Studies on Lewis Acid-Mediated Intramolecular Cyclization Reactions of Allene–Ene Systems

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Allene compounds have received much attention so far in regard to their unique chemical reactivity and specific stereochemical behavior, which arises from the structural characteristics of allenes; thus have been widely employed as a carbon three unit in organic synthesis.1–11) Currently, much interest is being focused on the transition metal- or Lewis acid-catalyzed reactions of allenes, and our attention is paid to the use of the chirality of allenes in asymmetric synthesis.12,13) We describe in this report our recent works on allene chemistry, in particular, the unprecedented intramolecular [2+2]cycloaddition reactions16–21) of inactivated allene and ene functionality by the assistance of Lewis acids. A paper concerning Lewis acid-mediated [2+2]cycloaddition reactions of activated allenes (conjugated allenic esters) has appeared22) however there has been no intramolecular Lewis acid-mediated [2+2] cycloaddition of simple allenes and enes.23)

Previously, we reported Lewis acid-catalyzed asymmetric intramolecular ene reactions of 1,7-diene systems bearing a chiral sulfinyl group as a chiral electrophile. Further detailed studies on these reactions reveal that the mode of the cyclization depends on the activity of the electrophilic functional groups in the dienophiles and on the Lewis acid used.24) Therefore we have taken much interest in the mode of cyclization of allene–ene systems, namely ene, hetero Diels–Alder, and/or [2+2]cycloaddition reactions, by the assistance of Lewis acids.

Allene–ene systems were constructed in the following way. Lithium or magnesium acetylides of 2a–c attacked aldehyde in 3-methylcitronellal (1) derived from citral to give propargylic alcohol derivatives 3a–c in excellent yields (83–96%). The corresponding acetates 4a–c of the alcohols were reacted with methyl- or phenylmagnesium bromide in the presence of copper(I) iodide to afford allenyl compounds 5a–d in fairly good yields.

Allenylmalonate was prepared in the usual way. An allenyl part 14 was prepared starting from 1,3-propanediol (6). The selective monosilylation of the diol25) with tert-butyl(dimethyl)silyl chloride (TBDPSCI), followed by Swern oxidation, gave 3-(tert-butyl(dimethyl)silyloxy)propanal (8). The addition of 1-propynylmagnesium bromide to the aldehyde in 8 afforded a propargylic alcohol derivative 9 in good yield. The acetate 10 of the alcohol 9 was reacted with methylmagnesium bromide in the presence of copper(I) iodide to furnish allene 11 in 90% yield. Removal of the silyl group in 11 by treatment with tetrabutylammonium fluoride (TBAF), followed by tosylation with TsCl-triethylamine and iodination of the tosylate 13 with NaI, gave 5-methyl-3,4-hexadienyl iodide (14). Alkylation of dimethyl malonate with 3-methyl-2-butenyl bromide was carried out in the presence of sodium hydride to produce dimethyl (3-methyl-2-buten-1-yl)propanedioate (15)26) in 89% yield. The reaction of 15 with allenyl iodide 14 using sodium hydride as a base gave an allene–ene compound, dimethyl (3-methyl-2-butenyl)(5-methyl-3,4-hexadienyl)propanedioate (16), in 47% yield.

Studies on Lewis acid-mediated cyclization reactions of the allenyl compounds 5a–d were undertaken under various reaction conditions using typical Lewis acids such as ethyldimethylaluminum chloride (EtAlCl2), diethylaluminum chloride (Et2AlCl), titanium tetrachloride (TiCl4), boron trifluoride etherate (BF3·OEt2), zinc chloride etherate (ZnCl2·OEt2), and zinc bromide (ZnBr2). Upon treatment with EtAlCl2 (1.5
or 3.0 eq) at −78 °C, the allenyl compound 5b unexpectedly underwent a [2+2]cycloaddition reaction to give 8-isopropylidene-3,3,7,7-tetramethylbicyclo[4.2.0]octane (17) in a fairly good yield, as listed in Table 1.

However, polymerization occurred upon treatment with EtAlCl2 (1.5 eq) at 0 °C, whereas the reaction using weaker acids, ZnBr2 or BF3· OEt2 (3.0 eq), at room temperature recovered the starting material.

Thus, the reactions of 5b with more acidic Lewis acids under milder reaction conditions gave a [2+2]cyclization product, whereas the reactions under more severe reaction conditions (at a much higher reaction temperature) resulted in polymerization of the starting material, or the reactions with weaker acids provided no cyclization product with recovery of the starting material.

