Chelation Control through the Coordination of Lewis Acids to an Acetylenic π-Bond

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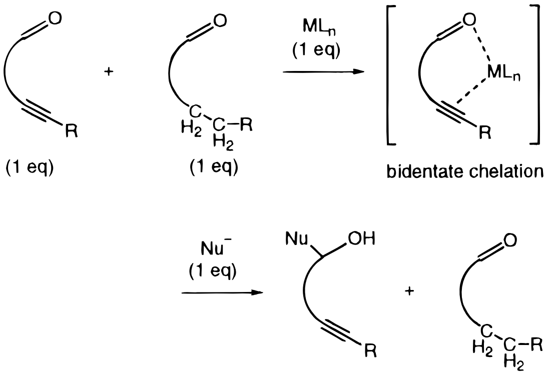
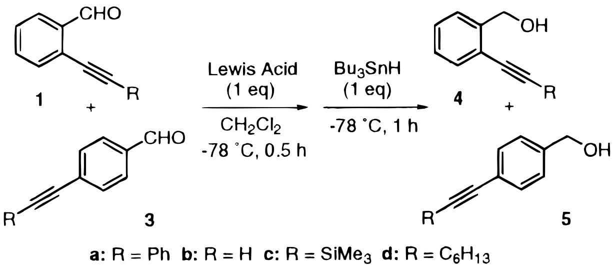
The Lewis acid-mediated chelation control is one of the most fundamental and practically important concepts in modern organic chemistry.[1] It is well accepted that the chelating controlled reaction proceeds through the coordination of a Lewis acid to *a lone pair of heteroatoms*, such as an oxygen of aldehydes and a nitrogen atom of imines. To the best of our knowledge, there is no precedent for a synthetically useful level of the chelation-controlled reaction which proceeds via the coordination of Lewis acids to *π-electrons of C−C multiple bonds*.[2] We wish to report the first example for the regio- and chemoselective reactions which are most probably controlled by the chelation to π-electrons of alkynes (eq 1).

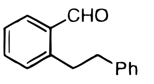


(1)

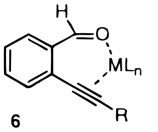
The reaction of a 1:1 mixture of **1a** (1 equiv) and **2** (1 equiv) with Bu_3SnH (1 equiv) in the presence of $GaCl_3$ (1 equiv) in CH_2Cl_2 at −78 °C gave **4a** in 73% yield along with the 2-(phenylethyl)benzyl alcohol in 19%. The remarkable chemoselectivity suggested that the bidentate chelation between the carbonyl oxygen and alkyne of **1a**, as shown in eq 1, would enhance the reactivity of the aldehyde of **1a** in comparison with that of **2**. However, there is a possibility that the chemoselectivity is due to the electronic effect of the alkyne group, since it is less sterically demanding and more electron-withdrawing than the phenylethyl group of **2**. Accordingly, we next examined the reaction of an equimolar mixture of **1** and its para-isomer **3** with Bu_3SnH (1 equiv) in the presence of Lewis acids (1 equiv). It was thought that the electronic effect of the alkyne groups upon the aldehyde group of **1** would be nearly equal to that of **3** and sterically the aldehyde of **1** is more crowded than that of **3** (eq 2). The results are summarized in Table 1. High chemoselectivity was observed in the Bu_3SnH reduction of **1a** and **3a** with $GaCl_3$; **4a** was obtained in 63% yield along with the recovered **1a** (32% yield), and **5a** was obtained only in 2% yield along with the recovered **3a** (92%) (entry 1).[3] Utilization of Ph_3SnH instead of Bu_3SnH elevated the selectivity up to 43:1 (entry 2). The reactions promoted by aluminum Lewis acids also tended to afford **4a** as a major product though the selectivities were lower than those of the $GaCl_3$ mediated reactions (entries 3−7).[4] The selective reductions were also observed with the starting materials having other alkynyl groups (entries 8−12). In all the above reactions, the material balance of substrates was high; large amounts of **3** (98∼60%) were recovered, and small amounts (38∼8%) of **1** was recovered in the case where the yields of **4** were not necessary high (for example, entries 3−11). Accordingly, the selective activation of **1** is ascribed most probably to the preferred formation of the bidentate chelation **6** rather than the monodentate coordination **7**.[5−8]



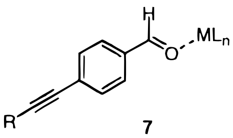
(2)



2



6



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However, all of the reactivity data might be explained by a strong electron-withdrawing effect of the alkyne: the ortho-isomer

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[1] For reviews, see: (a) Yamamoto, H. *Lewis Acid Chemistry: A Practical Approach*; Oxford University Press: Oxford, 1999. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (c) Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, 1996. (d) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 283−324.

