groups were protected with a thioalkyl linker. The oligonucleotides were deprotected with DTT immediately before reaction with 2Py-SS-CLIO.[11]

Synthesis of magnetic oligonucleotide nanoparticles: Complementary (5′TAC-GAG-TTG-AGA-ATC-CTG-AAT-GCG3′), half-complementary (5′TAC-GAG-TTG-AGA-GAG-TGC-CCA-CAT3′), and noncomplementary (5′ATG-CTA-AAT-GAC-GAC-TGC-CCA-CAT3′) oligonucleotides were synthesized using standard phosphoramidite chemistry (underlined bases will hybridize). Either 5′- or 3′-alkanethio-oligonucleotide (550 μg) was added to of 2Py-SS-CLIO (1.1 mL; 3 mg of Fe in 0.1 M phosphate buffer, pH 8.0), and the mixture incubated overnight at room temperature. The mixture was purified using an LS+ high-gradient magnetic separation column (Miltenyi Biotec, Auburn, CA) equilibrated with 0.1 M phosphate buffer, pH 7.5. The number of oligonucleotides attached per particle was determined by treatment with DTT, followed by separation of the iron and oligonucleotide using a microconcentrator as described.[6] The oligonucleotide concentration was then determined from absorbance spectroscopy at 260 nm using an extinction coefficient of $1.2 \times 10^5\,M^{-1}\,cm^{-1}$. The probes are denoted **P1** (CLIO-SS-$(CH_2)_6$-CGC-ATT-CAG-GAT) and **P2** (TCT-CAA-CTC-GTA-$(CH_2)_3$-SS-CLIO).

Hybridization: For Figure 1 equal volumes (25 μL) of **P1** and **P2** (both at 550 μg Fe mL^{-1}) were mixed with a solution of 1 M NaCl and 0.1 M phosphate at pH 7.5 (14 μL). Various oligonucleotides (2 μL, 400 ng) were then added. The mixture was heated to 50 °C for 5 min and allowed to react at room temperature overnight. The precipitate shown in Figure 2B was obtained after overnight incubation of **P1**/**P2** with complementary oligonucleotide; the precipitate was washed with 0.1 M NaCl and 0.1 M phosphate buffer, and re-suspended in the same buffer (300 μL). The sample was split into two portions (15 μL) and examined by electrophoresis without DTT (lane 1) or with 4 mM DTT (lane 2) under nondenaturing conditions (Figure 2A) or denaturing conditions (Figure 2B).

Gel electrophoresis: Nondenaturing gels (10% polyacrylamide) and denaturing gels (20% polyacrylamide) were used. Gels were stained with SYBR Gold dye (Molecular Probes,Eugene OR).

Determination of proton relaxation times: Relaxation time measurements were performed at 0.47 T and 40 °C or 80 °C (Bruker NMR Minispec, Billerica, MA). To determine the effect of hybridization on the $T2$ values of water, equal amounts of **P1** and **P2** (5 μL) were diluted in a solution of 1 M NaCl and 0.1 M phosphate buffer at pH 7.5 (1 mL) to give a total iron content of 10 μg mL^{-1}. $T2$ values were obtained before and after addition of 1 μL (390 ng) of complementary, half-complementary, or noncomplementary oligonucleotides and plotted as a function of time. The relaxivity was determined by plotting $1/T2$ and $1/T1$ values of water as a function of the iron concentration. The size of the conjugates was determined by light scattering (Coulter N4, Hialeah, FL).

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Do More Electrophilic Aldehydes/Ketones Exhibit Higher Reactivity toward Nucleophiles in the Presence of Lewis Acids?

