Mediation of the Reactivity of the Strong Lewis Acid $TiCl_4$ by Complexation with XPh_3

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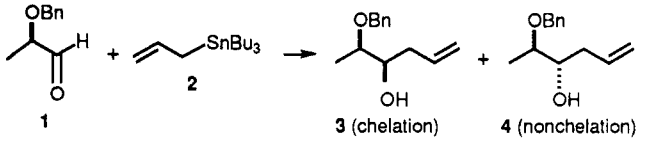
Summary: Lewis acid–base combinations $TiCl_4$·XPh_3 (X = As, Sb, Bi) have been developed to mediate the Lewis acidity of $TiCl_4$. The inverse addition of $TiCl_4$·$AsPh_3$ to 2-(benzyloxy)propanal (1) and allystannane 2 provided a chelation-controlled product 3 with high diastereoselectivity. Diels–Alder reaction of the acrylate of (*S*)-ethyl lactate 5 with cyclopentadiene in the presence of $TiCl_4$–$SbPh_3$ afforded an endo-adduct 6 with high diastereoselectivity and without cyclopentadiene polymerization.

Lewis acids have frequently been used in organic synthesis to enhance the electrophilicity of substrates by coordinating a constituent heteroatom. For example, Lewis acid-mediated allylsilane and allylstannane additions to carbonyl compounds[1] and Lewis acid-accelerated Diels–Alder reactions[2] fall under this category. Strong Lewis acids enhance the electrophilicity of substrates significantly, but often cause side reactions such as polymerization and substrate decomposition. In order to avoid such side reactions and to control Lewis acidity, a strongly electron-withdrawing ligand is replaced by a weak one, e.g., $TiCl_4$ by $TiCl_n(OR)_{4-n}$. However, these modifications lead to less effective Lewis acids. We wish to report an entirely new approach that controls the reactivity of strong Lewis acids and avoids side reactions without compromising effective Lewis acidity. The Lewis acid–base combination $TiCl_4$·XPh_3 (X = As, Sb, Bi) can, in situ, generate $TiCl_4$, which selectively coordinates electrophiles just before the reaction takes place.



(eq 1)

First, we tested the Lewis acid–base combination system for the allylstannane–aldehyde condensation (eq 1 and Table I). The normal addition mode (A) for the $TiCl_4$-mediated reaction procedure gave 3 exclusively (entry 1), as expected from previous studies.[3] The mode A reaction with $TiCl_4$·$AsPh_3$ or $TiCl_4$·$SbPh_3$ also afforded 3 exclusively (entry 2) or nearly so (entry 3). On the other hand,

Table I. Reaction of 1 with 2 in the Presence of $TiCl_4$·XPh_3

entry	Lewis acid	mode of addn[a]	isolated yield (%)	3:4
1	$TiCl_4$	A	76	100:–
2	$TiCl_4$·$AsPh_3$	A	70	100:–
3	$TiCl_4$·$SbPh_3$	A	76	95:5
4	$TiCl_4$·PPh_3	A	70	52:48
5	$TiCl_4$	B	76	52:48
6	$TiCl_4$·$AsPh_3$	B	70	94:6
7	$TiCl_4$·$SbPh_3$	B	73	82:18

[a] (A) To a CH_2Cl_2 solution of a Lewis acid (1 mmol) was added 1 (1 mmol) at −78 °C. After the solution was stirred for a while, 2 (1 mmol) was added at −78 °C. The mixture was stirred for 1 h and then quenched at −78 °C with aqueous NH_4Cl solution. (B) To a CH_2Cl_2 solution of 1 (1 mmol) and 2 (1 mmol) was added a cold CH_2Cl_2 solution of $TiCl_4$ (or $TiCl_4$·XPh_3) (1 mmol) at −78 °C. A similar workup as above was used.