[2] The Lewis basicity of the lone pair of imine's nitrogen and aldehyde's oxygen atom is, in general, stronger than that of the π-electron of C−C double and triple bonds. Accordingly it is reasonable that all the previous examples for the synthetically useful chelation controlled reactions are concerning the coordination to lone pair electrons. The interaction of alkynes with Lewis acids was studied by NMR and IR spectroscopy, see: (a) Hogeveen, H.; Kok, D. M. *Tetrahedron Lett.* **1980**, *21*, 659−662. (b) Perkampus, H. H.; Weiss, W. *Z. Naturforsch.* **1974**, *29b*, 61−64.

[3] It was difficult to obtain the product ratio at lower conversion, since the reduction was very rapid. Accordingly, the reduction using smaller amounts of Bu_3SnH (0.2 and 0.4 equiv) was carried out. The ratios of **4a**/**5a**, determined both by NMR and by GC analysis, were essentially identical with those shown in entry 1.

[4] The $BF_3{\cdot}OEt_2$-promoted reduction of a 1:1 mixture of **1a** and **3a** gave a 62:38 mixture of **4a** and **5a** in 52% combined yield.

[5] Several examples of aluminum pentacoordinate complexes have been isolated and characterized, see: (a) Heitsch, C. W.; Nordman, C. E.; Parry, P. W. *Inorg. Chem.* **1963**, *2*, 508. (b) Palenick, G. *Acta Crystallogr.* **1964**, *17*, 1573−1580. (c) Beattie, I. R.; Ozin, G. A. *J. Chem. Soc. A* **1968**, 2373−2377. (d) von Vliet, M. R. P.; Buysingh, P.; von Koten, G.; Vrieze, K.; Kojic-Prodic, B.; Spek, A. L. *Organometallics* **1985**, *4*, 1701−1707. (e) Bennett, F. R.; Elms, F. M.; Gardiner, M. G.; Koutsantonis, G. A.; Raston, C. L.; Roberts, N. K. *Organometallics* **1992**, *11*, 1457−1459. (f) Muller, G.; Lachmann, J.; Rufinska, A. *Organometallics* **1992**, *11*, 2970−2972. (g) Fryzuk, M. D.; Giesbrecht, G. R.; Olovsson, G.; Rettig, S. J. *Organometallics* **1996**, *15*, 4832−4841.

[6] Aluminum and gallium Lewis acids are known to act as bidntate Lewis acids. For aluminum Lewis acid, see: (a) Maruoka, K.; Ooi, T. *Chem. Eur. J.* **1999**, *5*, 829−833. (b) Ooi, T.; Kagoshima, N.; Ichikawa, H.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 3328−3333. (c) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457−4460. (d) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. For gallium Lewis acid, see: (e) Ooi, T.; Morikawa, J.; Ichikawa, H.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 5881−5884.

[7] The hypercoodinated aluminum Lewis acids have been used for asymmetric reactions; see: (a) Heller, D. P.; Goldberg, D. R.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 10551−10552. (b) Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713−11714. (c) Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441−442.

[8] Recently, the $GaCl_3$-mediated carbogallation of alkynes was reported, see: (a) Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* **1999**, *121*, 4074−4075. (b) Yamaguchi, M.; Sotokawa, T.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1997**, 743−744. (c) Yamaguchi, M.; Kido, Y.; Hayashi, A.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1313−1315. (d) Yamaguchi, M.; Hayashi, A.; Hirama, M. *Chem. Lett.* **1995**, 1093−1094.

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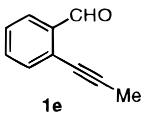
Table 1. Chelation-Induced Reduction of a Mixture of **1** and **3**[a]

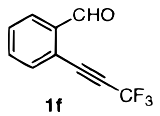
	substrate				yield		yield		
entry	R	**1**	**3**	Lewis acid	**4**	%[b]	**5**	%[b]	ratio **4**:**5**
1	Ph	**1a**	**3a**	$GaCl_3$	**4a**	63	**5a**	2	>30:1
2[c]	Ph	**1a**	**3a**	$GaCl_3$	**4a**	85	**5a**	2	>40:1
3	Ph	**1a**	**3a**	$AlBr_3$	**4a**	40	**5a**	26	1.5:1
4	Ph	**1a**	**3a**	$MeAlCl_2$	**4a**	61	**5a**	16	4:1
5	Ph	**1a**	**3a**	$EtAlCl_2$	**4a**	64	**5a**	17	4:1
6	Ph	**1a**	**3a**	Et_2AlCl	**4a**	67	**5a**	9	7:1
7	Ph	**1a**	**3a**	Me_2AlOPh	**4a**	56	**5a**	6	9:1
8	H	**1b**	**3b**	Et_2AlCl	**4b**	61	**5b**	8	8:1
9	H	**1b**	**3b**	$GaCl_3$	**4b**	49	**5b**	7	7:1
10	C_6H_{13}	**1c**	**3c**	$GaCl_3$	**4c**	66	**5c**	18	4:1
11	$SiMe_3$	**1d**	**3d**	$GaCl_3$	**4d**	59	**5d**	6	10:1
12[c]	$SiMe_3$	**1d**	**3d**	$GaCl_3$	**4d**	89	**5d**	7	13:1

[a] Equimolar mixtures of **1** and **3** were treated with Lewis acids (1 equiv) in CH_2Cl_2 at −78 °C for 30 min, followed by addition of Bu_3SnH (1 equiv), except where otherwise indicated. [b] Determined by ^1H NMR spectra of the reaction products using *p*-xylene as an internal standard. [c] A mixture of **1** and **3** was reduced with Ph_3SnH.

