# New Synthesis and Diels-Alder Reactions of 2-Aminomethyl-1,3-butadienes and Related 1,3-Dienes

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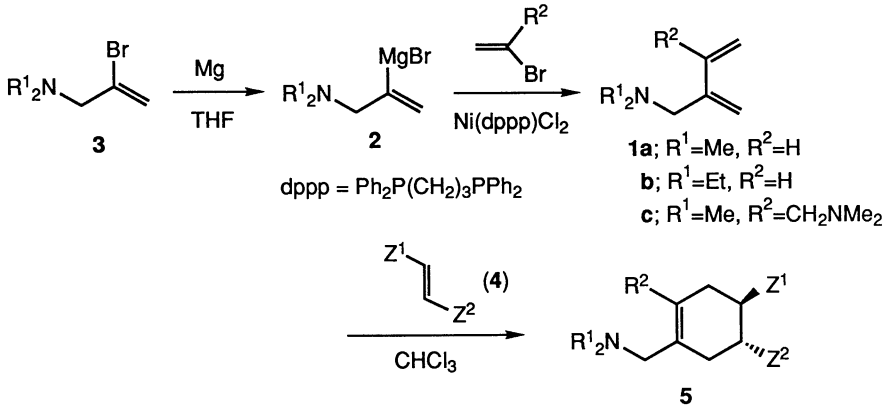
**Synopsis.** 2-Aminomethyl-1,3-butadienes and 2,3-bis-(aminomethyl)-1,3-butadienes, readily prepared by the Grignard cross-coupling reaction of 2-bromo-2-aminopropene and vinylic bromides, are good Diels–Alder dienes toward various activated dienophiles to afford aminomethyl-substituted cyclohexenes.

The Diels–Alder reaction is important and convenient for the stereo- and regioselective construction of six-membered ring compounds and many efforts have been directed to prepare new 1,3-dienes.[1] We have shown that the organosilyl and organostannyl groups on the methyl group of isoprene dramatically improve both reactivity and regioselectivity, and that these reagents are an excellent building block for the synthesis of isoprene derivatives.[2] Furthermore 2-aminomethyl-3-silylmethyl-1,3-butadiene acts formally as the synthetic equivalent of the 2,2′-bis(allyl) diradical and zwitterion.[3] As a part of a program aimed at exploring a new class of 1,3-dienes, we report here the preparation of new aminomethyl-substituted 1,3-dienes and their cycloaddition.

The starting 1,3-dienes **1** were readily prepared by the cross-coupling of the Grignard reagent **2** with vinylic bromide as shown in Scheme 1.

1,3-Dienes **1**, thus obtained, react smoothly with various dienophiles to give the corresponding cycloadducts **5**. The results are listed in Table 1. In all cases aminomethyl-substituted cyclohexenes were obtained in good yield. The reaction proceeded in a stereospecific mode as it was seen in the reaction with dimethyl fumarate and dimethyl maleate which gave exclusively a *trans* and *cis* adduct, respectively. However the regioselectivity in this reaction with methyl acrylate (3-$Me_2NCH_2$-:4-$Me_2NCH_2$-=38:62) decreased presumably due to the electronegative amino




Scheme 1.

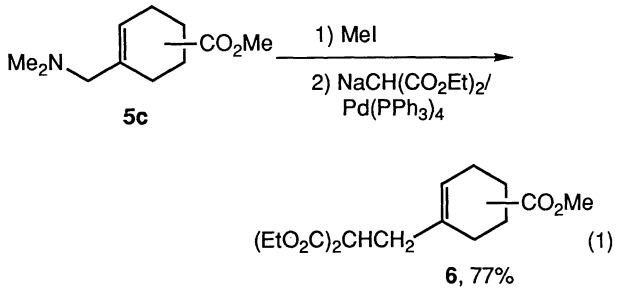
Table 1. The Diels–Alder Reaction of **1**[a]

