, 74% yield) as a yellow oil. (Step 2) A 1.0 M sodium bis(2-methoxyethoxy)aluminum hydride toluene solution (3.9 mL, 3.9 mmol) was added to a solution of **24** (1.03 g, 3.24 mmol) in toluene (16 mL) at 0 °C under an argon atmosphere and the mixture was stirred for 1 h at the same temperature. The resulting mixture was quenched with water at 0 °C and treated with a 1 M aqueous potassium hydrogen sulfate to dissolve inorganic salts. The mixture was extracted with ethyl acetate and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) to obtain (*S*,*E*)-*tert*-butyl (4-hydroxy-4-methylpent-2-en-1-yl)(1-phenylethyl)carbamate (**25**) (986 mg, 95% yield) as a yellow viscous oil. (Step 3) A solution of **25** (986 mg, 3.09 mmol) in THF (16 mL) was treated with sodium hydride (60 wt.% in oil, 0.19 g, 4.8 mmol) at 0 °C under an argon atmosphere and stirred for 30 min. The mixture was treated with iodomethane (0.29 mL, 4.7 mmol) at the same temperature and stirred for 5 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C 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 (hexane/ethyl acetate = 20/1 to 10/1 as the eluent) gave *E*-**1f** (918 mg, 89% yield)

as a pale yellow oil; $[\alpha]^{23}_{589}$ –80.3 (*c* 1.00, EtOH); IR (film) 3088, 3061, 3029, 2975, 2933, 2822, 1686, 1495, 1450, 1401, 1364, 1327, 1304, 1251, 1207, 1170, 1076, 1041, 1026, 976, 913, 864, 835, 773, 734, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (5H, m, Ph), 5.75-5.05 (3H, br, CH=CH and NC*H*CH_3), 3.73 (1H, br, CH_2), 3.51 (1H, br, CH_2), 3.08 (3H, s, OCH_3), 1.53 (3H, d, *J* = 7.2 Hz, NCHC*H*$_3$), 1.46 (9H, s, *t*-Bu), 1.18 (3H, s, 4-CH_3), 1.17 (3H, s, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 141.9, 136.6, 128.2, 127.2, 127.1, 127.0, 79.6, 74.5, 53.0, 50.3, 44.9, 28.4, 25.8, 25.6, 17.5; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{31}NO_3Na$: 356.2196. Found: 356.2190 (aq. HCO_2Na was added to improve sensitivity).

(*E*)-*tert*-Butyl (4-methoxy-4-methylpent-2-en-1-yl)(methyl)carbamate (*E*-1g): prepared by the same procudure with *E*-**1f** using **17** as a starting material (30% overall yield from **17**); colorless oil; IR (film) 2976, 2932, 2823, 1701, 1480, 1458, 1420, 1390, 1364, 1306, 1246, 1210, 1173, 1148, 1077, 977, 923, 880, 846, 813, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.58-5.45 (2H, m, CH=CH), 3.82 (2H, br, CH_2), 3.15 (3H, s, OCH_3), 2.82 (3H, s, NCH_3), 1.46 (9H, s, *t*-Bu), 1.27 (6H, s, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 138.1-137.3 (m), 125.4-124.6 (m), 79.3, 74.5, 50.7-49.5 (m), 50.2, 33.5, 28.3, 25.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{25}NO_3Na$: 266.1727. Found: 266.1714 (aq. HCO_2Na was added to improve sensitivity).



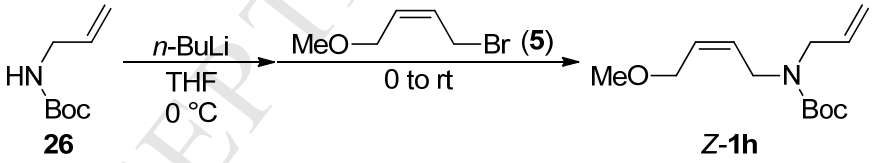
(*E*)-*tert*-Butyl allyl(4-methoxybut-2-en-1-yl)carbamate (*E*-1h)



(Step 1) Di-*tert*-butyl dicarbonate (1.2 mL, 5.2 mmol) was added to a solution of allylamine (0.41 mL, 5.5 mmol) in THF (10 mL) at 0 °C. The solution was stirred for 2 h at room temperature and concentrated to obtain crude *tert*-butyl allylcarbamate (**26**) (730 mg, 89% yield) as a colorless oil. (Step 2) A solution of **26** (730 mg, 4.64 mmol) in DMF (9.3 mL) was treated with sodium hydride (60 wt.% in oil, 0.22 g, 5.5 mmol) at 0 °C under an argon atmosphere. After stirring for 10 min at room temperature, 3-bromo-1-propyne (0.42 mL, 5.6 mmol) was added to the mixture at 0 °C. The mixture was stirred for 17 h at room temperature and quenched with saturated aqueous ammonium chloride at 0 °C. Extractive workup and purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 10/1 as the eluent) afforded *tert*-butyl allyl(prop-2-yn-1-yl)carbamate (**27**) (602 mg, 66% yield) as a yellow oil. (Step 3) A solution of **27** (561 mg, 2.87 mmol) in THF (9.6 mL) was treated with a 1.64 M *n*-butyllithium hexane solution (1.84 mL, 3.02 mmol) at –78 °C under an argon atmosphere and stirred for 30 min at the same temperature. Paraformaldehyde (0.13

g, 4.3 mmol) was added to the solution and the mixture was stirred for 15 min at –78 °C and for 2.5 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 as the eluent) to obtain *tert*-butyl allyl(4-hydroxybut-2-yn-1-yl)carbamate (**28**) (416 mg, 64% yield) as a brown oil. (Step 4) A 1.0 M sodium bis(2-methoxyethoxy)aluminum hydride toluene solution (2.2 mL, 2.2 mmol) was added to a solution of **28** (416 mg, 1.85 mmol) in toluene (9.3 mL) at 0 °C under an argon atmosphere and the mixture was stirred for 1 h at the same temperature. The resulting mixture was quenched with saturated aqueous potassium sodium tartrate and stirred for 1 h at room temperature. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine. The organic layer was dried over sodium sulfate and concentrated to obtain (*E*)-*tert*-butyl allyl(4-hydroxybut-2-en-1-yl)carbamate (**29**) (251 mg, 60% yield) as a brown oil. (Step 5) A mixture of **29** (251 mg, 1.10 mmol), tetrabutylammonium iodide (20 mg, 0.054 mmol), and 50 wt.% aqueous sodium hydroxide solution (1.1 mL) in benzene (5.5 mL) was treated with dimethyl sulfate (0.12 mL, 1.3 mmol) and stirred for 22 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride 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 (hexane/ethyl acetate = 3/1 as the eluent) gave *E*-**1h** (255 mg, 96% yield) as a colorless oil; IR (film) 3081, 2977, 2929, 2822, 1692, 1644, 1536, 1454, 1407, 1365, 1246, 1172, 1142, 1123, 1054, 975, 922, 875, 772, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84-5.58 (3H, m, CH=CH and $CH_2CH{=}CH_2$), 5.21-5.04 (2H, m, $CH_2CH{=}CH_2$), 3.91 (2H, dt, J = 4.4, 1.2 Hz, CH_2), 3.80 (4H, br, CH_2), 3.33 (3H, s, OCH_3), 1.45 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 133.9, 129.0, 128.6, 117.0-115.9 (m), 79.6, 72.4, 57.8, 48.6, 47.5, 28.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{23}NO_3Na$: 264.1570. Found: 263.1566 (aq. HCO_2Na was added to improve sensitivity).

(*Z*)-*tert*-Butyl allyl(4-methoxybut-2-en-1-yl)carbamate (*Z*-1h)

