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Titanium Fluoride Complexes as Catalysts for the Enantioselective Addition of Me_3Al to Aldehydes

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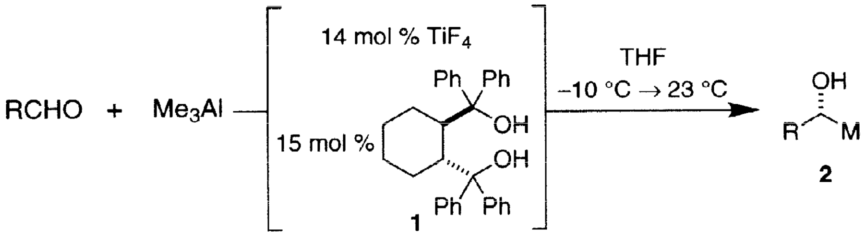
Abstract. We report a Ti(IV) catalyst prepared *in situ* from TiF_4 for the asymmetric addition of trimethylaluminum to aldehydes. The process we detail herein does not necessitate the use of excess trimethylaluminum or Ti(IV) reagent. Good enantioselectivities are achieved with a variety of aromatic and heteroaromatic aldehydes with the products isolated in high yield. © 1998 Elsevier Science Ltd. All rights reserved.

Key words: asymmetric induction, alkylation, fluorine, titanium.

The Ti(IV)-catalyzed nucleophilic addition of organometallic reagents to aldehydes has been the subject of extensive investigations and is one of the hallmarks of reliable processes for the preparation of optically active secondary alcohols. Numerous catalysts and processes have been ingeniously developed for the addition of various alkyl, aryl, alkenyl, and alkynyl zinc carbanions to aldehydes.[1] By contrast, the addition of the simplest member of this class, methyl carbanion, has not received comparable attention in the literature.[2] The best of such additions documented are substrate specific[3] or demand reagents requiring preparation in the laboratory.[4] Although the addition reactions of R_2Zn typically prescribe 2-10 mol % of the chiral Ti(IV) catalyst, importantly, they also necessitate the use of excess (1.2 equiv) of $Ti(OR)_4$.[1,5] The ability to effect the addition of methyl carbanion to aldehydes in an enantioselective manner following an experimentally practical process would considerably expand the scope of this important class of reactions.

We have been interested in studying and developing the chemistry of metal fluorides as catalysts and reagents for asymmetric C-C bond-forming addition reactions.[6,7] In this context, we report a unique characteristic of a putative fluoro-Ti(IV) complex giving unprecedented catalytic activity in the enantioselective addition of Me_3Al to aldehydes (Eq 1). The experimental protocol simply prescribes mixing Me_3Al, chiral diol ligand **1** (15 mol %), and TiF_4 (14 mol %) in THF at −10 °C followed by addition of the aldehyde substrate. The unique properties of this titanium fluoride complex are exemplified by the fact that, in contrast to the other existing Ti(IV)-catalyzed additions, the process we detail herein does not necessitate the use of excess alkyl metal or Ti(IV) reagent.



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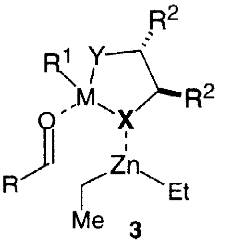
Pioneering studies on metal-catalyzed additions of dialkylzinc reagents to aldehydes have underscored important criteria for the successful design of competent catalysts. A common structural feature of such catalysts **3** is the heteroatom donor in the chelate (X in **3**) that functions as a bridging ligand between the electrophilic metal (M) and nucleophilic ethylzinc components. The operation of a synergistic effect in the bimetallic complex serves to activate the catalyst M as a Lewis acid while concomitantly increasing the nucleophilicity of the diorganozinc reagent.[1a]



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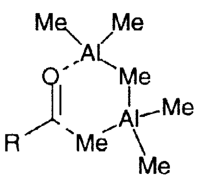

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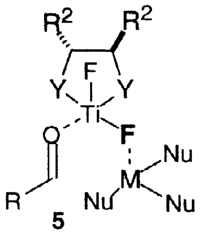