Lewis acid-mediated reactions of other allene–ene compounds 5a,c, and d provided no cycloaddition product, presumably due to the high reactivity of the allenyl system 5a resulting in polymerization, the lability of the allene 5c leading to decomposition, and the inaccessibility of 5d by steric hindrance recovering the starting material.

Similarly, the Lewis acid-mediated reactions of another allenyl compound 16 provided the corresponding [2+2]cycloaddition product, dimethyl 8,8-dimethyl-7-isopropylidenebicyclo[4.2.0]octane-3,3-dicarboxylate (18) in considerably good yield, as shown in Table 1; however, the reactions were dependent upon the Lewis acids employed, much different from that of 5.

Upon treatment with more weakly acidic Lewis acids such as TiCl4, ZnCl2· OEt2, or BF3· OEt2 at room temperature (r.t.), the allene–ene compound 16 was converted into a [2+2]cycloaddition product 18 in 87, 77, and 92% yield, respectively. In contrast to the previous cases mentioned above, upon mediation with more acidic Lewis acids (3.0 eq) such as EtAlCl2 (0 °C), Et2AlCl (r.t.) or ZnBr2 (r.t.), the allene–ene compound 16 underwent no desired cycloaddition, recovering the starting material. Upon treatment of 16 with stronger Lewis acid (EtAlCl2) at r.t., however, polymerization occurred.

The results thus obtained are rationalized as follows. One of the π-bonds in the allenes 5b and 16 is activated by the assistance of the Lewis acid used, generating more cationic β-carbon centers, and the intramolecular ene parts in 5b and 16 attack the cationic β-carbon of the allenes to give [2+2]cycloaddition products 17 and 18. The existence of a quaternary carbon close to the reaction center (allene) in 5b makes the activation by the Lewis acid sterically rather inaccessible, compared with the case of 16. However, in the case of the 1,7-allene–ene system 16 bearing ester groups, the preference of coordination of the ester carbonyl groups to the more acidic Lewis acids provides large steric interference by the two methoxy groups of the esters owing to the conformational fixation resulting from the coordination, thus giving the recovered starting material without any cycloaddition product. With weaker acids, insufficient coordination of the two ester carbonyl groups allows steric access from the allene to the ene part, giving a [2+2]cycloaddition product.

In conclusion, the [2+2]cycloaddition reactions of 1,7-allene–ene systems were largely dependent upon the acidity of the Lewis acid used and the reaction temperature. The simple 1,7-allene–ene compound 5b without any functional group underwent a [2+2]cycloaddition reaction upon treatment with more acidic Lewis acid (EtAlCl2) at milder reaction conditions (at −78 °C) in dichloromethane, however, poly-

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Lewis acid (eq)</th>
<th>Solvent</th>
<th>Reaction temp. (°C)</th>
<th>Reaction time (h)</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b</td>
<td>EtAlCl2 (1.5)</td>
<td>CH2Cl2</td>
<td>−78</td>
<td>0.5</td>
<td>82 (17)</td>
</tr>
<tr>
<td>5b</td>
<td>EtAlCl2 (3.0)</td>
<td>CH2Cl2</td>
<td>−78</td>
<td>1</td>
<td>93 (17)</td>
</tr>
<tr>
<td>5b</td>
<td>Et2AlCl (1.5)</td>
<td>Toluene</td>
<td>−78</td>
<td>1</td>
<td>79 (17)</td>
</tr>
<tr>
<td>16</td>
<td>TiCl4 (3.0)</td>
<td>CH2Cl2</td>
<td>r.t.</td>
<td>22</td>
<td>87 (18)</td>
</tr>
<tr>
<td>16</td>
<td>ZnCl2· OEt2 (3.0)</td>
<td>CH2Cl2</td>
<td>r.t.</td>
<td>24</td>
<td>77 (18)</td>
</tr>
<tr>
<td>16</td>
<td>BF3· OEt2 (7.0)</td>
<td>CH2Cl2</td>
<td>r.t.</td>
<td>23</td>
<td>92 (18)</td>
</tr>
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</table>
merization occurred at a higher reaction temperature (0 °C). On the other hand, the 1,7-allene–ene system 16 bearing ester groups gave a [2 + 2]cycloaddition product upon treatment with rather weaker acids (3.0–7.0 eq) such as TiCl₄, ZnCl₂, ZnCl₂·2Et₂O, and BF₃·OEt₂ at r.t., whereas with more acidic Lewis acids (3.0 eq) such as EtAlCl₂ (0 °C), Et₂AlCl (r.t.), and ZnBr₂ (r.t.), no reaction occurred with recovery of the starting material.