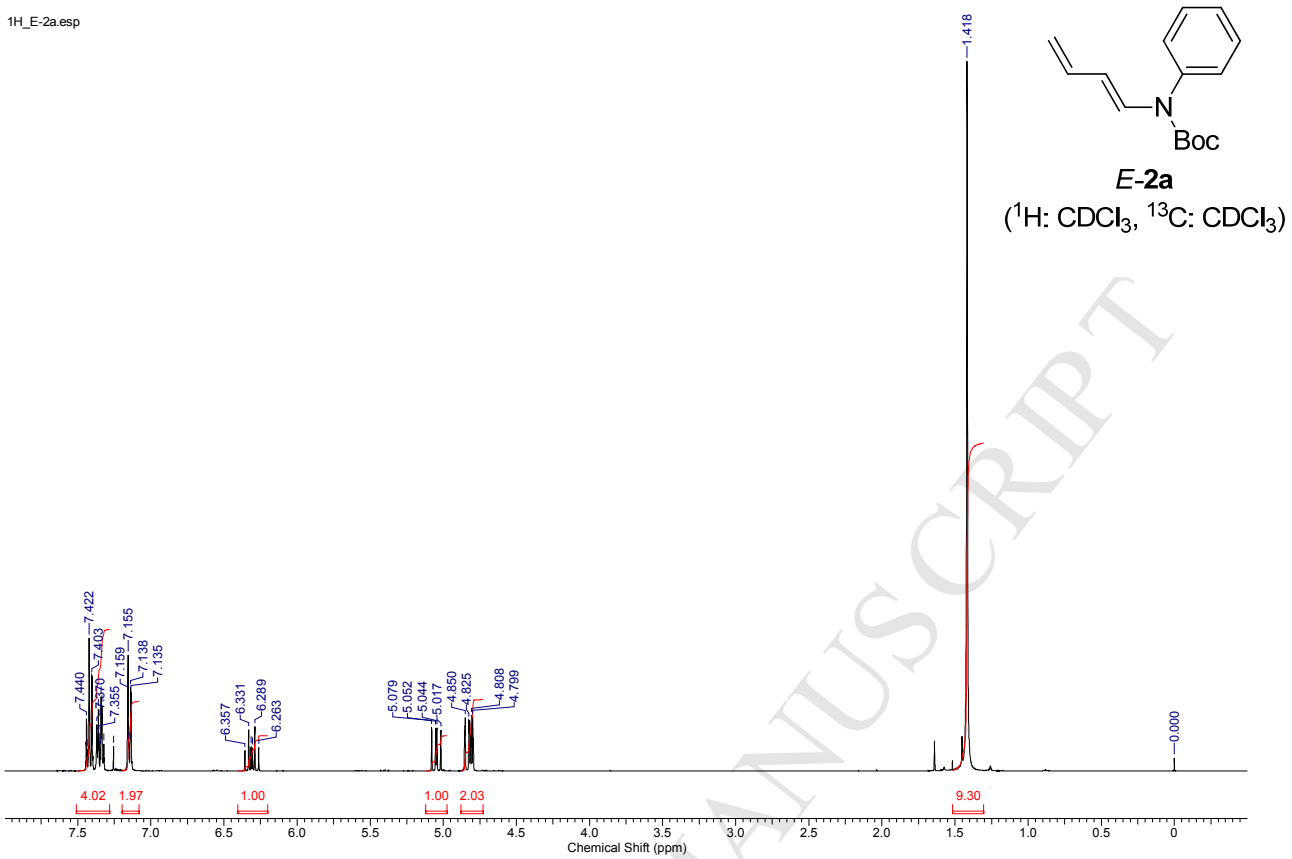


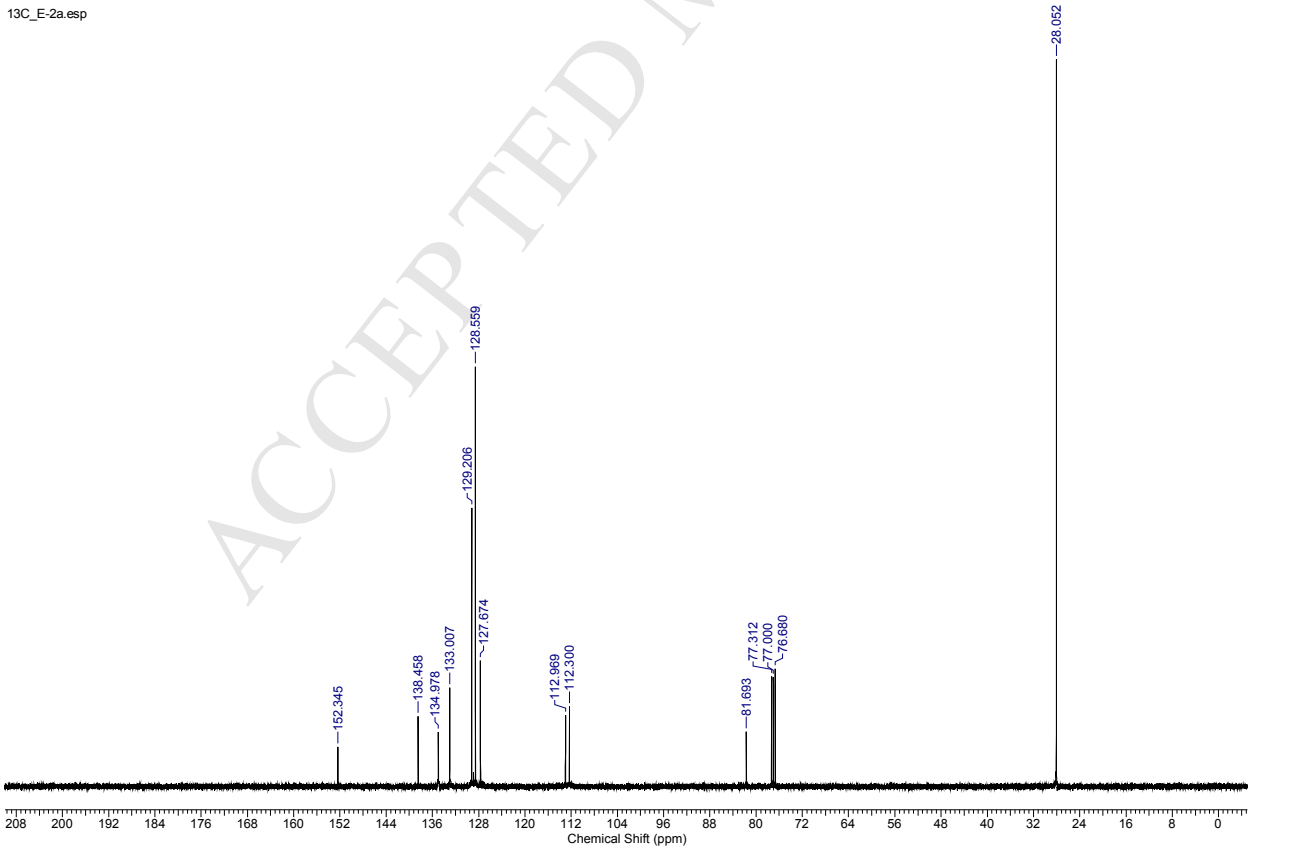
A solution of **26** (348 mg, 2.21 mmol) in THF was treated with a 1.64 M *n*-butyllithium hexane solution (1.35 mL, 2.21 mmol) at 0 °C under an argon atmosphere. After stirring for 30 min at the same temperature, the mixture was treated with **5** (276 mg, 1.67 mmol) and stirred for 23 h at room temperature. The resulting mixture was quenched with saturated aqueous ammonium chloride 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 (hexane/ethyl acetate = 15/1 to 10/1 as the eluent) gave *Z*-**1h** (162 mg, 40% yield) as a colorless oil; IR (film) 3080, 2977, 2929, 2817, 1698, 1644, 1541, 1456, 1405, 1365, 1345, 1325, 1289, 1248, 1171, 1145, 1114, 994, 954, 922, 874, 771, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84-5.48 (3H, m, CH=CH and $CH_2CH{=}CH_2$), 5.19-5.05 (2H, m, $CH_2CH{=}CH_2$), 3.98 (2H, d, J = 6.4 Hz, CH_2), 3.95-3.70 (4H, br, CH_2), 3.33 (3H, s, OCH_3), 1.46 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 134.0, 129.4-128.0 (m), 129.2, 117.0-116.0 (m), 79.7, 67.9, 58.1, 48.7, 43.5-42.5 (m), 28.4; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{24}NO_3$: 242.1751. Found: 242.1746.

(*E*)-*tert*-Butyl (4-methoxyoct-2-en-1-yl)(phenyl)carbamate (*E*-1i): prepared by the same procudure with *E*-**1f** using **7** and valeraldehyde instead of **14** and acetone (51% overall yield from **7**); yellow oil; IR (film) 2957, 2931, 2860, 2819, 1702, 1597, 1497, 1455, 1386, 1366, 1341, 1298, 1278, 1253, 1170, 1096, 1046, 1010, 972, 866, 765, 757, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (2H, m, Ph), 7.23-7.13 (3H, m, Ph), 5.68 (1H, dddd, *J* = 15.6, 6.0, 6.0, 0.8 Hz, CH=CH), 5.35 (1H, dd, *J* = 15.6, 7.8 Hz, CH=CH), 4.27 (1H, ddd, *J* = 15.6, 6.0, 0.8 Hz, 1-H), 4.22 (1H, ddd, *J* = 15.6, 6.0, 0.8 Hz, 1-H), 3.48 (1H, dt, *J* = 7.8, 6.8 Hz, 4-H), 3.16 (3H, s, OCH_3), 1.62-1.49 (1H, m, $CH_2CH_2CH_2CH_3$), 1.49-1.11 (5H, m, $CH_2CH_2CH_2CH_3$), 1.44 (9H, s, *t*-Bu), 0.87 (3H, t, *J* = 7.0 Hz, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 142.5, 133.5, 128.8, 128.5, 126.6, 125.8, 81.9, 80.3, 55.9, 51.6, 35.1, 28.3, 27.4, 22.6, 14.0; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{31}NO_3Na$: 356.2196. Found: 356.2189 (aq. HCO_2Na was added to improve sensitivity).

(*E*)-*tert*-Butyl (4-methoxy-4-phenylbut-2-en-1-yl)(phenyl)carbamate (*E*-1j): prepared by the same procudure with *E*-**1a** using benzaldehyde instead of paraformaldehyde (58% overall yield from **7**); yellow oil; IR (film) 3061, 3028, 2977, 2929, 2820, 1698, 1597, 1495, 1454, 1388, 1366, 1299, 1279, 1252, 1167, 1093, 1028, 1010, 970, 907, 861, 757, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (7H, m, Ph), 7.19-7.12 (3H, m, Ph), 5.80 (1H, dtd, *J* = 15.7, 6.0, 1.2 Hz, CH=CH), 5.63 (1H, ddt, *J* = 15.7, 6.8, 1.2 Hz, CH=CH), 4.60 (1H, d, *J* = 6.8 Hz, 4-H), 4.29-4.17 (2H, m, 1-H), 3.26 (3H, s, OCH_3), 1.38 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 142.5, 140.9, 133.3, 128.6, 128.3, 128.2, 127.5, 126.6, 126.5, 125.7, 83.5, 80.3, 56.2, 51.6, 28.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{27}NO_3Na$: 376.1883. Found: 376.1877 (aq. HCO_2Na was added to improve sensitivity).

Copies of NMR spectra of 2 and 3





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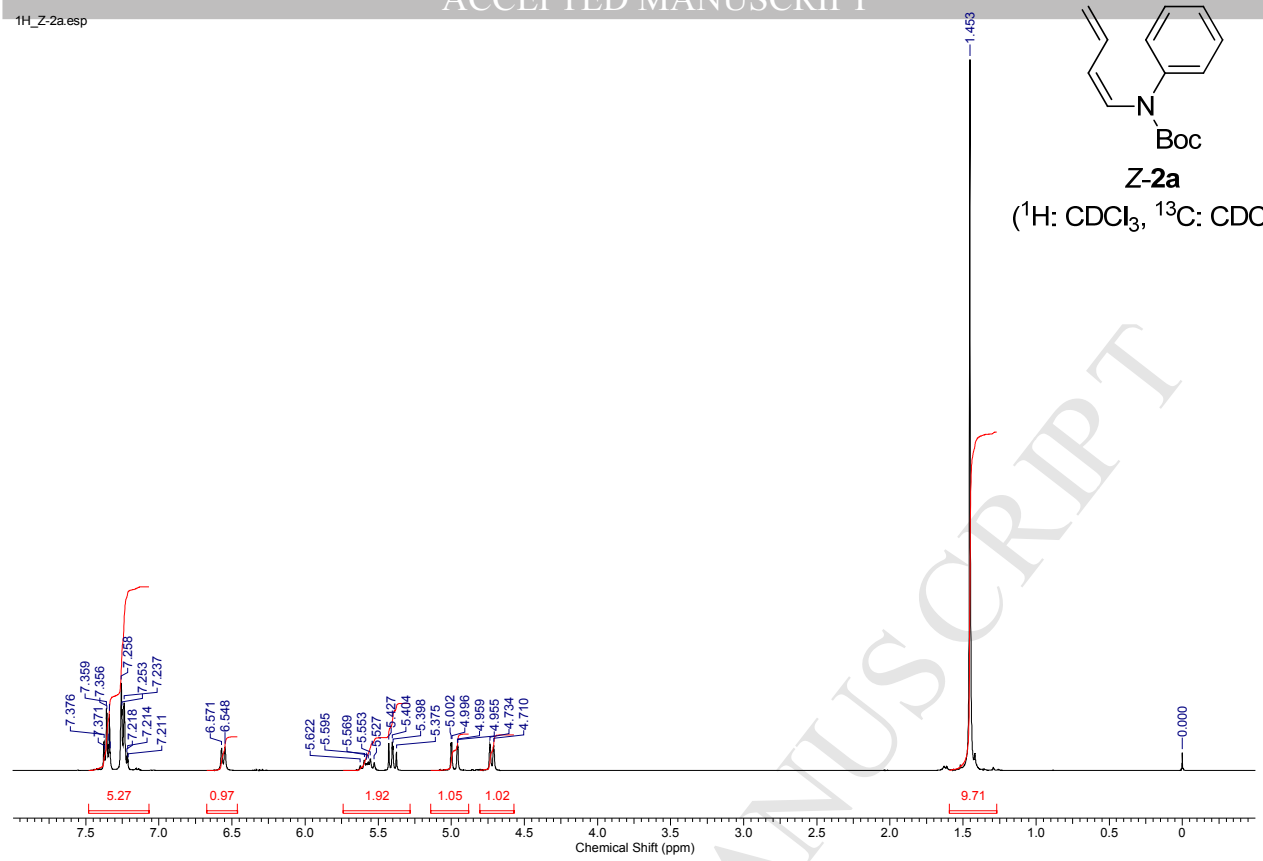

Z-**2a**

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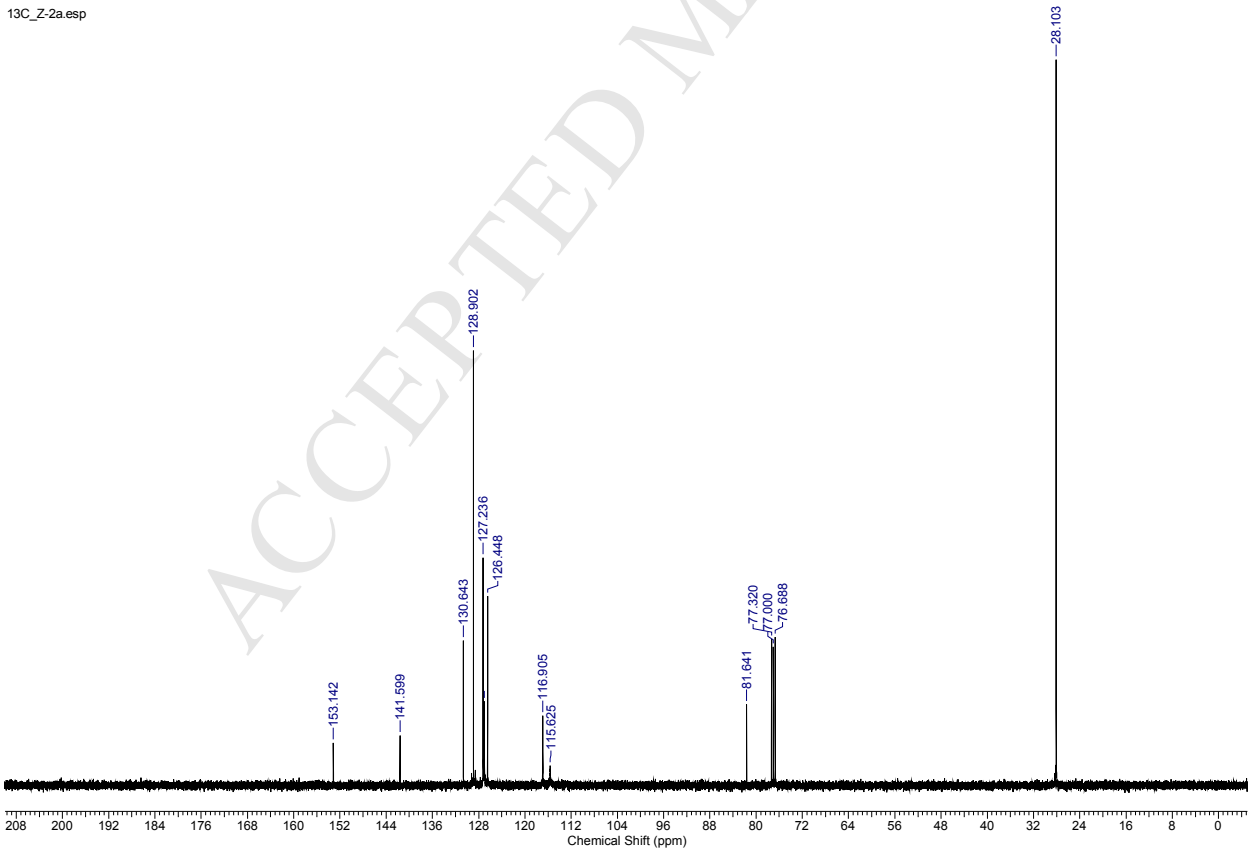

