J|A|C|S
COMMUNICATIONS

Published on Web 09/27/2002

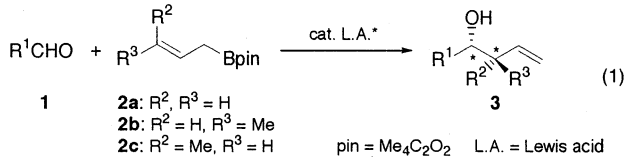
# Acceleration Effect of Lewis Acid in Allylboration of Aldehydes: Catalytic, Regiospecific, Diastereospecific, and Enantioselective Synthesis of Homoallyl Alcohols†

Tatsuo Ishiyama,* Taka-aki Ahiko, and Norio Miyaura*

*Contribution from the Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan*

Received July 29, 2002

Lewis acid-catalyzed addition of allylsilicon and -tin reagents to carbonyl compounds is a most important and powerful tool to construct a regio- and stereodefined carbon framework.[1] The reactions generally proceed in an $S_E2'$ manner through an acyclic transition state to provide *syn*-homoallyl alcohols regiospecifically and diastereoselectively when using $\gamma$-substituted reagents. Another efficient candidate for the synthesis of regio- and stereodefined homoallyl alcohols is the addition of allylboron reagents, which takes place regio- and diastereospecifically through a chairlike six-membered cyclic transition state in the absence of a Lewis acid.[2] Namely, one major advantage of the allylboration over the allylsilation and -stannation is that both *syn*- and *anti*-homoallyl alcohols can be obtained with high isomeric purities from (*Z*)- and (*E*)-allylboron reagents, respectively.[3] On the other hand, allylsilation and -stannation are superior to allylboration with respect to enantioselective synthesis because the former reactions only require a catalytic amount of a chiral source.[4] We presumed that if a Lewis acid could catalyze allylboration while maintaining the chairlike six-membered cyclic transition state, the reaction would allow a *catalytic*, *regiospecific*, *diastereospecific*, and *enantioselective* approach to homoallyl alcohols.[5] However, to our knowledge, there is no report concerning the effects of Lewis acids in the allylboration of carbonyl compounds.[6] We disclose herein the acceleration effect of Lewis acids in the regio- and diastereospecific addition of pinacol allylboronic esters (**2**) to aldehydes (**1**) to give the corresponding homoallyl alcohols (**3**), as well as the preliminary results of an extension of the protocol toward catalytic enantioselective reactions (eq 1).



(1)

Our initial studies were focused on elucidating the acceleration effect of a Lewis acid. The allylboration of benzaldehyde (1.0 mmol) with pinacol 2-propenylboronic ester (**2a**) (1.1 mmol) in the presence of a Lewis acid (0.1 mmol) in toluene (6 mL) at −78 °C for 16 h was followed by treatment of the mixture with DIBAH[7] (2.0 mmol) at −78 °C for 1 h to trap an unreacted aldehyde. To our surprise, most representative Lewis acids exhibited high catalytic activity. Although the addition did not proceed at all in the absence of a Lewis acid, $AlCl_3$ (88%), $Sc(OTf)_3$ (80%), $TiCl_4$ (63%), $BF_3{\cdot}OEt_2$ (56%), and $SnCl_4$ (30%) all catalyzed the reaction to afford the corresponding homoallyl alcohol. The high catalytic activity of $Sc(OTf)_3$ is notable from the view of practical usefulness, because it can be handled in air without special precautions.[8] A series of the reaction was also investigated in $CH_2Cl_2$, and the yields were comparable to those of the reaction in toluene.

***Table 1.*** Lewis Acid-Catalyzed Allylboration of Aldehydes with **2a** ($R^2$, $R^3$ = H) (eq 1)[a]

| | | yield/%[b] | |
|---|---|---|---|
| entry | aldehyde **1** | $AlCl_3$ | $Sc(OTf)_3$ |
| 1 | 4-$CF_3C_6H_4CHO$ | 80 (16 h) | 69 (16 h) |
| 2 | PhCHO | 88 (16 h) | 80 (16 h) |
| 3 | 4-$MeC_6H_4CHO$ | 47 (24 h) | 62 (24 h) |
| 4 | 4-$MeOC_6H_4CHO$ | 82 (36 h) | 84 (36 h) |
| 5 | *n*-$C_{10}H_{21}CHO$ | 54 (16 h) | 73 (16 h) |
| 6 | *c*-$C_6H_{11}CHO$ | 48 (16 h) | 74 (16 h) |
| 7 | (*E*)-PhCH=CHCHO | 69 (24 h) | 74 (24 h) |

[a] Allylboration of an aldehyde (1.0 mmol) with **2a** (1.1 mmol) in the presence of a Lewis acid (0.1 mmol) in toluene (6 mL) at −78 °C for the period shown in the table was followed by treatment of the resulting mixture with DIBAH (2.0 mmol) at the temperature for 1 h. [b] Isolated yields based on aldehydes.