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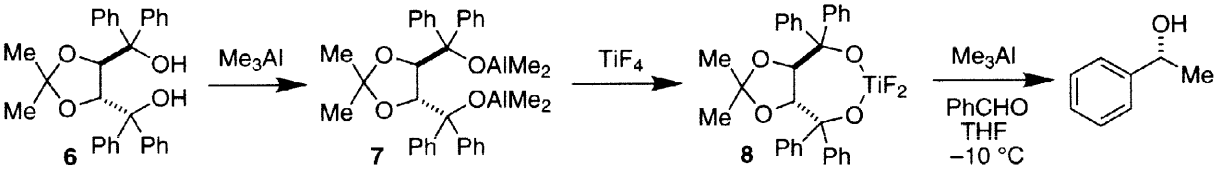
The intermediacy of a six-membered bimetallic transition-state structure **4** has been implicated in the addition of Me_3Al addition to aldehydes.[8] With these mechanistic models as the underpinning background, we speculated that fluoride on a Lewis-acid center could also serve to participate as a bridging component and provide bimetallic complexes **5** that function in a manner similar to those that have been described for dialkylzinc additions. In this regard, in coordination chemistry the propensity of fluoride to participate as a bridging ligand is well documented.[7] The fact that the typical M^1–F–M^2 bridge is considerably shorter than that of the heavier halogens (i.e., Mo–F–Mo = 1.90 Å in MoF_4O versus Mo–Cl–Mo = 2.36 Å in $MoCl_4O$) in principle provides for tighter, more rigid transition-state structures incorporating nucleophile and electrophile partners. However, an important difference between Me_2Zn and Me_3Al is worth noting: while Me_2Zn fails to react with aldehydes and ketones in the absence of catalysts, Me_3Al is known to add to aldehydes and ketones at room temperature within hours in the absence of any additives. Therefore, it was critical that the fluorotitanium complex be able to successfully steer the reaction at a rate that outpaces the competing known background reaction.

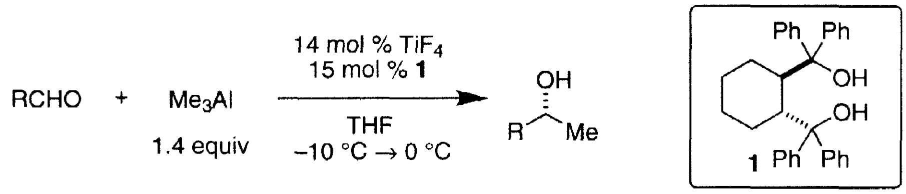
In the first set of experiments, we investigated the use of Ti(IV) TADDOL complexes as a consequence of the remarkable success that these have had in dialkylzinc additions.[4] An operationally simple protocol was devised that would assemble a reactive catalyst in solution and obviate the use of additives such as molecular sieves and Brønsted bases. We envisaged assembling the putative (TADDOLate)TiF_2 complex depicted simplistically as **8** by direct transmetallation from **7** (formed by reaction of Me_3Al with the diol ligand **6**) with TiF_4.[9] Such a metathetical reaction is reasonable: the bond strengths of Al–F and Ti–F are of comparable magnitude (139 kcal/mol each) as well as the fact that the Ti complex enjoys stabilization by forming a chelate.[10]

When a solution of TADDOL **6** and Me_3Al (1.0 M in hexanes) were mixed in THF at 23 °C gas evolution was observed. This reaction mixture was subsequently treated with a solution of TiF_4 (0.5 M in CH_3CN)[11] prior to cooling to −10 °C. Following introduction of benzaldehyde, the adduct was isolated within 12 hr in 32% ee and 79% yield.[12,13]



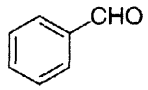
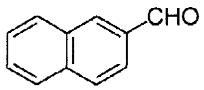
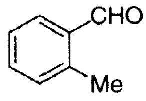
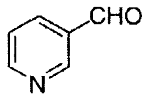
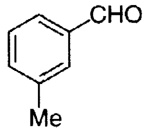
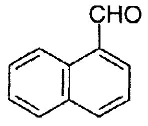
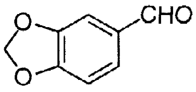
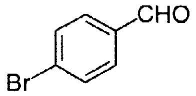
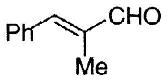
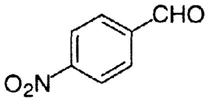
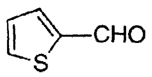
(2)

A survey of dialkoxy ligands revealed *trans*-1,2-cyclohexanedimethanol **1** as the best compromise between substrate generality and product enantiomeric excesses.[14] Thus for a range of aldehydes, adducts were isolated in up to 85% ee and 93% yield (Table 1). Remarkably, this addition reaction proceeds with good enantioselectivity for a variety of substrates at about 0 °C; by contrast, asymmetric carbonyl addition reactions of dialkylzinc reagents typically require much lower temperatures (e.g., −78 °C).[15] The use of catalyst loads above 5 mol % provided improved enantioselectivity (e.g., 72% ee at 5 mol % vs 82% ee at 20 mol % for benzaldehyde) but continued enhancement ceased at about 20 mol % loading. Benzaldehyde derivatives were effective substrates displaying only a slight drop in enantioselectivity with increasing substitution (Table 1, entries 2 through 6). Interestingly, 4-nitrobenzaldehyde (entry 6) underwent smooth addition without complication by the potentially reducible nitro functionality. Unsaturated aldehydes were also suitable substrates, without any detectable conjugate addition products (entries 10 and 11).[16,17]