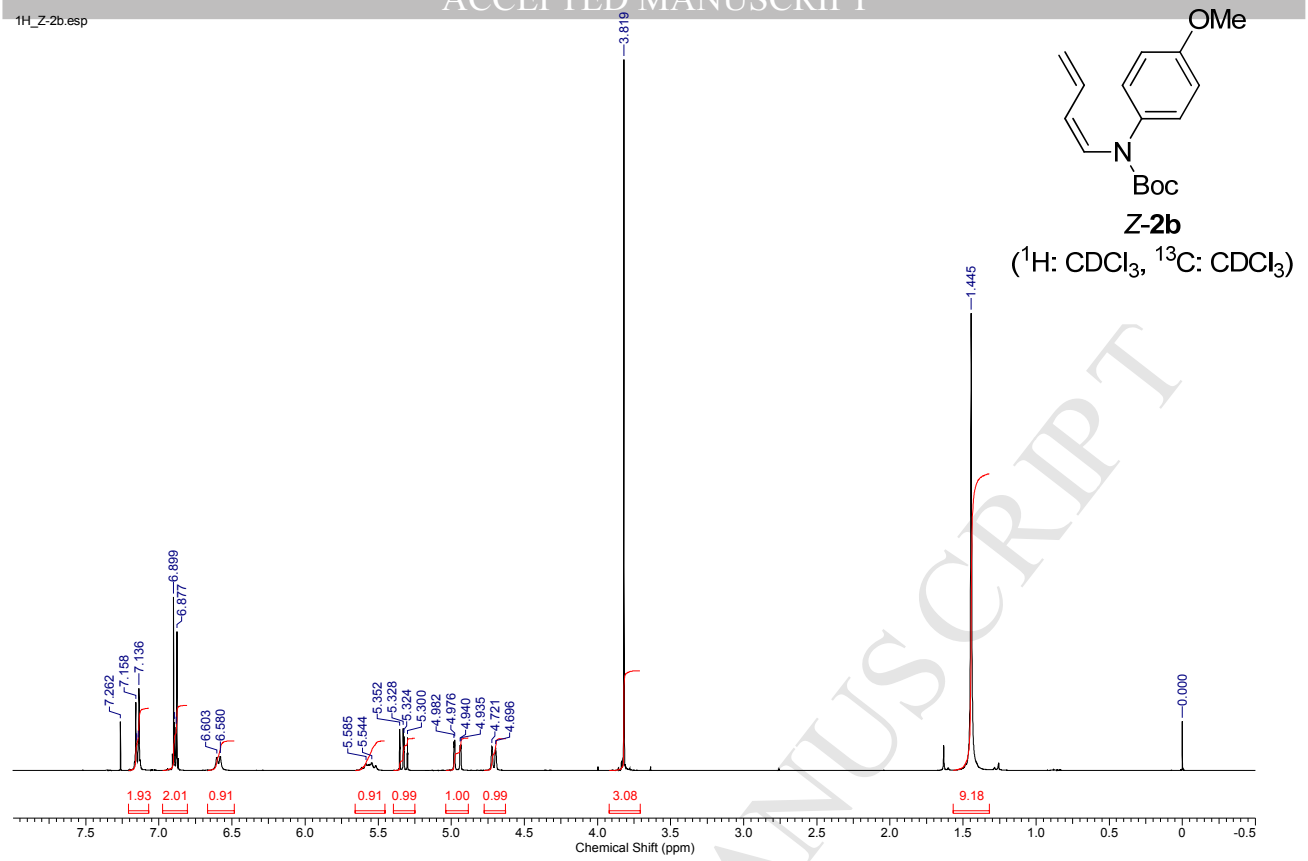

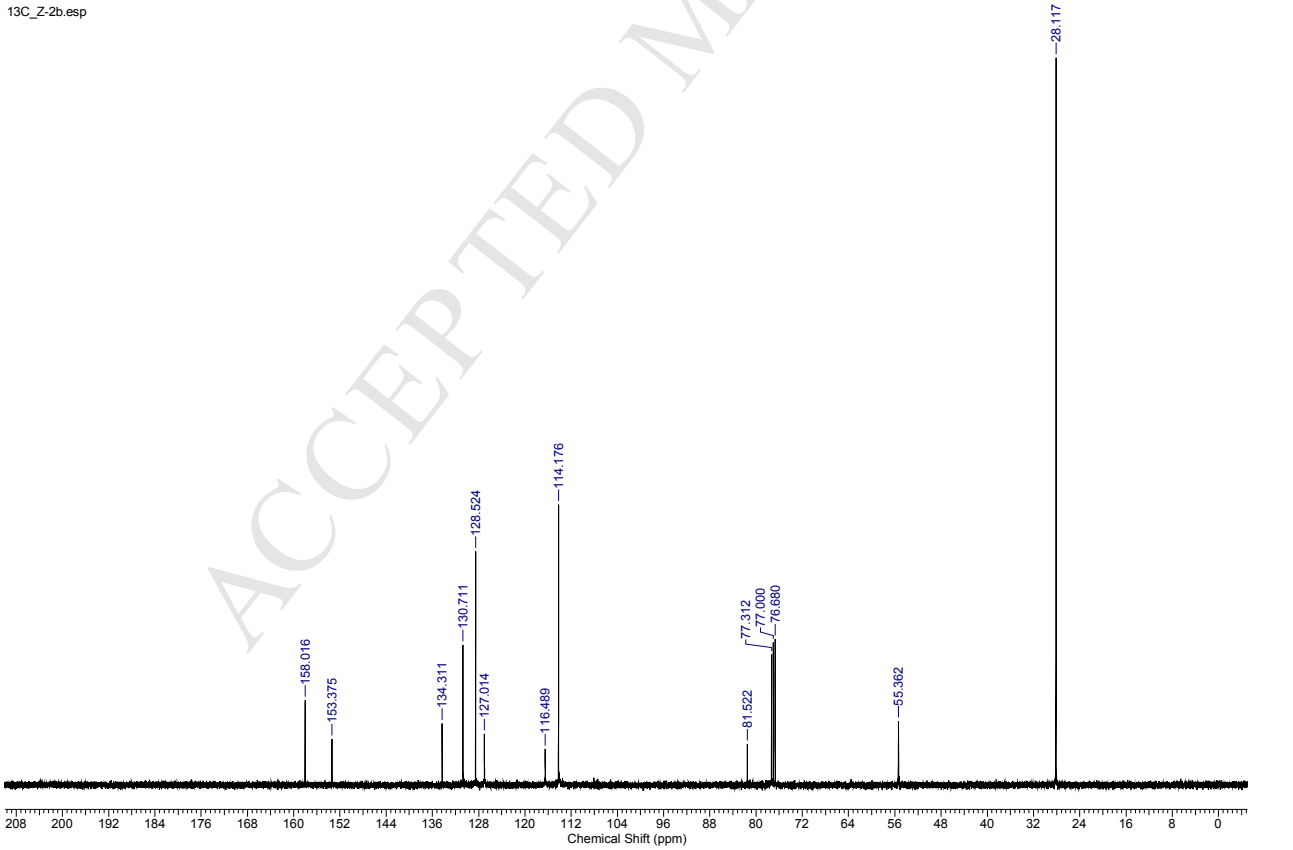

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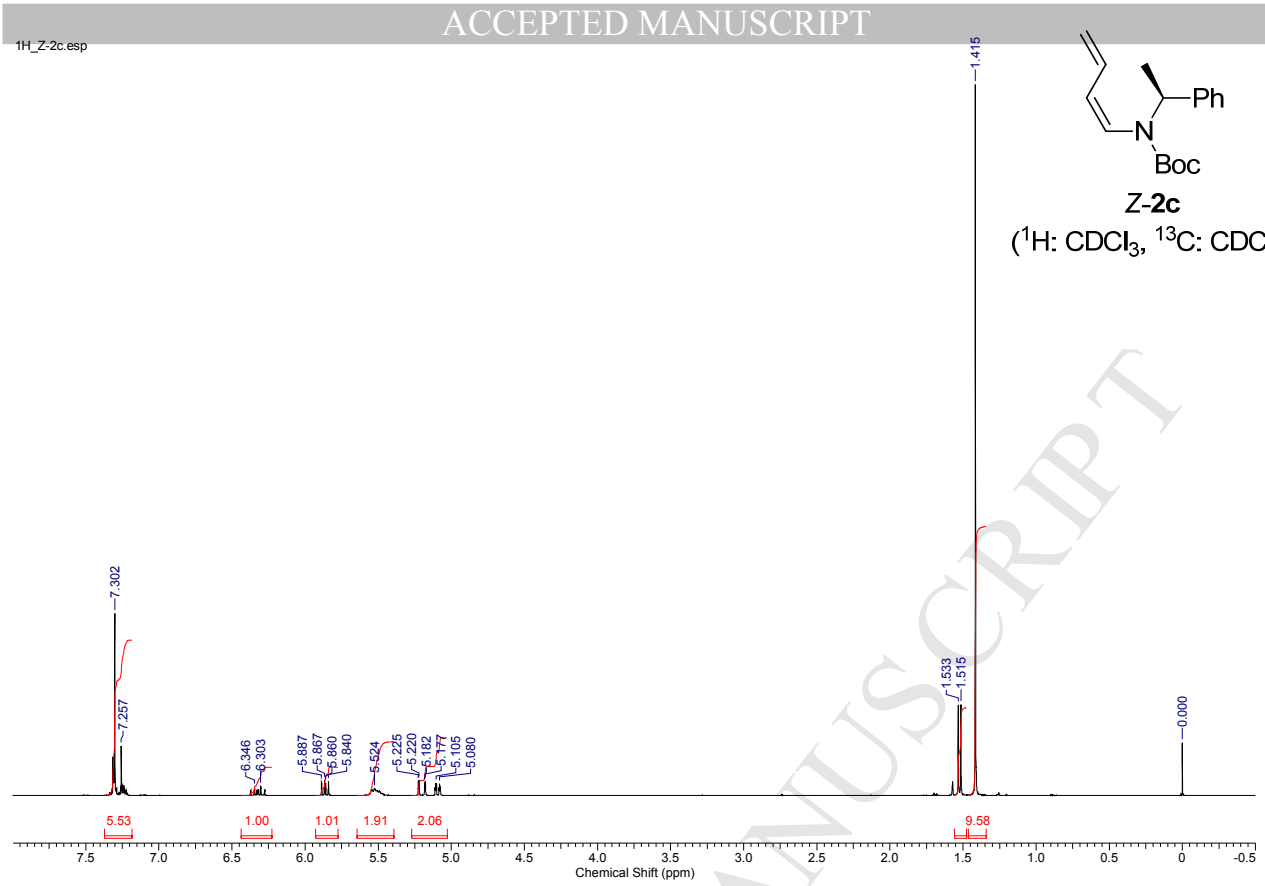