| Entry | Diene **1** | Dienophile **4** | Product **5** (Yield/%)[b] | |
|---|---|---|---|---|
| 1 | **1a** ($R^1$=Me, $R^2$=H) | Dimethyl fumarate (**4a**) | **5a** (*trans*) | (92) |
| 2 | **1a** | Dimethyl maleate (**4b**) | **5b** (*cis*) | (67) |
| 3 | **1a** | Methyl acrylate (**4c**) | **5c**[c] | (95) |
| 4 | **1a** | Ethyl acrylate (**4d**) | **5d** | (80) |
| 5 | **1a** | 3-Buten-2-one (**4e**) | **5e**[d] | (98) |
| 6 | **1a** | Dimethyl acetylenedicarboxylate (**4f**) | **5f** | (73) |
| 7 | **1b** ($R^1$=Et, $R^2$=H) | **4a** | **5g** (*trans*) | (92) |
| 8 | **1b** | **4b** | **5h** (*cis*) | (50) |
| 9 | **1b** | **4f** | **5i** | (83) |
| 10 | **1c** ($R^1$=Me, $R^2$=$CH_2NMe_2$) | **4a** | **5j** (*trans*) | (83) |
| 11 | **1c** | **4b** | **5k** (*cis*) | (79) |
| 12 | **1c** | **4c** | **5l** | (85) |
| 13 | **1c** | **4f** | **5m** | (84) |

a) In $CHCl_3$ at reflux for 20 h. b) Isolated by TLC. c) 3-$Me_2NCH_2$-:4-$Me_2NCH_2$=38:62. d) A mixture of regioisomers.

group, compared with the results using isoprene (30:70),[4] 2-silylmethyl-1,3-butadiene (16:84) and 2-stannylmethyl-1,3-butadiene (8:92).[2] The ratio was further close to ca. 1:1 when the reaction was carried out in the presence of a Lewis acid (44:56 for $AlCl_3$ and 43:57 for $BF_3OEt_2$) or hydrochloric acid (47:53). This result can be reasonably explained by the formation of more electronegative ammonium ion or a Lewis acid–amine complex.

The cycloadducts **5** include an allylamine unit which would form an electrophilic part after quaternization with an alkyl halide.[3] Therefore we studied the reaction of **5** with nucleophilic reagent. Thus, diethyl sodiomalonate reacted with the ammonium salt of **5c** in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium to give the substitution product **6** in 77% yield (Eq. 1).




Thus, **1** is an important reagent for construction of aminomethyl-substituted six-membered ring products which are further subjected to electrophilic reactions.

## Experimental

The IR spectra were recorded on a Shimadzu IR-460 spectrometer. The NMR spectra were determined on JEOL-JMN-60SI, FX-90Q spectrometers using TMS(tetramethylsilane) as an internal standard. MS spectra were recorded on JEOL-DX303 and Shimadzu QP2000 spectrometers. The microanalyses were performed at the Analytical Center of Nagasaki University and University of Tsukuba. Ether and tetrahydrofuran were distilled from sodium diphenylketyl. All experiments were carried out under an argon atmosphere. Purification of the product was carried out by thin layer chromatography (TLC) on silica gel. Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification.

**Synthesis of Aminomethyl-Substituted 1,3-Butadienes 1. A Typical Procedure.** A Grignard reagent **2**,[3] readily prepared from 2-bromo-3-dimethylaminopropene (**3a**, $R^1$= Me) (16.4 g, 0.10 mol) and magnesium (4.8 g, 0.20 mol) in THF (10 ml), was added to vinyl bromide (12.8 g, 0.12 mol) in the presence of dichloro[1,3-bis(diphenylphosphino)propane]nickel (200 mg, 0.37 mmol) in THF (10 ml) at 0 °C. After stirring for 17 h at room temperature, hydrolysis of the reaction mixture and successive usual workup were carried out. After evaporation of solvent, the residue was distilled to give a colorless **1a** (9.8 g, 0.088 mol) in 88% yield. Bp 56 °C ($1.24\times10^4$ Pa). Similarly, **1b**, and **1c**, bp 84 °C ($5.6\times10^3$ Pa) and bp 85 °C ($5.3\times10^3$ Pa), were prepared from the corresponding starting materials in 47 and 75% yields, respectively.