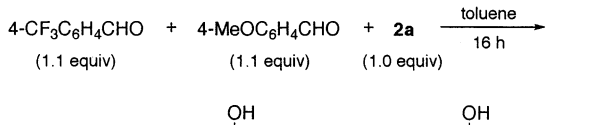
To examine the scope and limitations of the Lewis acid-catalyzed allylboration, the addition of **2a** to representative **1** was carried out in the presence of an $AlCl_3$ or a $Sc(OTf)_3$ catalyst. The results are summarized in Table 1. Either aromatic (entries 1−4) or aliphatic (entries 5 and 6) **1** are viable substrates to produce the corresponding **3** in high yields. $\alpha,\beta$-Unsaturated **1** also underwent the 1,2-addition selectively (entry 7). The addition catalyzed by $Sc(OTf)_3$ provided better yields than that by $AlCl_3$ in most cases. Especially, the $Sc(OTf)_3$ catalyst was effective for the reaction of sterically hindered **1** (entry 6). Electron-poor **1** (entry 1) exhibited higher reactivity than electron-rich **1** (entry 4), the tendency of which is similar to that in uncatalyzed allylboration.[2] All attempts at the reaction of pivalaldehyde were unsuccessful presumably due to its large steric hindrance.

An example of the synthetic utility of the present method is shown in eq 2. When a mixture of 4-(trifluoromethyl)benzaldehyde (1.1 mmol) and 4-methoxybenzaldehyde (1.1 mmol) was allowed to react with **2a** (1.0 mmol) in the absence of a Lewis acid in toluene (6 mL) at room temperature for 16 h, two homoallyl alcohols resulting from the reaction with both aldehydes were obtained in a ratio of 81:19. On the other hand, the $AlCl_3$- or $Sc(OTf)_3$-catalyzed reaction at −78 °C provided an adduct of 4-(trifluoromethyl)-benzaldehyde as the sole product. The results indicate the possibility that stepwise transformations of formyl groups exhibiting different

* Corresponding author. E-mail: ishiyama@org-mc.eng.hokudai.ac.jp.
† After our manuscript was submitted, we became aware of a related study by Hall: Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*. Published ASAP, September 6, 2002.

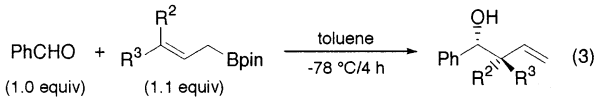

**10.1021/ja0210345 CCC: $22.00** 

electrophilicity in a molecule can be completely controlled by the present method.




none (r.t.): 89% (81:19)
$AlCl_3$ (10 mol%/-78 °C): 57% (99:1)
$Sc(OTf)_3$ (10 mol%/-78 °C): 72% (99:1)

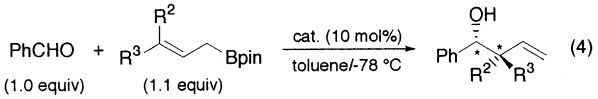
Regio- and diastereochemistry of the $AlCl_3$- or $Sc(OTf)_3$-catalyzed allylboration is shown in eq 3. As expected, the addition of pinacol (*E*)- or (*Z*)-2-butenylboronic esters (**2b** or **2c**) to benzaldehyde occurred regio- and diastereospecifically to yield isomerically pure *anti*- and *syn*-homoallyl alcohols from **2b** and **2c**, respectively. The results are quite different from those reported in the allylsilation and -stannation.[1] Although we have not studied the reaction mechanism yet, the observed diastereochemistry strongly suggests the allylboration through a chairlike six-membered cyclic transition state similar to uncatalyzed reactions.[2]




| | **2b** ($R^2$ = H, $R^3$ = Me) | **2c** ($R^2$ = Me, $R^3$ = H) |
|---|---|---|
| none | trace | trace |
| $AlCl_3$ (10 mol%) | 92% (*anti* = 99%) | 87% (*syn* = 98%) |
| $Sc(OTf)_3$ (10 mol%) | 94% (*anti* = 99%) | 89% (*syn* = 98%) |