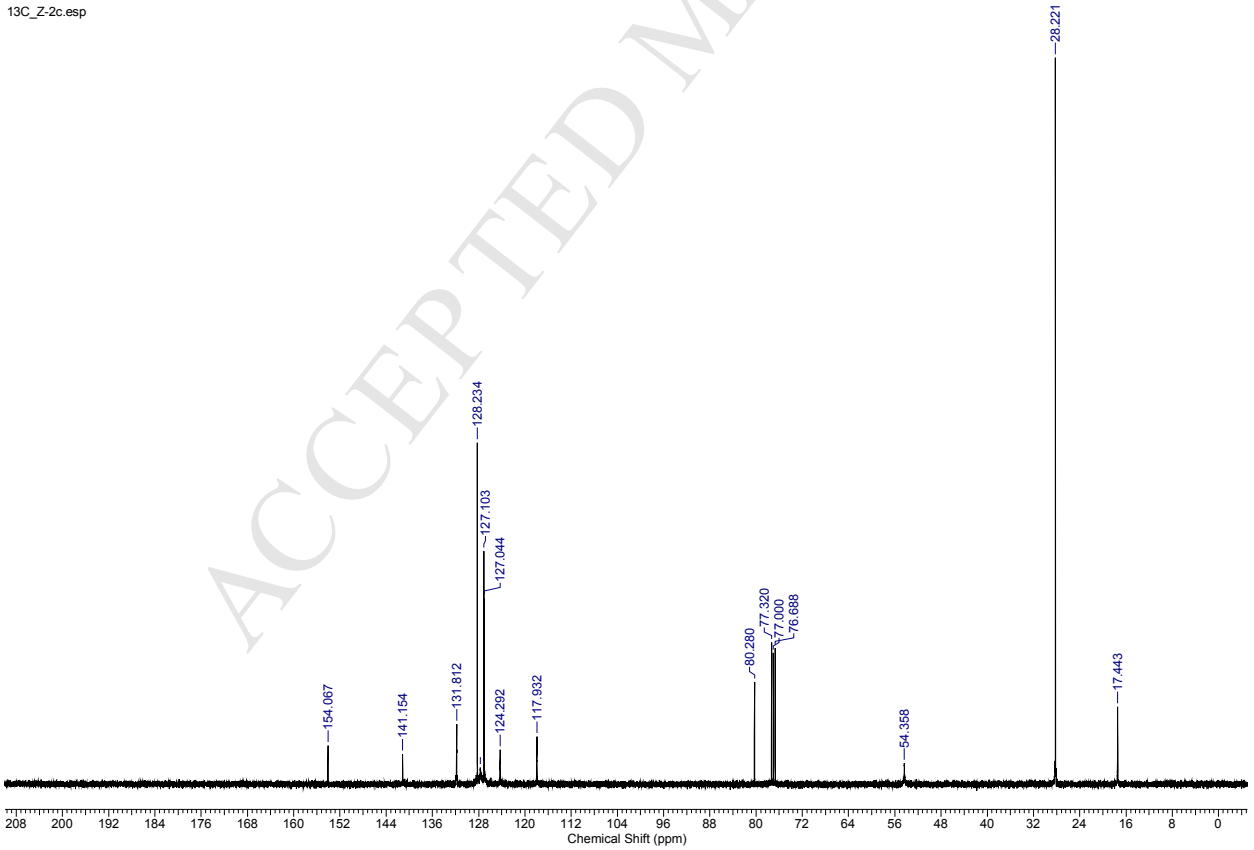
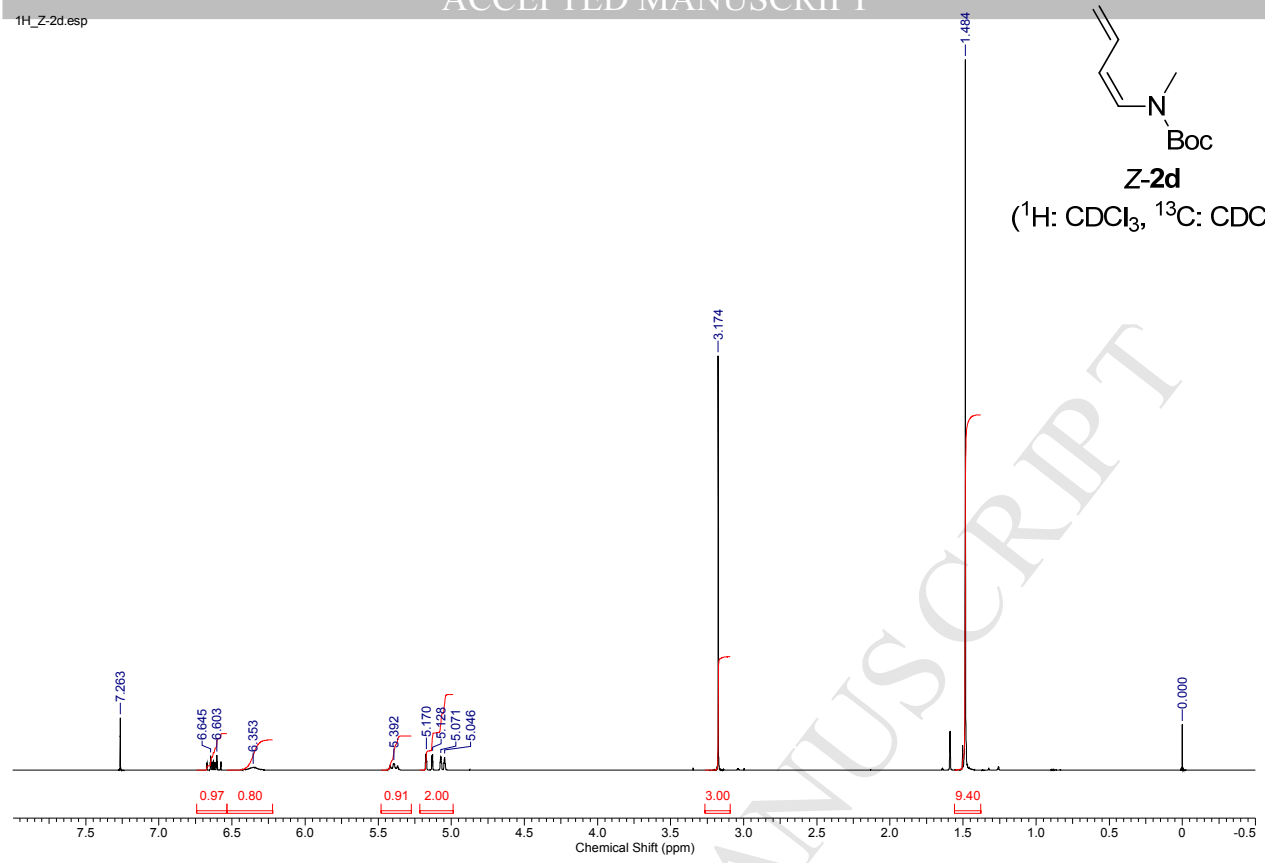


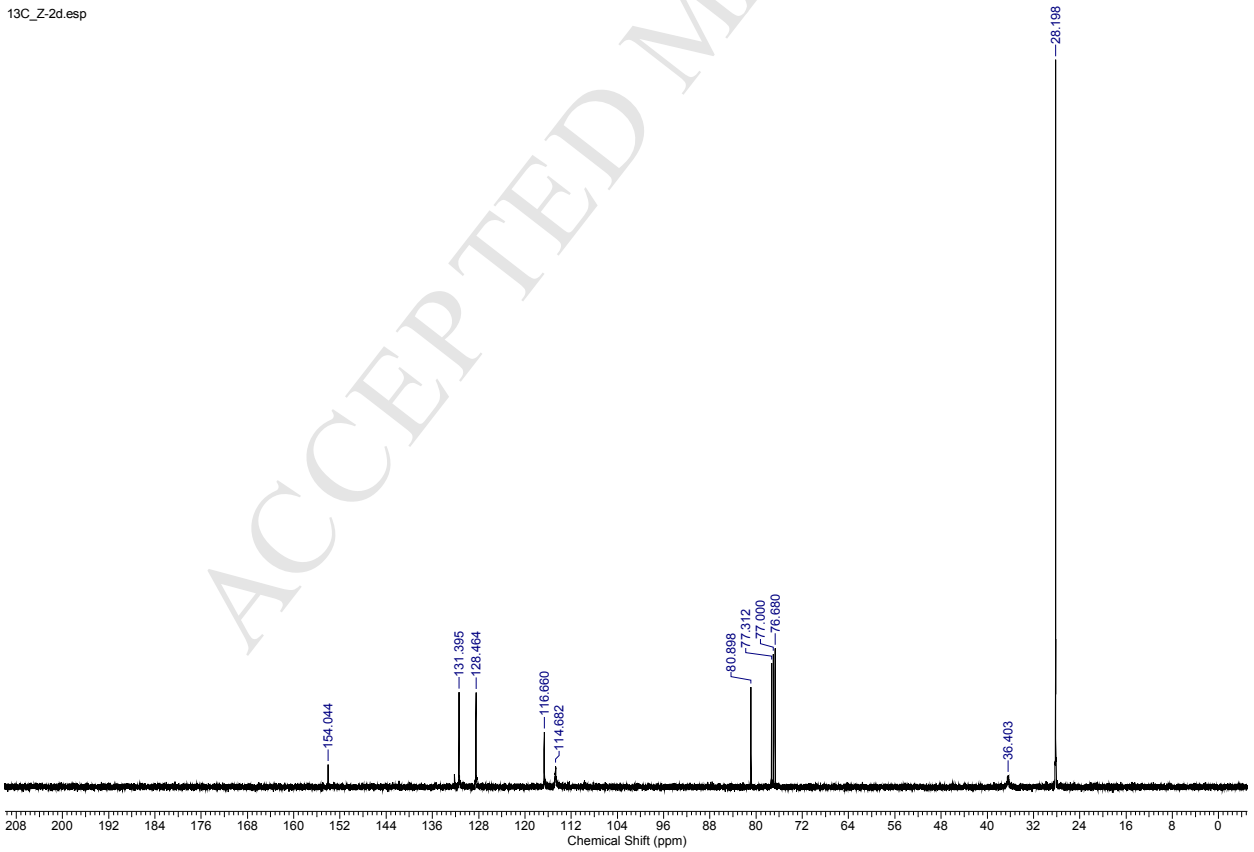
Z-2c

(^{1}H: $CDCl_3$, ^{13}C: $CDCl_3$)