Experimental

Infrared (IR) spectra were obtained in the indicated state with a JASCO DRIFTS fourier-transform IR spectrometer. NMR spectra were determined in the indicated solvent with a JOEL EX-270 [1H-NMR: 270 MHz high-resolution NMR spectrometer; chemical shifts are given in ppm from tetramethylsilane as an internal standard. Splitting patterns are designated as s: singlet, br s: broad singlet, d: doublet, dd: double of doublet, dt: triple of doublet, t: triplet, q: quartet of triplet, m: multiplet. Mass spectra were taken on a JEOL JMS-DX 303/JMA-DA 5000 system. Flash column chromatography was performed with Merck Silica gel 60 (230–400 mesh).

5,5,9-Trimethyl-8-decen-1-yn-3-ol (3a)

A 0.5 m tetrahydrofuran (THF) solution of ethynylmagnesium bromide (40.9 ml, 20.45 mmol) was carried out using a mesh). Column chromatography was performed with Merck Silica gel 60 (230–400 mesh).

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was added to the above solution at 0 °C, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was allowed to warm to room temperature, was diluted with ether, then the solution was washed with saturated aqueous NaHCO3 and saturated aqueous NaCl, dried over anhydrous MgSO4, and concentrated in vacuo. The crude product was subjected to flash column chromatography (ether–hexane, 1:1) to give 7 (413, 100% yield).

7: IR (neat, cm−1): 3260 (alcohol), 1580 (aromatic). 1H-NMR (CDCl3): δ: 1.03 (9H, s, C(CH3)3), 1.77 (2H, t, J = 5.7 Hz, CH2CH2), 2.33 (1H, m, OH), 3.58—3.92 (4H, m, CH2CH2), 7.04—7.65 (10H, m, CH×2). MS m/z: 314 (M+).

3-(tert-Butyldiphenylsilyl)-1-propanal (8) A solution of dimethyl sulfoxide (0.68 ml, 9.54 mmol) in dichloromethane (10 ml) was added to a solution of triethylamine (1.87 ml, 13.40 mmol) in dichloromethane (15 ml) at room temperature for 3.5 h. The reaction mixture was subjected to flash column chromatography (ether–hexane, 1:4) to give 8 (948 mg, 95% yield).

8: IR (neat, cm−1): 1720 (aldehyde), 1580 (aromatic). 1H-NMR (CDCl3) δ: 1.04 (9H, s, C(CH3)3), 2.57 (2H, dt, J = 5.8, 1.8 Hz, CH2O), 4.00 (2H, t, J = 5.8 Hz, CH2O), 7.16—7.81 (10H, m, CH×2), 9.75 (1H, t, J = 1.8 Hz, CHO). MS m/z: 312. Exact mass determination: 312.1499 (Calcd C17H14O2Si: 312.1546).

3-Acetoxy-1-(tert-butyldiphenylsilyl)-4-hexyne-3-ol (9) A 0.5 M THF solution of 1-propynylmagnesium bromide (19.2 ml, 9.60 mmol) was added at 0 °C to a solution of 8 (2.00 g, 6.40 mmol) in THF (19.2 ml), and the reaction mixture was stirred at room temperature for 3.5 h. The reaction mixture was diluted with ether, and the solution was washed with 20% aqueous NaHCl and saturated aqueous NaCl, dried over anhydrous MgSO4, and concentrated in vacuo. The crude product was subjected to flash column chromatography (ether–hexane, 1:4) to give 9 (2.14 g, 95% yield).

9: IR (neat, cm−1): 3400 (alcohol), 2240 (acetylene), 1590 (aromatic). 1H-NMR (CDCl3) δ: 1.07 (9H, s, C(CH3)3), 1.62—2.17 (5H, m, CH2CH2CH2CH2C), 3.05 (1H, d, J = 5.6 Hz, OH), 3.87 (2H, t, J = 5.2 Hz, CH2O), 4.65 (1H, br s, CHO), 7.12—7.82 (10H, m, CH×2). MS m/z: 352 (M+).

Exact mass determination: 352.1812 (Calcd C23H26O2Si: 352.1859).

5b. Lewis Acid–Mediated Intramolecular Cyclization Reactions of 16. A 50 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar, and containing sodium hydride (50% oil dispersion in mineral oil, 1.00 mmol) was flushed with argon, and concentrated in vacuo. The crude product was subjected to flash column chromatography (ether–hexane, 1:1) to give compound 16 (118 g, 47% yield).