1, in which the alkyne is proximal to aldehyde, might be more reactive than the para-counterpart **3**. The $GaCl_3$-mediated reduction of a 1:1 mixture of **1e** and **1f** under the same reaction conditions as above gave a 1.9:1 mixture of **4e** (R = Me) and **4f** (R = CF_3) in 99% combined yield. If the electron-withdrawing effect of the alkyne is operative, **1f** should be reduced preferentially. Therefore, the reactivity difference observed in Table 1 is not due to the inductive effect of alkyne.[9]

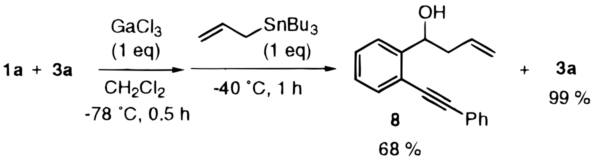


1e



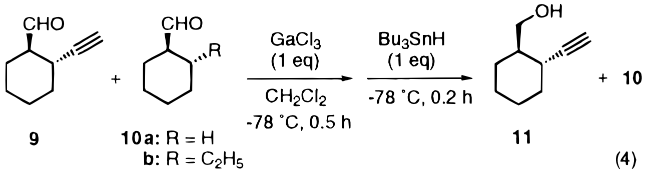
1f

The strong chelation effect of $GaCl_3$ upon alkyne π-bond was found also in the allylation with allyltributyltin. A 1:1 mixture of **1a** and **3a** was treated with 1 equiv of allyltin in the presence of 1 equiv of $GaCl_3$ under the same reaction conditions as above. The allylation product **8** was obtained in 68% yield together with the recovered **1a** (29%), and **3a** was recovered quantitatively (eq 3).

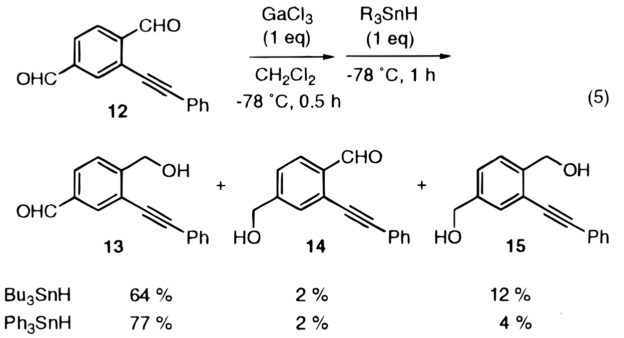


(3)

The above high chemo- and regioselectivities were obtained for the aromatic aldehydes. To know whether the present chelation effect can be extended to aliphatic aldehydes, we investigated the reaction of a 1:1 mixture of 2-ethynyl-1-cyclohexanecarboxaldehyde **9** and cyclohexanecarboxaldehyde **10a** with Bu_3SnH under the same reaction conditions as above (eq 4). Again, extremely high chemoselectivity was observed; the reduced alcohol **11** was produced in 91% yield, and none of cyclohexylmethanol, derived from **10a**, was detected at all. The starting material **10a** was recovered nearly quantitatively. Furthermore, we compared the reactivity of **9** and 2-ethylcyclohexanecarboxaldehyde **10b**. Here also, the alcohol **11** was obtained in 81% yield and none of the 2-ethyl-1-(hydroxymethyl)cyclohexane was detected at all.



Finally, the regioselective reduction of phenylethynyl-substituted terephthaldicarboxaldehyde **12** was examined (eq 5). The formyl group located on the ortho-position to the alkynyl group was reduced with Bu_3SnH selectively to give the reduction product **13** predominantly being accompanied with the alcohol **14** and the bis-reduction product **15** in 2% and 12%, respectively. The selectivity was improved when the reaction was reduced with Ph_3SnH. The chemical yield of **13** was increased to 77% and the formation of **15** was reduced to 4% yield.



The high chemo- and regioselectivities observed here are most probably due to the effective bidentate chelation of Lewis acids to alkynyl groups. We believe that the present finding will provide a conceptual advance in chelation-controlled chemistry, and further extension in this area is going on in our laboratories.

Supporting Information Available: Spectroscopic and analytical data for **4a**−**f**, **5a**−**d**, **8**, **11**, and **13**−**15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) One referee mentioned the rate difference between **1a** and **2**: it is only 4:1, while the difference between **1a** and **3a** is 32:1. The following results clearly indicate that the presence of an electron-donating group at the ortho position facilitates the reduction. Accordingly, the rate difference of **1a**/**2** is lower than that of **1a**/**3a**.