13C_Z-2c.esp







Z-**2d**

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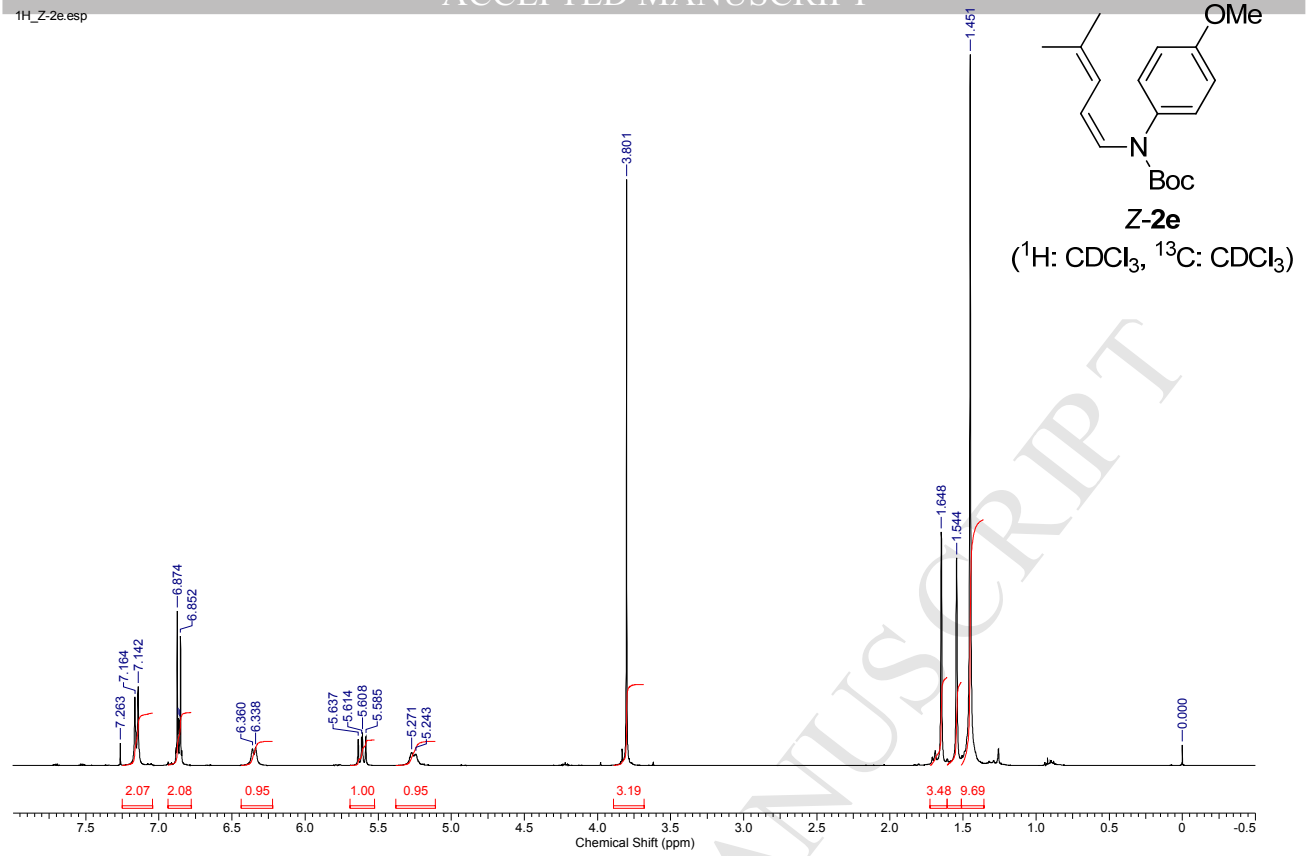
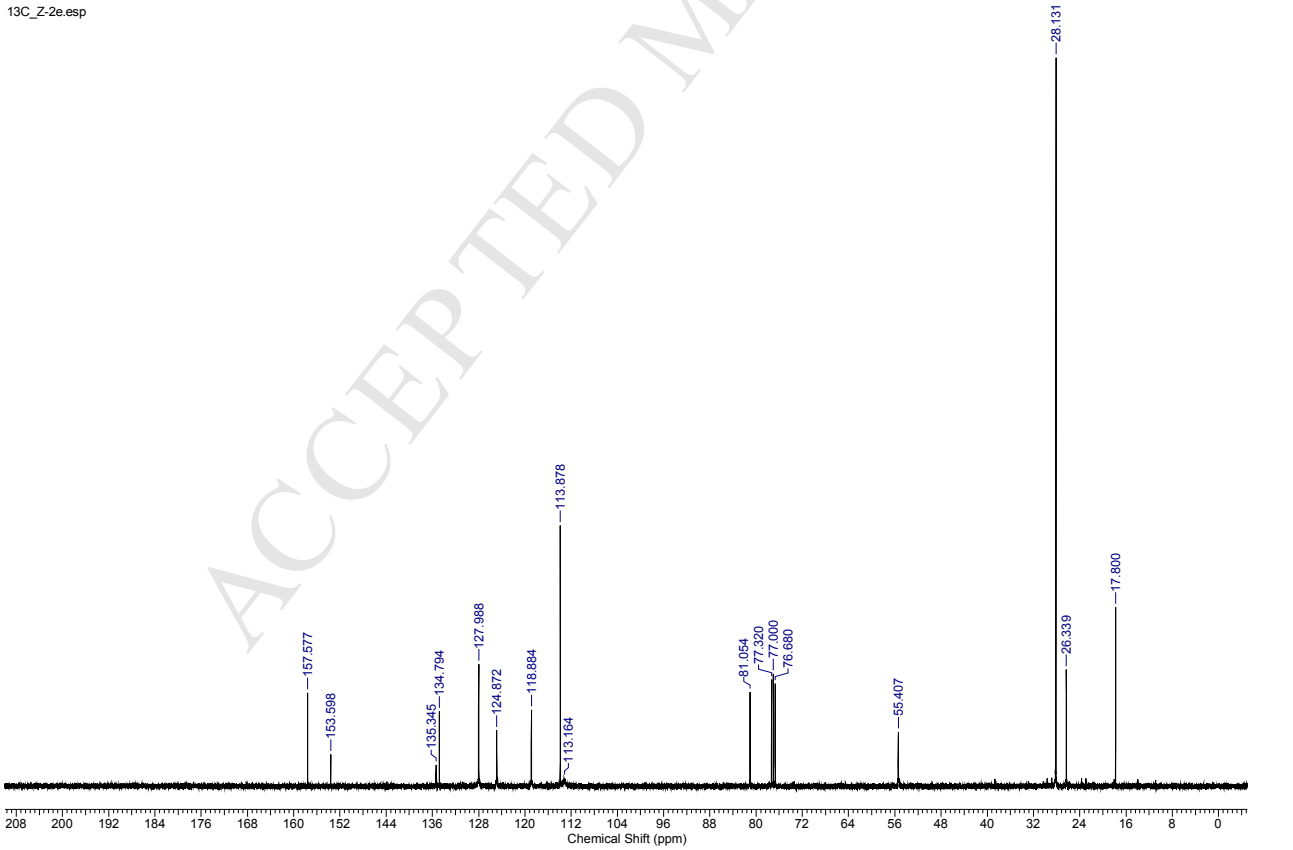
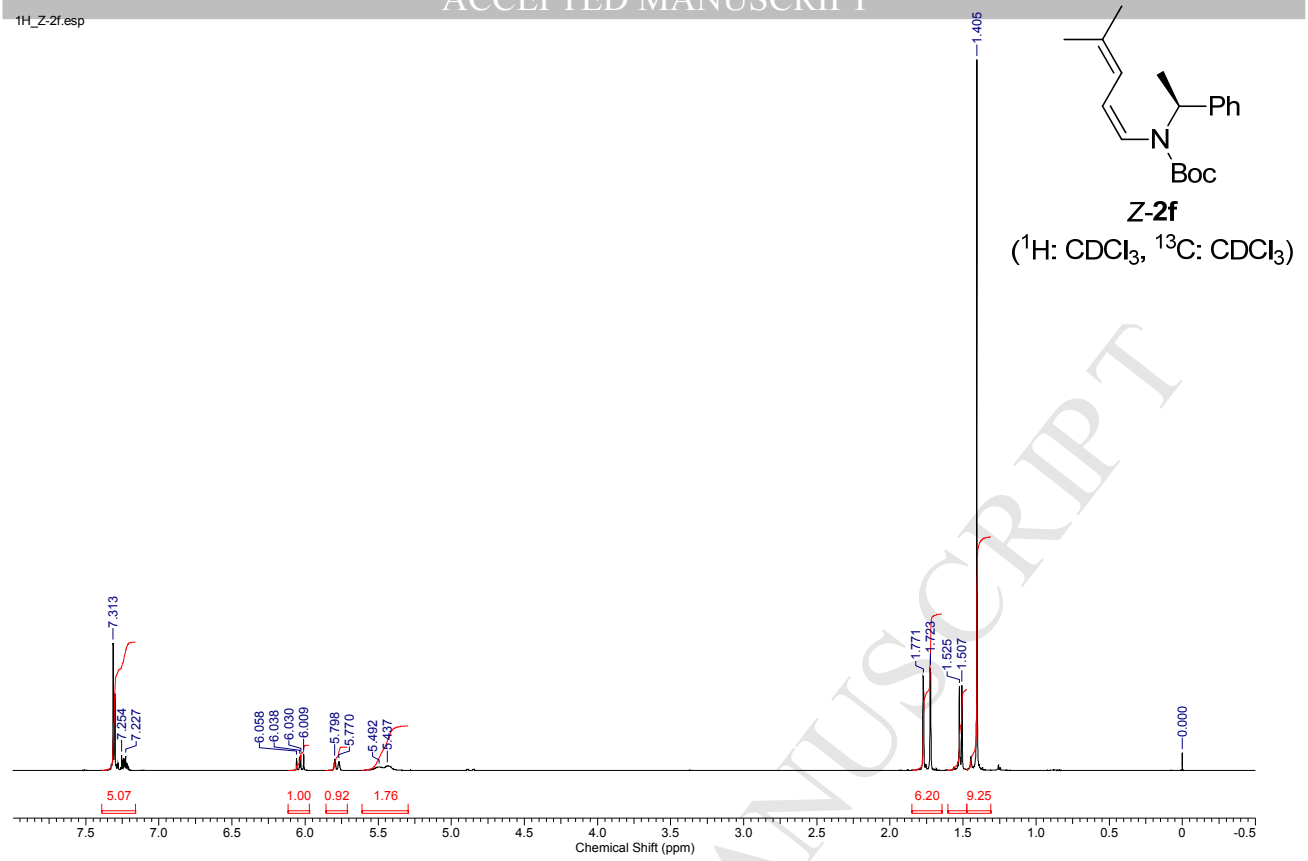
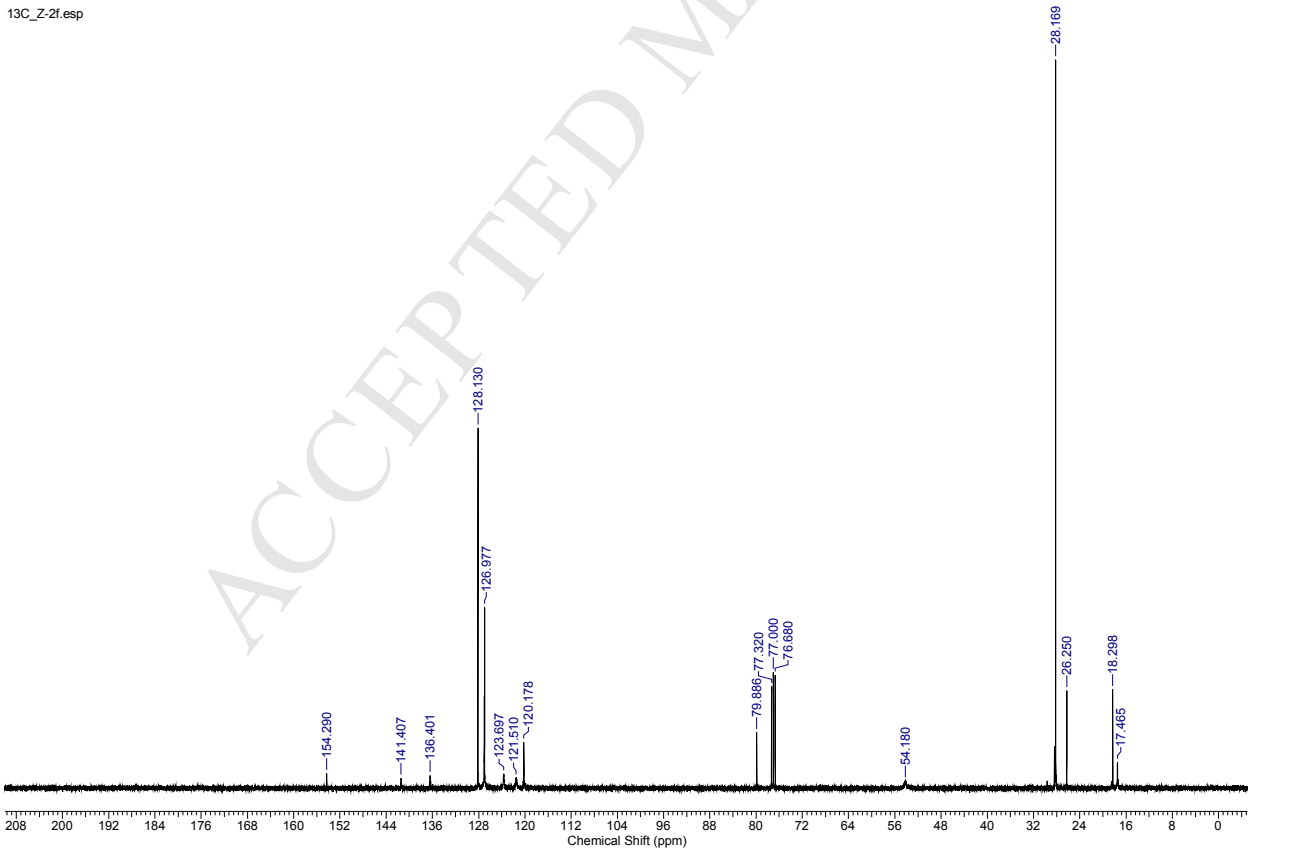