**2-Dimethylaminomethyl-1,3-butadiene (1a):** $^1$H NMR ($CDCl_3$, 90 MHz) $\delta$=2.22 (s, 6H), 2.99 (s, 2H), 4.97 (1H, d, $J$=12 Hz), 5.14 (2H, s), 5.38 (1H, d, $J$=18 Hz), 6.37 (1H, dd, $J$=12 and 18 Hz); IR (neat) 3030, 2980, 2860, 2830, 2780, 1810, 1457 cm$^{-1}$. MS $m/z$ 111 ($M^+$, 100), 96 (13), 67 (16). Found: $m/z$ 111.1053. Calcd for $C_7H_{13}N$: 111.1048. Anal. ($C_7H_{13}N$) C, H, N.

**2-Diethylaminomethyl-1,3-butadiene (1b):** $^1$H NMR ($CDCl_3$, 90 MHz) $\delta$=1.04. (t, $J$=7 Hz, 6H), 2.50 (q, $J$=7 Hz, 4H), 3.14 (bs, 2H), 4.90—5.70 (4H, m), 6.35 (1H, dd, $J$=10.5 and 16 Hz); MS $m/z$ 139 ($M^+$, 73), 124 (100). Found: $m/z$ 139.1339. Calcd for $C_9H_{17}N$: 139.1361. Anal. ($C_9H_{17}N$) C, H, N.

**2,3-Bis(dimethylaminomethyl)-1,3-butadiene (1c):** $^1$H NMR ($CCl_4$, 60 MHz) $\delta$=2.20 (s, 12H), 3.05 (s, 4H), 5.05 (bs, 2H), 5.30 (bs, 2H); IR (neat) 2975, 2895, 2860, 2820, 1598, 1457, 1357, 1265, 1177, 1034, 902, 855 cm$^{-1}$; MS $m/z$ 168 ($M^+$, 6), 108 (17), 58 (100). Anal. ($C_{10}H_{20}N$) C, H, N.

**General Procedure for the Diels–Alder Reaction of 1.** In a 20 ml flask a mixture of a 1,3-diene **1** (0.5 mmol) and a dienophile (1.0 mmol) was heated at reflux in chloroform (3 ml) for 20 h. After the solvent was evaporated, the product was purified by TLC on silica gel. The physical properties and analytical data of the adducts obtained are listed below.

**Dimethyl 4-Dimethylaminomethyl-4-cyclohexene-*trans*-1,2-dicarboxylate (5a):** $^1$H NMR ($CCl_4$, 90 MHz) $\delta$=2.15 (s, 6H), 2.3—2.8 (m, 6H), 2.90 (s, 2H), 3.70 (s, 6H), 5.55 (bs, 1H); IR ($CCl_4$) 2950, 2015, 1738, 1674, 1257, 1234, 1107, 1030 cm$^{-1}$; MS $m/z$ 255 ($M^+$, 36), 240 (7), 224 (8), 196 (26), 151 (8), 58 (100). Anal. ($C_{13}H_{21}NO_5$) C, H, N.

**Dimethyl 4-Dimethylaminomethyl-4-cyclohexene-*cis*-1,2-dicarboxylate (5b):** $^1$H NMR ($CCl_5$, 90 MHz) $\delta$=2.05 (s, 6H), 2.2—2.7 (m, 6H), 2.90 (s, 2H), 3.80 (s, 6H), 5.50 (bs, 1H); IR ($CCl_4$) 2975, 2855, 1741, 1679, 1027 cm$^{-1}$; MS $m/z$ 255 ($M^+$, 39), 240 (6), 224 (6), 196 (31), 180 (4), 168 (3), 151 (10), 110 (13), 117 (39), 59 (100). Anal. ($C^{13}H_{21}NO_2$) C, H, N.

**Methyl 3- and 4-Dimethylaminomethyl-3-cyclohexene-1-carboxylates (5c, as a Mixture):** $^1$H NMR ($CCl_3$, 90 MHz) $\delta$=2.15 (s, 6H), 2.0—2.6 (m, 7H), 2.75 (s, 2H), 3.66 (s, 3H×0.38), 3.68 (s, 3H×0.62), 5.30 (bs, 1H); IR ($CCl_4$) 2975, 2855, 1793, 1673, 1256, 1150, 1021 cm$^{-1}$. Anal. ($C_{11}H_{19}NO_2$) C, H, N.