Finally, our preliminary results of catalytic, regiospecific, diastereospecific, and enantioselective allylboration are depicted in eq 4. The addition of **2b** to benzaldehyde catalyzed by Lewis acids comprised of $AlCl_3$ and (*S*)-BINOL gave a *1R,2R* isomer in 39% ee. The low enantioselectivity apparently is attributed to a competitive reaction catalyzed by HCl which would be generated from the reaction of $AlCl_3$ with BINOL.[9] The result prompted us to examine dialkylaluminum chloride[10] as a catalyst precursor that is expected not to form HCl during the catalyst generation. Indeed, the enantioselectivity was improved to 51% ee by using $Et_2AlCl$, while the rate of the reaction was much slower than that using the $AlCl_3$-based catalyst. In contrast, the allylboration did not take place at all when using an $Sc(OTf)_3$/(*S*)-BINOL catalyst.[11] An $Et_2AlCl$/(*S*)-BINOL-catalyzed reaction of **2c** was also examined; however, the reaction resulted in 8% ee.

In summary, we have found for the first time the acceleration effect of a Lewis acid in allylboration of carbonyl compounds. The protocol provides a *catalytic*, *regiospecific*, *diastereospecific*, and *enantioselective* method for the synthesis of homoallyl alcohols. Further studies on the mechanism and improvement of enantioselectivity are currently in progress in our laboratory.




| **2b** ($R^2$ = H, $R^3$ = Me) | | | | |
|---|---|---|---|---|
| $AlCl_3$/(*S*)-BINOL (4 h) | 39%ee | (*1R,2R*) | 92% | *anti* = 99% |
| $Et_2AlCl$/(*S*)-BINOL (6 h) | 51%ee | (*1R,2R*) | 40% | *anti* = 99% |
| $Sc(OTf)_3$/(*S*)-BINOL (4 h) | – | – | trace | – |

| **2c** ($R^2$ = Me, $R^3$ = H) | | | |
|---|---|---|---|
| $Et_2AlCl$/(*S*)-BINOL (6 h) | 8%ee | (N.D.) | 19% *syn* = 98% |

**Supporting Information Available:** Experimental procedures and spectral analyses of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References


(1) For reviews, see: (a) Fleming, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 563. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Colvin, E. W. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 11, p 313.

(2) For reviews, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1. (b) Matteson, D. S. Stereodirected Synthesis with Organoboranes; Springer: Berlin, 1995. (c) Vaultier, M.; Carboni, B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 11, p 191.

(3) For diastereospecific allylsilation, see: (a) Hosomi, A.; Kohara, S.; Tominaga, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1517. (b) Cerveau, G.; Chuit, C.; Corriu, R. J. P.; Reye, C. *J. Organomet. Chem.* **1987**, *328*, C17. (c) Kira, M.; Kobayashi, M.; Sakurai, H. *J. Am. Chem. Soc.* **1988**, *110*, 4599. For diastereospecific allylstannation, see: (d) Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1972**, *35*, C20. (e) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Chem. Soc., Chem. Commun.* **1983**, 489.

(4) For reviews, see: (a) Cozzi, P. G.; Tagliavini, E.; Umani-Ronchi, A. *Gazz. Chim. Ital.* **1997**, *124*, 247. (b) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12. (c) Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem.* **1999**, 527. (d) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis I−III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 965.

(5) For chiral Lewis base/allylic trichlorosilane approaches, see: (a) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (c) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977. (d) Denmark, S. E.; Fu, J. *J. Am. Chem.* Soc. **2001**, *123*, 9488 and references cited therein.

(6) (a) The related allyltrifluoroborate salts add to aldehydes using a strong Lewis acid catalyst, while it is not a formal mode of Lewis acid activation: Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990. (b) Hoffmann and co-workers have reported intramolecular allylboration of acetals, in which they have employed a Lewis acid to hydrolyze the acetal moiety to aldehyde. Although they have not discussed effects of the Lewis acids in the allylboration, the reactions may be accelerated by them: Hoffmann, R. W.; Krüger, J.; Brückner, D. *New J. Chem.* **2001**, *25*, 102 and references cited therein.

(7) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109.

(8) For a review, see: Kobayashi, S. *Synlett* **1994**, 689.

(9) The addition of **2a** (1.1 mmol) to benzaldehyde (1.0 mmol) in the presence of HCl (0.1 mmol) in toluene/ether solvent (6 mL) at −78 °C for 16 h resulted in a 21% yield of the corresponding homoallyl alcohol.

(10) Gothelf, A. S.; Hansen, T.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 854.

(11) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758.


JA0210345