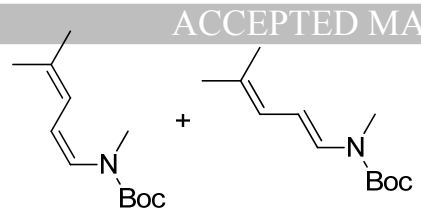




Z-**2f**

(^{1}H: $CDCl_3$, ^{13}C: $CDCl_3$)

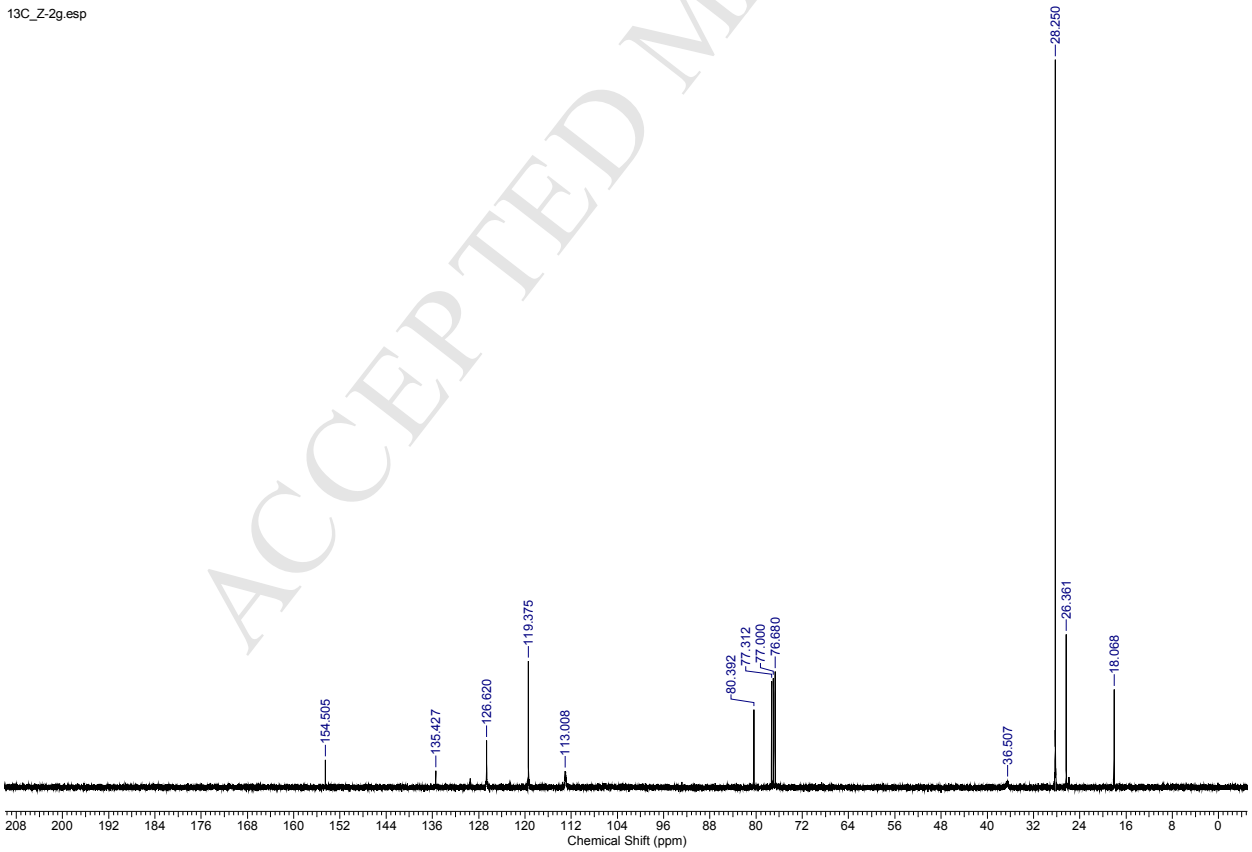
1H_Z-2g.esp



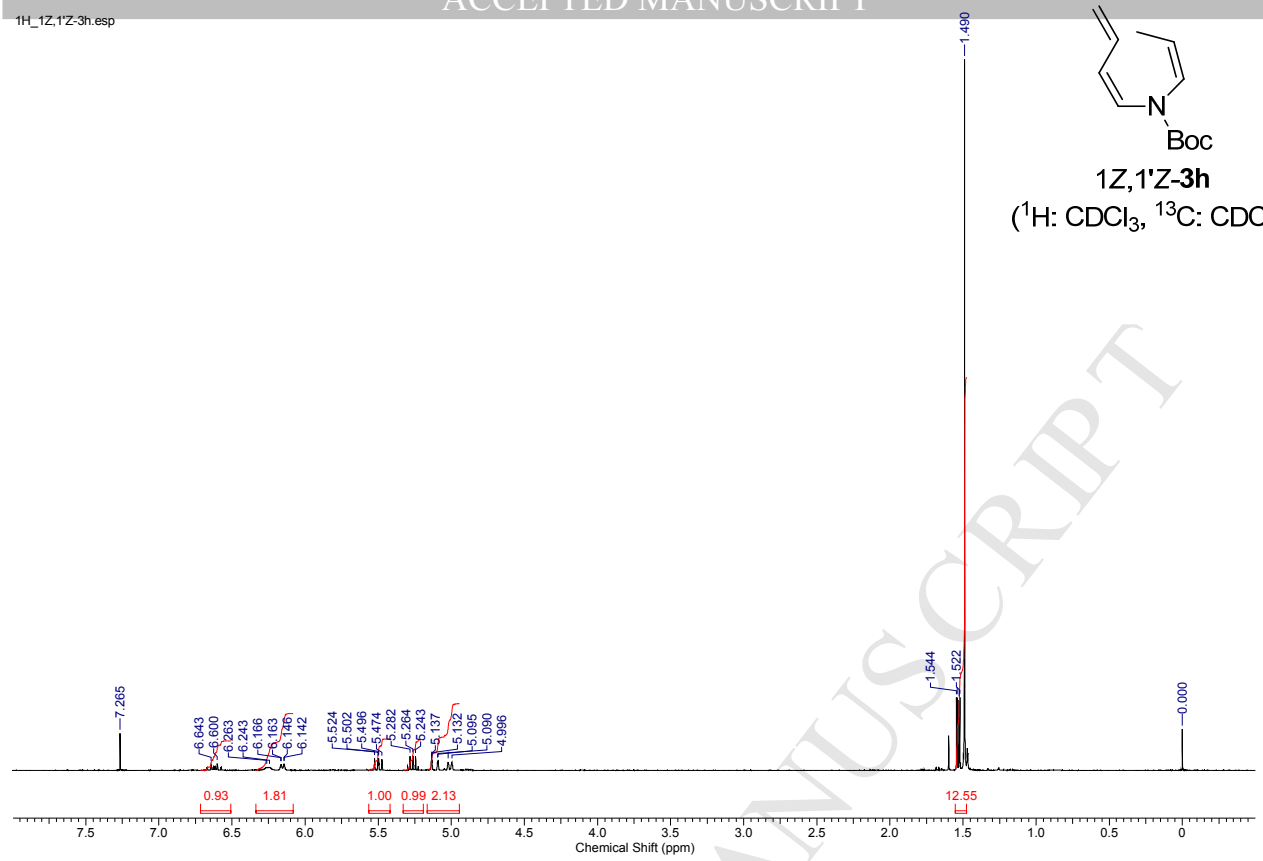
Z-**2g**/*E*-**2g** = 93/7

(^{1}H: $CDCl_3$, ^{13}C: $CDCl_3$)