**Ethyl 3- and 4-Dimethylaminomethyl-3-cyclohexene-1-carboxylates (5d, as a Mixture):** $^1$H NMR ($CDCl_3$, 90 MHz) $\delta$=1.25 (3H, t, $J$=7 Hz), 1.55—2.64 (7H, m), 2.15 (6H, s), 2.75 (2H, s), 4.31 (2H, q, $J$=7 Hz), 5.56 (1H, s); MS $m/z$ 211 ($M^+$, 27), 138 (11), 93 (18), 50 (100). Found: $m/z$ 211.1562. Calcd for $C_{12}H_{21}NO_2$: 211.1573.

**4- and 5-Acetyl-1-dimethylaminomethyl-1-cyclohexenes (5e, as a Mixture):** $^1$H NMR ($CCl_4$, 90 MHz) $\delta$=1.64—2.73 (m, 7H), 2.15 (s, 3H), 2.76 (s, 2H), 5.58 (bs, 1H); IR ($CCl_4$) 2945, 1713, 1455, 1356, 1180, 1023 cm$^{-1}$; MS $m/z$ 181 ($M^+$, 64), 166 (5), 110 (13), 93 (17), 59 (100). Found: $m/z$ 181.1481. Calcd for $C_{11}H_{19}NO$: 181.1466. Anal. ($C_{11}H_{19}NO$) C, H, N.

**Dimethyl 4-Dimethylaminomethyl-1,4-cyclohexadiene-1,2-dicarboxylate (5f):** $^1$H NMR ($CCl_4$, 60 MHz) $\delta$=2.10 (s, 6H), 2.80 (s, 2H), 3.15 (bs, 4H), 4.80 (s, 6H), 5.65 (bs, 1H); IR ($CCl_4$) 2955, 2820, 1742, 1655, 1214, 1165, 1020 cm$^{-1}$. Anal. ($C_{13}H_{19}NO_4$) C, H, N.

**Dimethyl 4-Diethylaminomethyl-4-cyclohexene-*trans*-1,2-dicarboxylate (5g)** $^1$H NMR ($CCl_4$, 60 MHz) $\delta$=1.33 (6H, t, $J$=7 Hz), 2.2—2.8 (6H, m), 2.45 (4H, q, $J$=7 Hz), 2.85 (2H, bs), 3.70 (6H, s), 5.53 (1H, bs). Anal. ($C_{15}H_{23}NO_4$) C, H, N.

**Dimethyl 4-Diethylaminomethyl-4-cyclohexene-*cis*-1,2-dicarboxylate (5h):** $^1$H NMR ($CCl_4$, 60 MHz) $\delta$=0.96 (6H, t, $J$=7 Hz), 1.98—2.67 (10H, m), 2.80 (2H, bs), 3.77 (6H, s), 5.75 (1H, bs); MS $m/z$ 283 ($M^+$, 42), 268 (96), 151 (100). Anal. ($C_{15}H_{23}NO_4$) C, H, N.

**Dimethyl 4-Diethylaminomethyl-1,4-cyclohexadiene-1,2-dicarboxylate (5i):** $^1$H NMR ($CDCl_3$, 60 MHz) $\delta$=0.97 (6H, t, $J$=7 Hz), 1.77—2.83 (8H, m), 2.93 (2H, s), 3.63 (6H, s), 5.83

(1H, bs); MS *m/z* 281 ($M^+$, 51), 266 (25), 222 (100). Found: *m/z* 281.1623. Calcd for $C_{15}H_{23}NO_2$: 281.1672.

**Dimethyl 4,5-Bis(dimethylaminomethyl)-4-cyclohexene-*trans*-1,2-dicarboxylate (5j):** $^1H$ NMR ($CCl_4$, 60 MHz) $\delta$=2.05 (s, 12H), 2.80 (s, 4H), 2.9—3.2 (m, 6H), 3.6 (s, 6H); IR ($CCl_4$) 2975, 2355, 1738, 1457, 1197, 1172, 1012 $cm^{-1}$; MS *m/z* 312 ($M^+$, 1), 281 (19), 236 (17), 220 (85), 58 (100). Anal. ($C_{16}H_{28}N_2O_4$) C, H, N.