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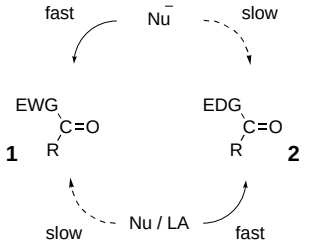
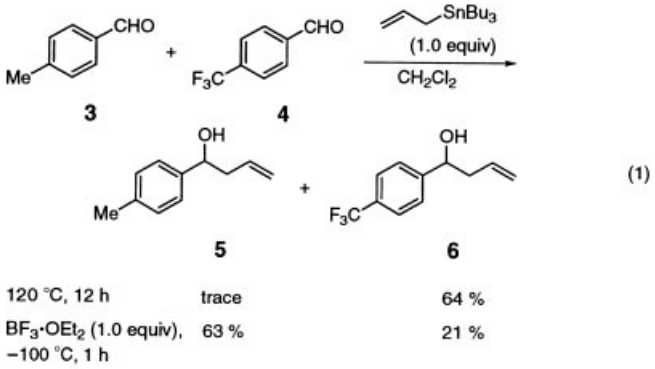
Lewis acid mediated electrophilic reactions of carbonyl compounds are among the most fundamental and important reactions in modern organic synthesis.[1] It is well known that the coordination of carbonyl groups to Lewis acids exerts a dramatic effect on the rates and selectivities of reactions at the carbonyl centers. While much research into the Lewis acid mediated stereoselective or regioselective reactions has been carried out, less attention has been paid to the chemoselective reactions in the presence of Lewis acids.[2–4] It is evident for organic chemists that more electrophilic aldehydes and ketones **1** react with nucleophiles (Nu^-) much faster than less electrophilic analogues **2**. We found that the reverse is the case in the Lewis acid mediated reactions: more electrophilic aldehydes and ketones **1** react much slower than the less electrophilic analogues **2** in the presence of Lewis acids (Scheme 1), with a chemoselectivity that is not attainable under ordinary conditions.



Scheme 1. Chemoselective reactions of equimolar mixtures of **1** and **2**. EWG = electron-withdrawing group, EDG = electron-donating group.

For many years, we have researched the Lewis acid mediated reaction of allyl stannanes and related organometallic compounds.[5] An interesting observation was made in the reaction of allyltributylstannane with aldehydes. The reaction of a 1:1 mixture of *p*-tolualdehyde (**3**) and α,α,α-trifluoro-*p*-tolualdehyde (**4**) with one equivalent of allylstannane at 120 °C gave the homoallylic alcohol **6** derived from **4**, in 64% yield, along with trace amounts of the homoallylic alcohol **5** derived from **3** [Eq. (1)]. This is an expected result,



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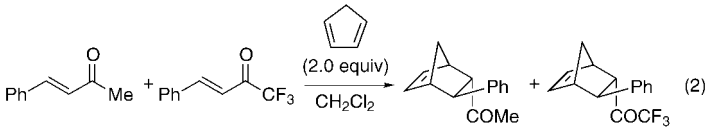
since **4** is more electrophilic than **3** as a result of an electron-withdrawing CF_3 group at the *para* position. On the other hand, the $BF_3 \cdot OEt_2$-mediated reaction at $-100\,^{\circ}C$ gave **5** in 63% yield together with 21% of **6**. This was an unexpected result for us. A similar observation was also made in a Diels–Alder reaction. The thermal reaction of a 1:1 mixture of **7** and **8** with cyclopentadiene at $40\,^{\circ}C$ afforded the [4+2] cycloadduct **10** derived from **8** in 90% yield, along with a small amount (8%) of **9** derived from **7** [Eq. (2)]. This is also an



7 **8** **9** **10**

40 °C, 12 h	8 %	90 %
BF_3•OEt_2 (1.0 equiv), −78 °C, 1 h	49 %	~0 %

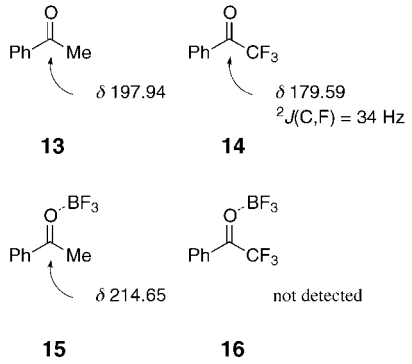
expected result, since **8**, which has an electron-withdrawing CF_3 group, is a better dienophile than **7**. However, the $BF_3 \cdot OEt_2$-mediated reaction at $-78\,^{\circ}C$ gave **9** as the sole product in 49% yield.[6]

The dramatic reversal of the chemoselectivity in the thermal and Lewis acid mediated reactions is understandable if the coordination ability of more electrophilic carbonyl groups to Lewis acids **11** is weaker than that of less electrophilic analogues **12**. This means that the observed chemoselectivities would be ascribed to a higher equilibrium constant for the formation of complex **12** rather than **11**.