13C_Z-2g.esp



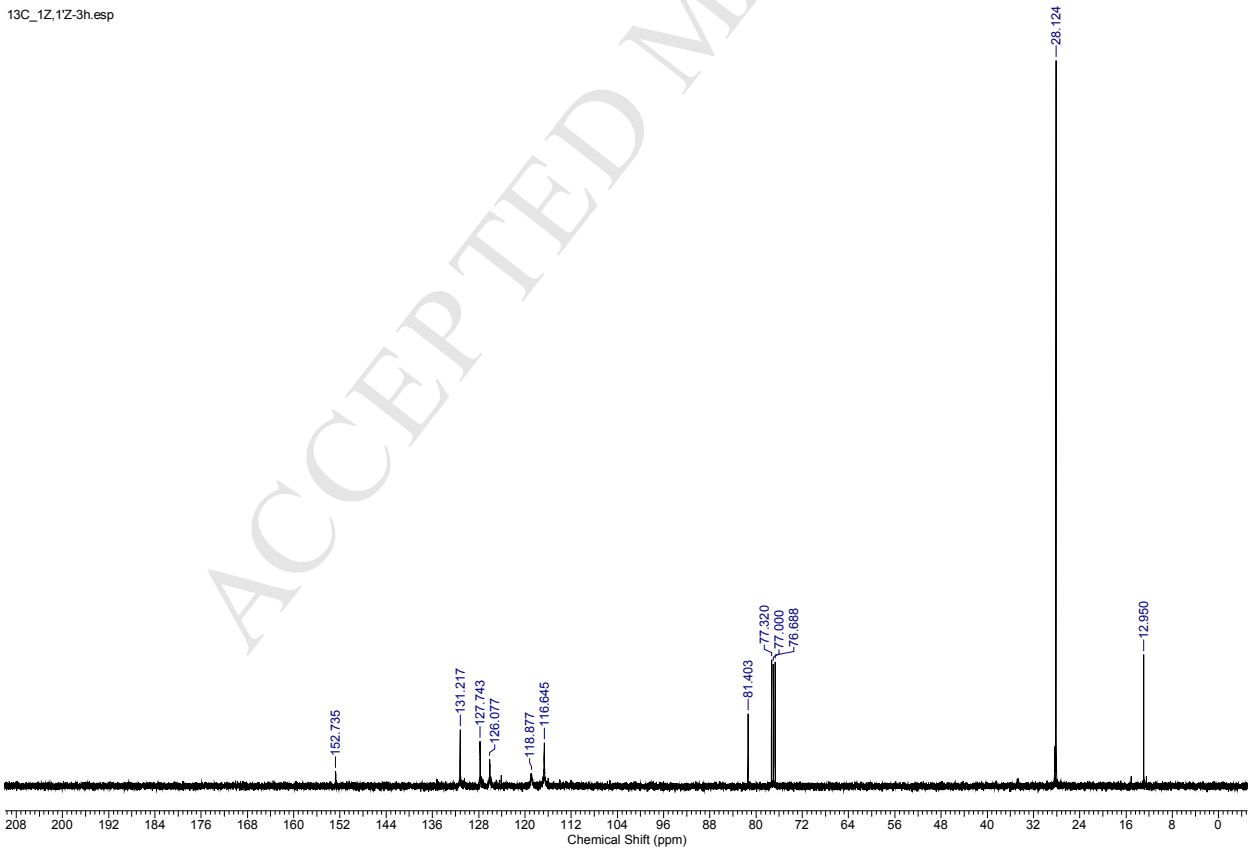
1H_1Z,1'Z-3h.esp

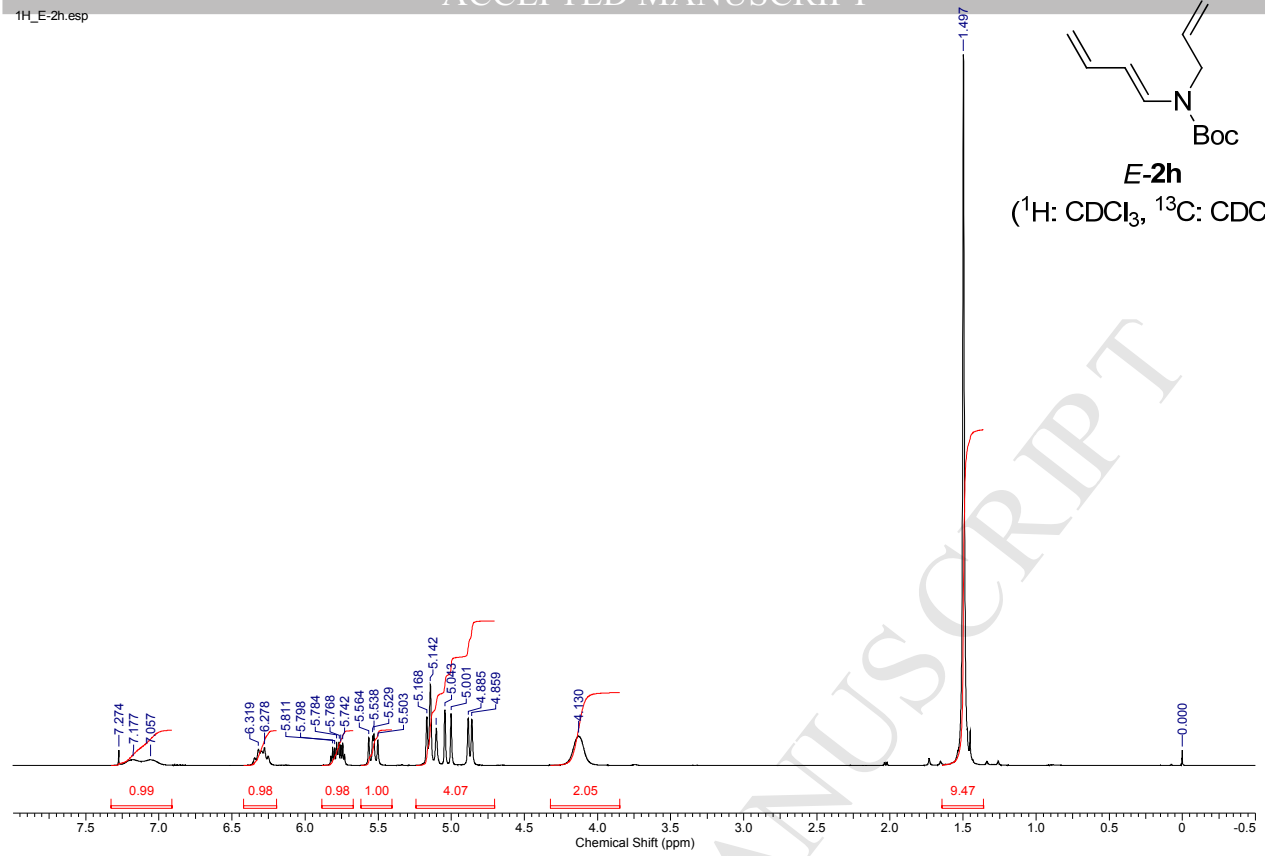


1Z,1'Z-**3h**

(^{1}H: $CDCl_3$, ^{13}C: $CDCl_3$)

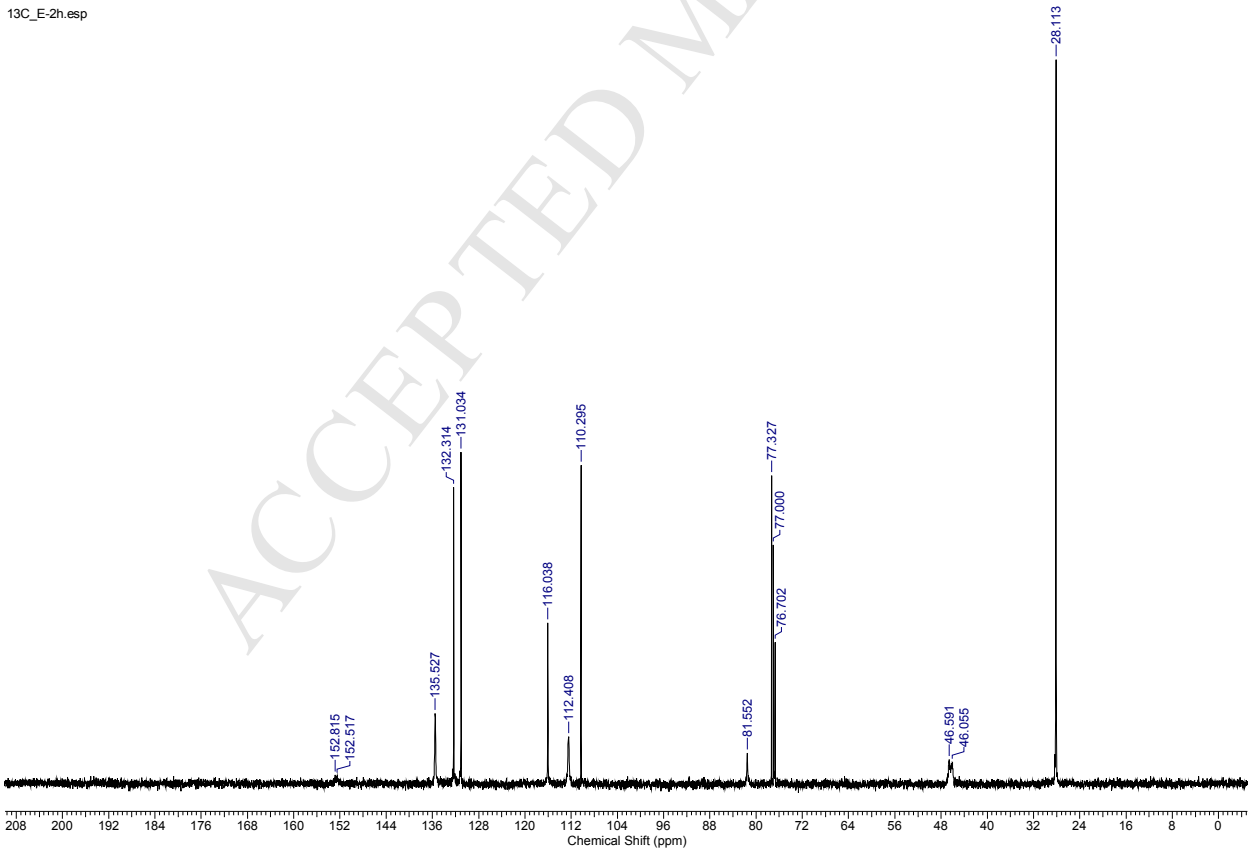
13C_1Z,1'Z-3h.esp



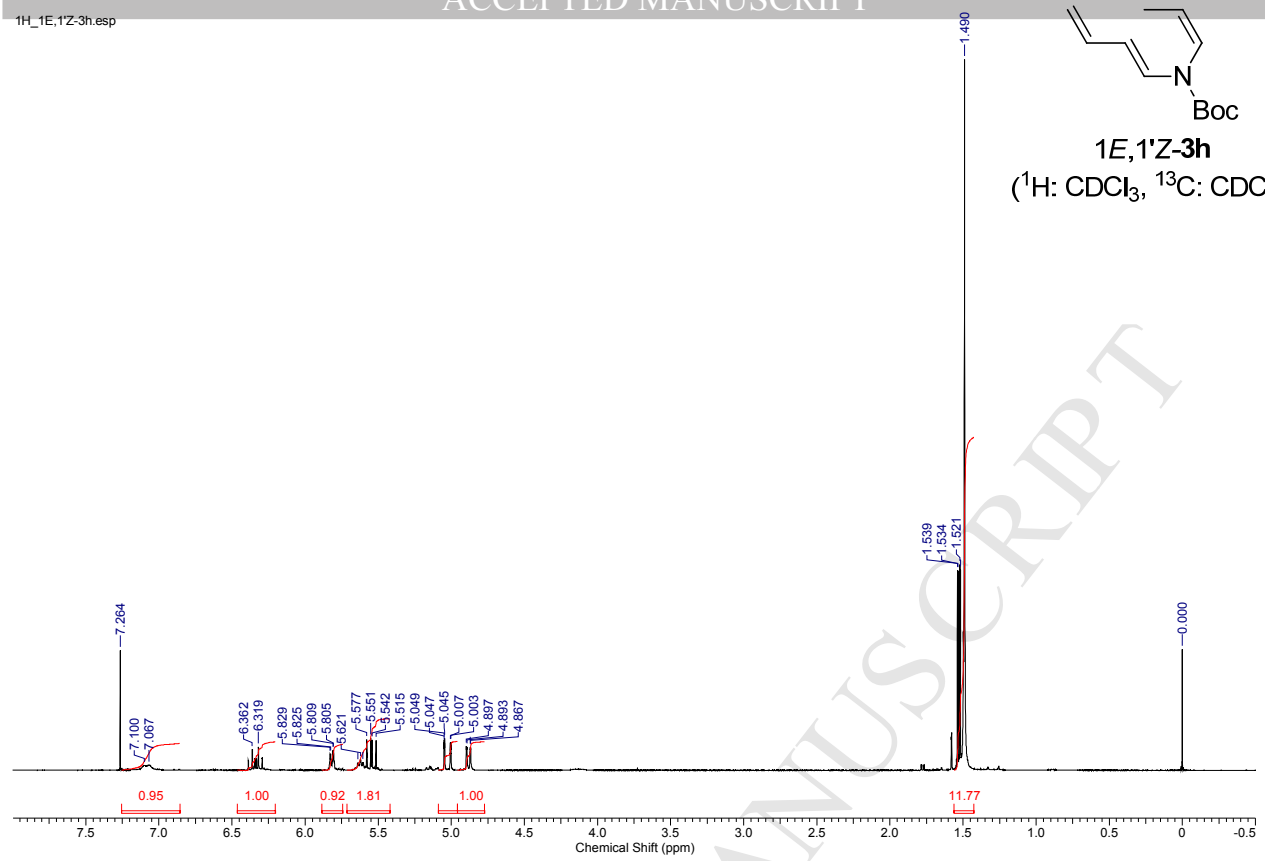


E-**2h**

(^{1}H: $CDCl_3$, ^{13}C: $CDCl_3$)