16: IR (neat, cm−1): 1790 (allene), 1740 (ester), 1590 (aromatic). 1H-NMR (CDCl3) δ: 0.87—1.24 (12H, m, C(CH3)2×2), 1.80—1.99 (4H, m, CH3×2), 2.60 (2H, d, J = 7.1 Hz, CH2CH3), 3.78 (6H, s, C(CH3)2×2), 4.71—5.14 (2H, m, CH=C=CH). MS m/z: 294 (M+).

Exact mass determination: 294.1876 (Calcd C17H26O2: 294.1831).

4-Lithio-6-(tert-butyldiphenylsilyl)-2,3-hexadiene (11) A 1.0 M THF solution of TBAF (6.9 ml, 6.90 mmol) was added at room temperature to a solution of 11 (1.21 g, 3.451 mmol) in THF (10 ml) and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with ether, then the solution was washed with water and saturated aqueous NaCl, dried over anhydrous MgSO4, and concentrated in vacuo. The crude product of 5-bromo-3,4-hexadien-1-ol (12) was used in the next step without further purification. The crude product 13 obtained above was dissolved in acetone (30 ml), then NaI (1.4 ml, 34.51 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 21 h, then filtered. The filtrate was concentrated in vacuo. The crude product was subjected to flash column chromatography (hexane) to give 14 (174 mg, 23% yield from 11).

14: IR (neat, cm−1): 1970 (allene). 1H-NMR (CDCl3) δ: 1.68 (6H, d, J = 2.3 Hz, C(CH3)2×2), 2.45 (2H, t, J = 7.5, 6.9 Hz, CH2CH3), 3.15 (2H, t, J = 7.0 Hz, CH3), 4.62—5.18 (1H, m, CH=C=CH). MS m/z: 222 (M+).

Exact mass determination: 221.9961 (Calcd C17H17I: 221.9906).

5. Lewis Acid–Mediated Intramolecular Cyclization Reactions of 5b. General Procedure A dry 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar was flushed with argon and maintained under a positive pressure of argon. A 1.0 M hexane solution of Lewis acid was added at −78 °C to a solution of 5b (100 mg, 0.49 mmol) in solvent (10 ml). The reaction mixture was stirred under the conditions listed in Table 1, then diluted with ether; the solution was then washed with saturated aqueous NaHCO3 and saturated aqueous NaCl, dried over anhydrous MgSO4, and concentrated in vacuo. The crude product was subjected to flash column chromatography (hexane) to give 8-(1-methylhexylidene)-3,3,7-tetramethylenecyclooctane (17). The yields of the product are summarized in Table 1.

17: IR (neat, cm−1): 1680 (olefin). 1H-NMR (CDCl3) δ: 0.87—1.00 (12H, m, C(CH3)2×2), 1.07—1.27 (6H, m, CH3×2), 1.29—1.46 (2H, m, CH×2), 1.54 (6H, s, C(CH3)2×2). MS m/z: 206 (M+).

Exact mass determination: 206.1197 (Calcd C17H26O: 206.2067).

6. Lewis–Meditated Intramolecular Cyclization Reactions of 16. General Procedure A dry 15 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar was flushed with argon and maintained under a positive pressure of argon. A solution of Lewis acid in dichloromethane (1 ml) was added at 0 °C to a solution of 16 (30 mg, 0.10 mmol) in dichloromethane (2 ml). The reaction mixture was stirred under the conditions listed in Table 1, then diluted with ether; the solution was then washed with saturated aqueous NaHCO3 and saturated aqueous NaCl, dried over anhydrous MgSO4, and concentrated in vacuo. The crude product was subjected to flash column chromatography (ether–hexane, 1:1) to give dimethyl [8,8-dimethy1-1-(1-methylhexylidene)cyclo[4.2.0]octane] 3,3-di-carboxylate (18). The yields of the product are summarized in Table 1.

18: IR (neat, cm−1): 1740 (ester), 1680 (olefin). 1H-NMR (CDCl3) δ: 0.92—1.05 (8H, m, C(CH3)2×2), 1.13—1.40 (2H, m, CH×2),
1.58 (6H, s, C=CH(CH₃)₂), 1.80—2.55 (4H, m, C(CH₂)₂), 3.73 (6H, s, C(O₂CH₃)₂). MS m/z: 294 (M⁺). Exact mass determination: 294.1863 (Calcd C₁₇H₂₆O₄: 294.1831).

References
22) Hiroi K., Watanabe T., to be published in due course.