**Dimethyl 4,5-Bis(dimethylaminomethyl)-4-cyclohexene-*cis*-1,2-dicarboxylate (5k):** $^1H$ NMR ($CCl_4$, 60 MHz) $\delta$=2.1 (s, 12H), 2.8 (s, 4H), 2.9—3.3 (m, 6H), 3.7 (s, 6H); IR 2975, 2860, 1738, 1458, 1440, 1260, 1198, 1173, 1023, 785, 761 $cm^{-1}$; MS *m/z* 312 ($M^+$, 2), 280 (29), 268 (85), 252 (85), 192 (54), 108 (57), 58 (100). Anal. ($C_{16}H_{28}N_2O_4$) C, H, N.

**Methyl 3,4-Bis(dimethylaminomethyl)-3-cyclohexene-1-carboxylate (5l):** $^1H$ NMR ($CCl_4$, 60 MHz) $\delta$=2.05 (s, 12H), 2.91 (s, 4H), 2.95—3.2 (m, 7H), 3.6 (s, 3H); IR 2975, 2855, 1737, 1457, 1438, 1259, 1108, 1020 $cm^{-1}$; MS *m/z* 254 ($M^+$, 2), 166 (6), 195 (100), 134 (90), 117 (100). Anal. ($C_{14}H_{26}O_2N_2$) C, H, N.

**Ethyl 3,4-Bis(dimethylaminomethyl)-3-cyclohexene-1-carboxylate (5m):** $^1H$ NMR ($CDCl_3$, 90 MHz) $\delta$=1.28 (3H, t, *J*=7 Hz), 2.22 (12H, s), 2.0—2.8 (7H, m), 2.90 (4H, bs), 4.14 (2H, q, *J*=7 Hz). Anal. ($C_{14}H_{26}N_2O_2$) C, H, N.

**Synthesis of Methyl 3- and 4-[2,2-Bis(ethoxycarbonyl)-ethyl]-3-cyclohexene-1-carboxylates (6, as a Mixture).** After **5c** (50 mg, 0.25 mmol) was quaternized with excess methyl iodide in THF (5 ml) at room temperature, a THF solution (10 ml) of sodiomalonate, prepared from diethyl malonate (1.6 g, 10 mmol) and sodium hydride (50% in paraffin, 0.48 g, 10 mmol), was added in the presence of tetrakis(triphenylphosphine)palladium (20 mg) and the mixture was stirred for 18 h at room temperature. After usual hydrolysis workup, **6** (60 mg, 0.193 mmol) was isolated by TLC (hexane/ether 1:1, $R_f$ 0.3) in 77% yield. $^1H$ NMR ($CCl_4$, 60 MHz) $\delta$=1.2 (t, *J*=7 Hz, 6H), 2.1—3.2 (m, 10H), 3.6 (s, 3H), 4.1 (q, *J*=7 Hz, 4H), 5.4 (bs, 1H); IR ($CCl_4$) 2920, 2860, 1738, 1450, 1250, 1120, 1012 $cm^{-1}$; MS *m/z* 312 ($M^+$, 28), 267 (7), 239 (14), 201 (52), 119 (100). Anal. ($C_{14}H_{20}O_6$) C, H.

## References

1) B. Potthoff and E. Brietmaier, *Chem. Ber.*, **120**, 255 (1987); Y. S. Kulkarni and B. B. Snider, *Org. Prep. Proced. Int.*, **18**, 7 (1986); H. J. Reich, K. E. Yelm, and I. L. Reich, *J. Org. Chem.*, **49**, 3438 (1984); S.-S. P. Chou and C.-Y. Tsai, *ibid.*, **53**, 5305 (1988) and references cited therein.

2) A. Hosomi, M. Saito, and H. Sakurai, *Tetrahedron Lett.*, **21**, 355 (1980); A. Hosomi, H. Iguchi, J. Sasaki, and H. Sakurai, *ibid.*, **23**, 551 (1982); A. Hosomi, Y. Sakata, and H. Sakurai, *ibid.*, **26**, 5175 (1985); A. Hosomi, *Acc. Chem. Res.*, **21**, 200 (1988); A. Hosomi, T. Masunari, Y. Tominaga, T. Yanagi, and M. Hojo, *Tetrahedron Lett.*, **31**, 6201 (1990).

3) A. Hosomi, K. Otaka, and H. Sakurai, *Tetrahedron Lett.*, **27**, 2881 (1986); A. Hosomi, K. Hoashi, S. Kohra, Y. Tominaga, K. Otaka, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, **1987**, 570.

4) T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 1121 (1966).