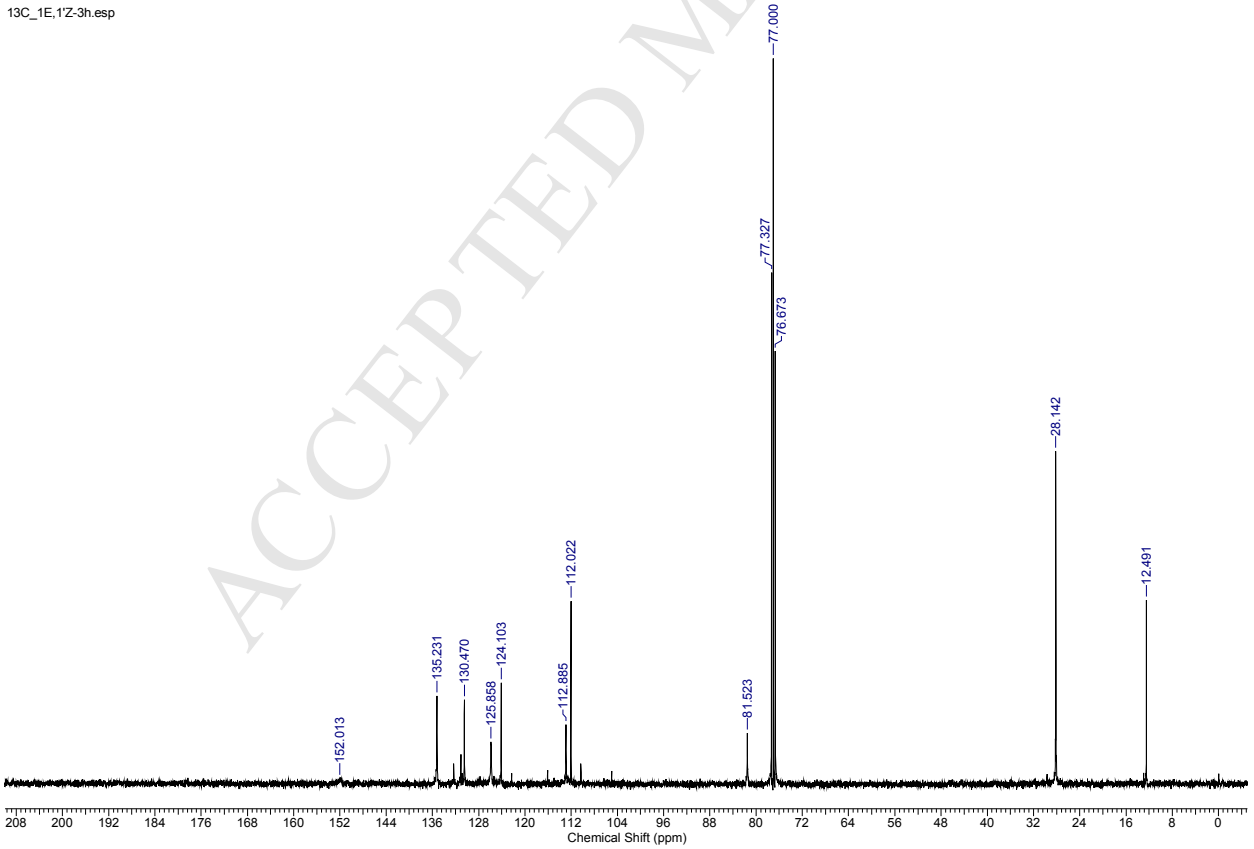
1H_1E,1'Z-3h.esp

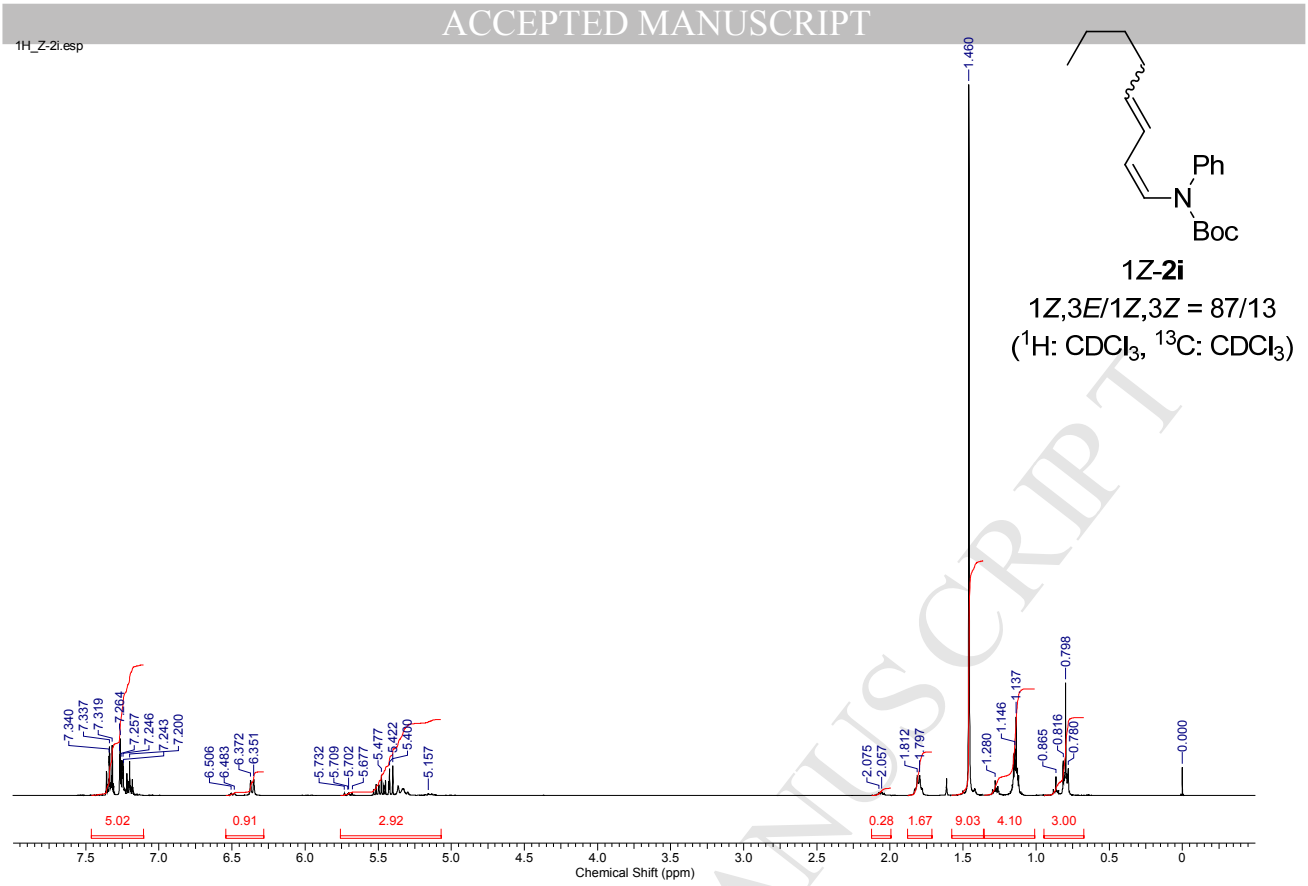


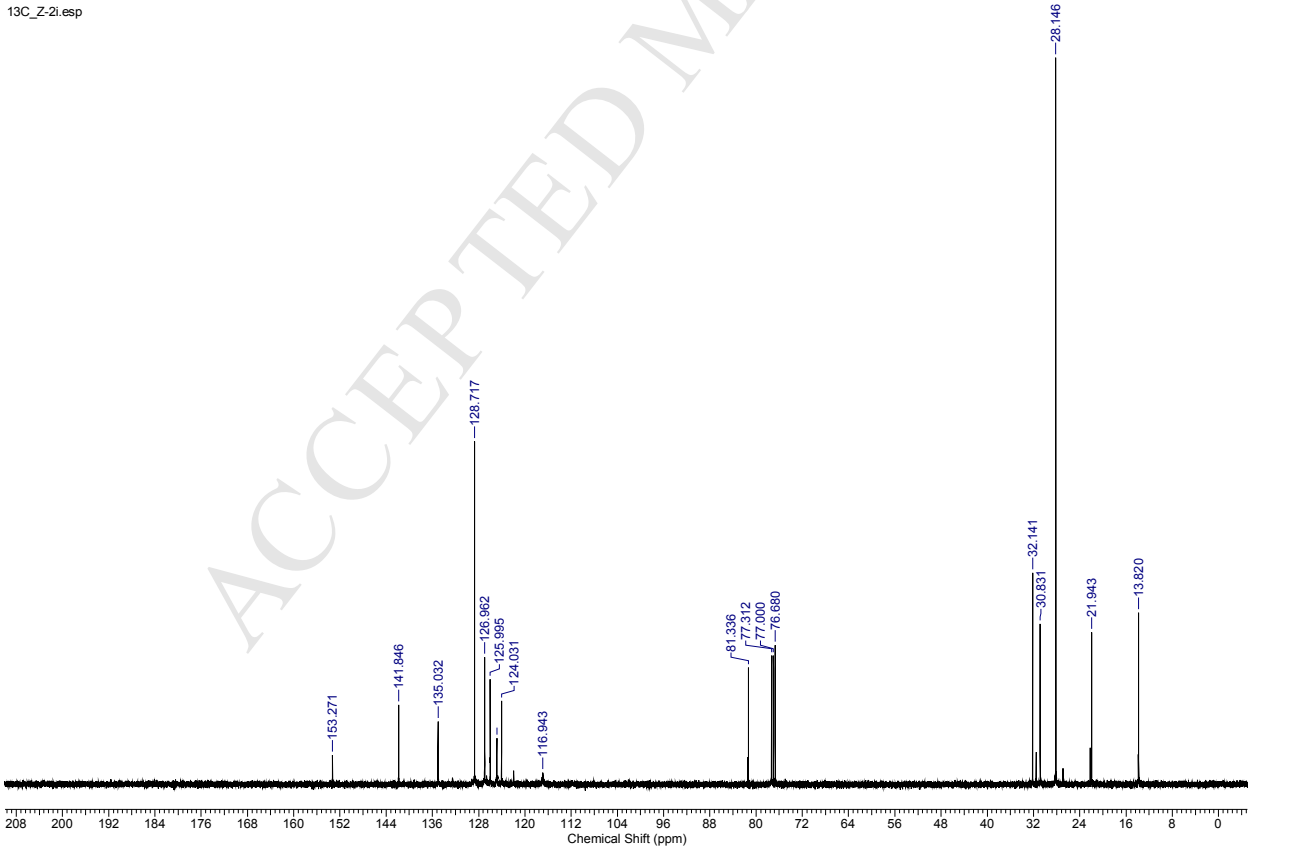
1*E*,1'Z-**3h**

(^{1}H: $CDCl_3$, ^{13}C: $CDCl_3$)

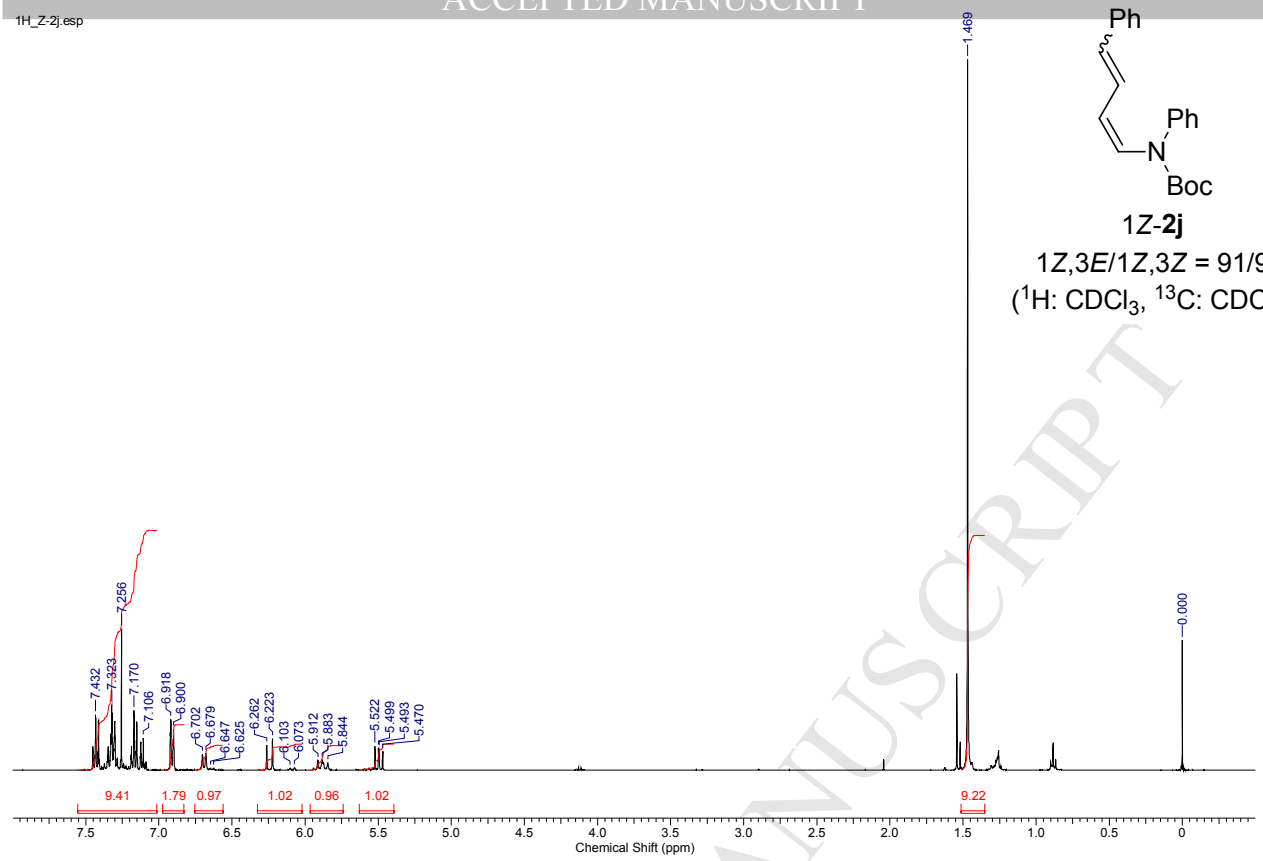
13C_1E,1'Z-3h.esp







1H_Z-2j.esp



1*Z*-**2j**

1*Z*,3*E*/1*Z*,3*Z* = 91/9

(^{1}H: $CDCl_3$, ^{13}C: $CDCl_3$)

13C_Z-2j.esp