11 **12**

To confirm this proposal, we carried out the ab initio study of the BF_3 complexes of acetaldehyde and trifluoroacetaldehyde by using the GAUSSIAN 94 program,[7] and the energies for all possible stable conformations of each complex were calculated (see Supporting Information).[8] A large difference in energy between $CF_3CHO \cdot BF_3$ and $CH_3CHO \cdot BF_3$ complexes were calculated at all levels of theory that were employed (3-21G, 6-31G*, and MP2/6-31G*). At the MP2/6-31G* level of theory, the most stable conformer of the $CF_3CHO \cdot BF_3$ complexes was 6.46 kcal mol^{-1} less stable than the most stable conformer of the $CH_3CHO \cdot BF_3$ complexes. In other words, the basicity of the oxygen atom of more electrophilic carbonyl groups is lower than that of less electrophilic analogues, making the formation of **12** much easier.[9]

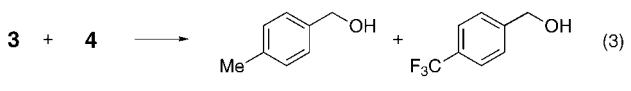
The preferred formation of complex **12** rather than of **11** was also supported by the low-temperature ^{13}C NMR spectroscopic experiments of ketones **13** and **14** in the presence of $BF_3 \cdot OEt_2$. The original signals of the carbonyl carbon atoms of acetophenone **13** and trifluoroacetophenone **14** appeared at $\delta = 197.94$ and 179.59, respectively. When **13** was treated with one equivalent of $BF_3 \cdot OEt_2$ in CD_2Cl_2 at $-78\,^{\circ}C$ to form complex **15**, a significant downfield shift occurred, and the signal for the carbonyl carbon atom was observed at $\delta = 214.65$; the integration ratio of **13**:**15** was 3.0:1.[10] In contrast, no signal for **16** was detected at all when **14** was treated with $BF_3 \cdot OEt_2$, and only the original peak of **14** was observed (Scheme 2). Next, the equilibrium study of an equimolar mixture of **13** and **14** with one equivalent of $BF_3 \cdot OEt_2$ was carried out. As expected, complex **16** was not observed, and



Scheme 2. ^{13}C NMR chemical shifts of **13**–**15** at $-78\,^{\circ}C$ in CD_2Cl_2.

the peak for the carbonyl carbon atom of **15** appeared at $\delta = 214.65$ (**13**:**15** 3.0:1). Even when an additional amount of $BF_3 \cdot OEt_2$ (two equivalents in total) was added to this mixture, the complex **16** was not formed and only an enhancement of the ratio of **15** (**13**:**15** 1.8:1) was observed. These results clearly imply that a carbonyl compound bearing an electron-donating group can form the complex **12** with a Lewis acid much more readily and can also be activated selectively.

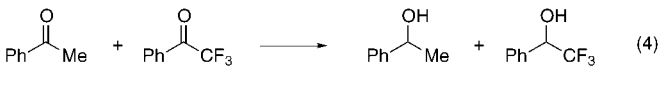
The aldehydes and ketones were reduced chemoselectively based on the above concept. The reduction of a 1:1 mixture of **3** and **4** with Bu_3SnH (1.0 equivalent) at room temperature gave **18** in 51% yield along with 3% of **17**, whereas the reduction with $Bu_3SnH - BF_3 \cdot OEt_2$ (1.0 equivalent)[11] at $-78\,^{\circ}C$ afforded **17** in 68% yield together with 31% of **18** [Eq. (3)]. Similarly, the reduction of a 1:1 mixture of **13** and **14**