(3)

Table 1. Asymmetric Addition of Me$_3$Al to Aromatic Aldehydes.[a]

Entry	Substrate	Yield	*ee*	Entry	Substrate	Yield	*ee*
1		80%	80%	7		84%	68%
2		85%	68%	8		83%	85%
3		87%	71%	9		71%	63%
4		89%	59%	10	$^{i}Pr_3Si-C\equiv C-CHO$	41%	58%
5		93%	58%	11		78%	54%
6		51%	58%	12		80%	67%

[a] All yields correspond to purified, isolated products. Enantiomeric excesses were determined by GC analysis with a J&W Scientific CDX-B column by comparison to authentic racemic material. Absolute stereochemistry was assigned by comparison of optical rotation with reported values.

In conclusion, we have demonstrated the unique reactivity of a fluoro titanium complex as a catalyst for the asymmetric addition of Me$_3$Al to aldehydes at 0 °C, a reaction which has little precedence. Importantly, in contrast to known alkylmetal additions to aldehydes involving Ti(IV) catalysis, the fluorotitanium complex obviates the need to use stoichiometric quantities of Ti(OR)$_4$ as additive. The novel reactivity of fluorotitanium complexes documented herein provide new directions for the development of second generation catalysts for this important class of carbonyl additions. The addition reactions of more functionally complex aluminum reagents as well as mechanistic studies is under current investigation and will be reported in due time.

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10. The role of Me_2AlF generated in this reaction on the course of catalysis has not been fully ascertained. In preliminary studies by ^1H NMR spectroscopy we have observed the presence of numerous methyl signals consistent with the presence of species containing the Me–Al bond. Further specroscopic studies are warranted that will allow for characterization of the observed species.
11. Stock solutions of commercial TiF_4 (0.5 M in MeCN) are often slightly cloudy and discolored. Purification of TiF_4 by slow percolation through celite with ether under argon then vacuum drying affords solid TiF_4 which gives colorless and homogeneous solutions in MeCN. No difference in % ee was observed with either stock solution.
12. Preparations of TADDOL Ti(IV) complexes: Haase, C.; Sarko, C. R.; Dimare, M. *J. Org. Chem.* **1995**, *60*, 1777.
13. General Experimental Procedure. A solution of diol **1** (15.0 mol %, 0.075 mmol, 33.6 mg) in THF (3 mL) was cooled to 0 °C, treated with Me_3Al (1.4 eq, 0.7 mmol, 0.35 mL, 2.0 M in hexane) and then allowed to warm to room temperature. After stirring for 20 min, a solution of TiF_4 (13.5 mol %, 0.068 mmol, 0.5 M in CH_3CN, 0.135 mL) was added, and the reaction mixture was stirred for an additional 20 min. The resulting solution was cooled to −10 °C and benzaldehyde was added neat (0.5 mmol, 0.051 mL). After stirring for 12 h at −10 °C, the flask was transferred to a 0 °C ice bath and allowed to gradually warm to room temperature. The reaction mixture was quenched by transfer of the solution into 5 mL of ice cold 10% aqueous sulfuric acid and then extracted with diethyl ether. Purification by chromatography on silica gel afforded the alcohol. The ligand may be recovered quantitatively without racemization.
14. Optically active *trans*-1,2-cyclohexane dicarboxylic acid is obtained from enzymatic hydrolysis of the corresponding *cis*-diester or by resolution of the *trans*-diacid with (*S*)-(−)-α-methylbenzylamine. (a) Kobayashi, S.; Kamiyama, K.; Ohno, M. *Chem. Pharm. Bull.* **1990**, *38*, 350. (b) Longeau, A.; Durand, S.; Spiegel, A.; Knochel, P. *Tetrahedron Asym.* **1997**, *8*, 987. (c) Applequist, D. E.; Werner, N. *J. Org. Chem.* **1963**, *28*, 48.
15. The enantioselectivity of the addition reaction displays only modest sensitivity to temperature. Thus, at −20 °C and 0 °C *sec*–phenethyl alcohol was isolated in 85 and 82% ee, respectively; when the addition was conducted at room temperature a further drop to 79% ee was observed. At −78 °C, the reaction rate becomes too slow to be preparatively useful.
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17. At the current level of development, aliphatic aldehydes are not good substrates for the process, giving product in low ee's and yields. Et_3Al could be employed in the catalytic reactions; however, the products were isolated in lower % ee's. It is interesting to note that when stoichiometric amounts of complex were utilized the addition of Et_3Al to benzaldehyde consistently gave high % ee's. We are investigating these observations along with developing modified conditions that will expand the scope of the process; these results will be reported in the future.