$TiCl_4$·PPh_3[4]-mediated addition produced very low diastereoselectivity (entry 4). These results indicate that $TiCl_4$·$AsPh_3$ and $TiCl_4$·$SbPh_3$ in the allylstannane condensation primarily act as bidentate Lewis acids, presumably by generating $TiCl_4$ in situ upon treatment with 1. Actually, the violet color of these combined Lewis acids changed immediately to yellow upon addition of 1, this color being typical of $TiCl_4$·aldehyde complexes. The phosphine complex[5] cannot liberate free $TiCl_4$ and thus acts as a monodentate Lewis acid and results in low diastereoselectivity. The synthetic utility of the combined Lewis acids is further demonstrated by procedures employing the inverse addition mode (B).[6] The use of $TiCl_4$ alone resulted in low selectivity (entry 5) due to the occurrence of transmetalation of 2 to an allyltitanium derivative.[7] The allylation did not take place with $TiCl_2(OiPr)_2$ at −78 °C owing to its weak Lewis acidity. However, $TiCl_4$·$AsPh_3$ provided high chelation selectivity (entry 6) even with the inverse addition; the transmetalation did not occur, and the selective transfer of $TiCl_4$ to 1 took place. Actually, allylstannane was recovered when it was treated with $TiCl_4$·$AsPh_3$ in CH_2Cl_2 at −78 °C. The stibine complex also circumvented the transmetallation for the most part (entry 7). Accordingly, the Lewis acid–base combination may be useful in a multicomponent system where selective coordination or activation is required (for example, in the intramolecular condensation of allylstannane–aldehydes).[8]

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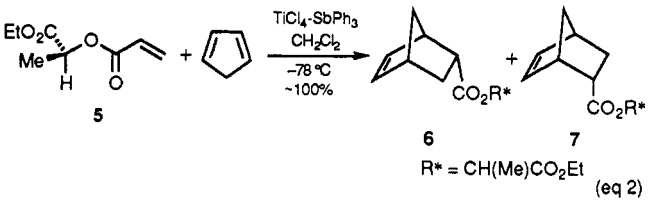
We next examined the Lewis acid-mediated Diels–Alder reaction of the acrylate of (*S*)-ethyl lactate with cyclopentadiene (eq 2).[9] As is usually found, polymerization



(eq 2)

of the diene was a serious occurrence in the $TiCl_4$-mediated reaction.[9] A CH_2Cl_2 solution of **5** (1 equiv) and cyclopentadiene (1.1 equiv) was treated with 1 equiv of $TiCl_4$·$SbPh_3$ at −78 °C to provide a 90:10 mixture of **6** and **7** in nearly quantitative yield, this ratio being similar to that of the free $TiCl_4$-mediated reaction.[9] When we utilized $TiCl_4$ alone in our system (**5**: cyclopentadiene = 1:1.1 in CH_2Cl_2), polymerization took place and the adducts were not obtained. These results clearly indicate that $TiCl_4$ is generated in situ from $TiCl_4$·$SbPh_3$ upon treatment with **5** and immediately forms a bidentate chelate with **5** (without polymerizing cyclopentadiene) which gives **6** with high diastereoselectivity. If $TiCl_4$·$SbPh_3$ acts as a monodentate Lewis acid, **7** should be the predominant product.[9] The use of $TiCl_4$·$AsPh_3$ or $TiCl_4$·$BiPh_3$ afforded a 86:14 or 88:12 mixture of **6** and **7**, respectively.

This method permits us to generate in situ a strong Lewis acid (such as $TiCl_4$), via $TiCl_4$·XPh_3, and to selectively activate a reactant without exerting undesired influences upon other coexisting substrates. It seems that the synthetic significance of $TiCl_4$·XPh_3 is similar to that of NBS, which generates Br_2 in situ very slowly. The determination of the synthetic scope of the Lewis acids·XPh_3 reagent is underway in our laboratories.[10]

Supplementary Material Available: Experimental procedures, compound characterization data, and spectra (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) Poll, T.; Helmchen, G.; Bauer, B. *Tetrahedron Lett.* **1984**, *25*, 2191. Normally, a large excess of cyclopentadiene is used, since it easily provides dicyclopentadiene with $TiCl_4$ even at low temperatures. Helmchen used CH_2Cl_2–*n*-hexane as a solvent to alleviate polymerization, but still excess cyclopentadiene was utilized. Polymerization has been avoided with $TiCl_3(OiPr)_2$ as catalyst (Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, 4781). However, this catalyst gave low acrylate face selectivity.

(10) The preparation of the triphenylarsine complex is representative. To a dry CH_2Cl_2 solution (10 mL) of Ph_3As (1 mmol, 0.306 g), cooled at −78 °C, was added a CH_2Cl_2 solution of $TiCl_4$ (1 M, 1 mmol). Immediately, the color of the solution changed to purple. This solution was used for the allylstannane condensation or Diels–Alder reaction.