17 **18**

Bu_3SnH (1.0 equiv), RT, 8 h	3 %	51 %
Bu_3SnH, BF_3•OEt_2 (1.0 equiv), CH_2Cl_2, −78 °C, 1 h	68 %	31 %

with Bu_3SnH (1.0 equivalent) in butyronitrile gave **20** in 40% yield as the sole product,[12] whereas the reduction with $Bu_3SnH - BF_3 \cdot OEt_2$ (1.0 equiv) afforded **19** in 82% yield as the sole product [Eq. (4)].



13 **14** **19** **20**

Bu_3SnH (1.0 equiv), C_3H_7CN, RT, 5 h	0 %	40 %
Bu_3SnH, BF_3•OEt_2 (1.0 equiv), CH_2Cl_2, −78 °C, 1 h	82 %	0 %

It is now clear that the chemoselectivities in the Lewis acid promoted reactions of certain aldehydes and ketones are opposite to those in the reactions in the absence of Lewis acid. By proper choice of the reaction conditions, either by carrying out the reaction in the presence or in the absence of Lewis acids, secondary and primary alcohols, homoallylic alcohols, and Diels–Alder adducts can be synthesized chemoselectively. A further extension of the above concept is being investigated in our laboratories.

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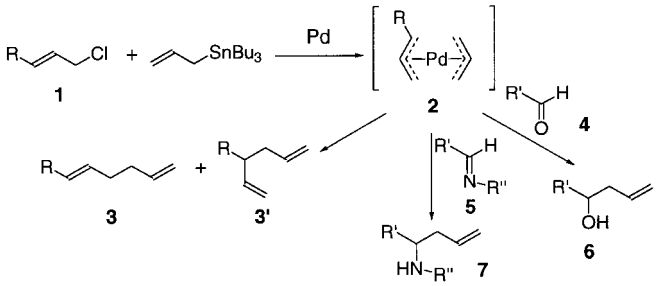
The Fate of Bis(η^3-allyl)palladium Complexes in the Presence of Aldehydes (or Imines) and Allylic Chlorides: Stille Coupling versus Allylation of Aldehydes (or Imines)

Hiroyuki Nakamura, Ming Bao, and Yoshinori Yamamoto*

Palladium-catalyzed Stille coupling between allylic chlorides **1** and allyltributyltin proceeds through bis(η^3-allyl)palladium intermediates **2** to give the allylic–allylic 1,5-hexadiene coupling products **3** and **3′** in moderate to high yields (Scheme 1).[1] Recently, we found that **2** (R = H), generated



Scheme 1. Different reaction pathways of bis(η^3-allyl)palladium intermediates **2**.

from allyl chloride and allyltributyltin in the presence of a palladium catalyst, reacts with aldehydes **4** and imines **5** to produce the corresponding homoallyl alcohols **6** and amines **7**, respectively, in high yields.[2, 3] Also, we found that unsymmetrical bis(η^3-allyl)palladium complexes **2** can selectively transfer the unsubstituted allyl group to aldehydes and imines.[4] Important questions are what factors control the reaction pathways of bis(η^3-allyl)palladium intermediates **2**, and why does the Stille coupling of **2** cease in the presence of aldehydes **4** or imines **5**?

We now report that phosphine ligands play a key role in this process; the Stille coupling reaction takes place in the presence of triphenylphosphine,[5] even if aldehydes **4** and imines **5** are present, whereas the allylation of aldehydes and imines occurs in the absence of the phosphine, even in the presence of allylic chlorides **1** (Scheme 2).

The palladium-catalyzed reactions of various aldehydes **4** and imines **5** with allylic chlorides were investigated in the presence or absence of PPh_3 (Table 1). In the absence of a phosphine ligand, the reaction of **1a** and allyltributyltin with benzaldehyde (**4a**) gave the homoallyl alcohol **6a** in 94% yield, and cinnamyl chloride **1a** was recovered in essentially

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