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The first asymmetric addition of organogallium to aldehydes catalyzed by chiral titanium catalysts

Zhenya Dai,[a] Chengjian Zhu,[a,b,*] Minghua Yang,[a] Yunfa Zheng[c] and Yi Pan[a,*]

[a]*School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[c]*Department of Chemistry, Lishui Normal University, Lishui 323000, China*

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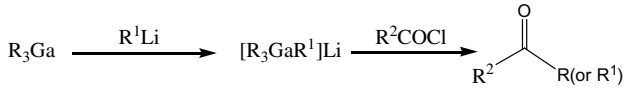
Abstract—The addition of organogallium to aldehydes was realized with titanium tetrachloride as a Lewis acid catalyst. For the first time, the catalytic asymmetric addition of organogallium to aldehydes was investigated with chiral titanium complexes, which were formed from titanium tetrachloride and salan ligands, with mediocre to good chemical yields and enantioselectivities.

1. Introduction

Since the first organogallium was synthesized in 1932, they have often been used as an organometallic precursors for CVD of film.[1] It is surprising that the synthetic potential of organogallium compounds has scarcely been explored, the reason being due to the very low reactivity of organogallium toward most organic electrophiles. Most of the studies on the utilization of organogallium are based on the Lewis acidity of gallium. Utimoto et al. reported that trimethylgallium could be used as a catalyst in the reaction of alkynyllithium with epoxides.[2a] Recently, our group presented the first example of enantioselective isocyanosilylation of *meso*-epoxides using TMSCN to form β-isocyanohydrins catalyzed by chiral organogallium and organoindium complexes with moderate to excellent enantioselectivities.[2b,c] The only example of the utilization of trialkylgallium as an alkylation reagent was reported by Huang et al. in the synthesis of ketones from acyl chlorides with the formation of lithium tetraorganogallates (Scheme 1).[3] Over the course of our continuing studies on organogallium, we herein report the first enantioselective addition of organogallium to aldehydes using chiral salan titanium complexes as catalysts.



Scheme 1.

2. Results and discussions

Initially we examined the addition of trimethylgallium to benzaldehyde in THF in the presence of catalytic amount (10 mol %) of different Lewis acids. We found that titanium tetrachloride was a good catalyst for the reaction and provided a high yield (80%, room temperature, 24 h) of the expected α-methylbenzyl alcohol, while $Ti(O^iPr)_4$ and $BF_3{\cdot}Et_2O$ showed no catalytic activity in the reaction, and $Yb(OTf)_3$ afforded only 10% yield (room temperature, 24 h) of α-methylbenzyl alcohol. These results reveal that only a very strong Lewis acid can efficiently catalyze the addition of trialkylgallium to an aldehyde.

Having established the reaction of trimethylgallium and benzaldehyde catalyzed by Lewis acid, we turned our attention to a catalytic asymmetric version of this reaction using chiral titanium complexes. Nitrogen-containing ligands are one of the most important types of the chiral ligands, which are becoming applicable for asymmetric synthesis.[4] It has been reported that the chiral ligands, which contain a secondary or a tertiary amine

* Corresponding authors. Tel.: +86 25 83594886; fax: +86 25 83317761; e-mail: cjzhu@nju.edu.cn

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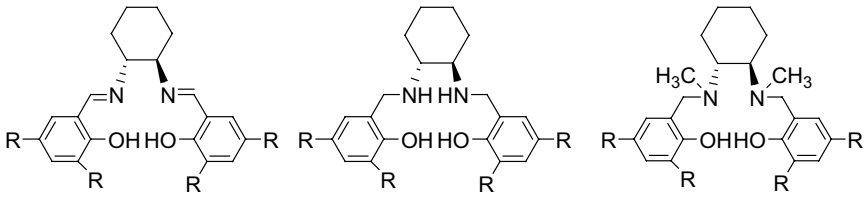
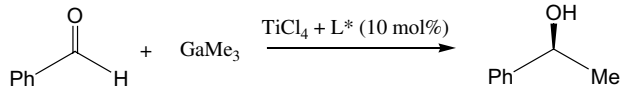


Figure 1.

group (sp^3-hybrided nitrogen atom) are superior in terms of reactivity and enantioselectivity to imino analogues (sp^2-hybrided nitrogen atom).[5] We choose to employ the (*R*,*R*)-1,2-diaminocyclohexane backbone based tetradentate salen ligands **1a** and **1b**, and salan ligands **2a**, **2b**, and **3** as chiral auxiliaries (Fig. 1).[5b,6–8] The salan ligand **3** has been employed in the formation and characterization of different metal complexes,[6b,c] while, to the best of our knowledge, no example of their chemistry in asymmetric catalysis has been reported.

Treatment of the chiral ligands with an equal equivalent of titanium tetrachloride provided the catalysts. We studied the reactivity and enantioselectivity of the addition of trimethylgallium to aldehydes using benzaldehyde as a model substrate (Scheme 2). As shown in Table 1, the complexes, formed from the reaction of titanium tetrachloride with an equal equivalent of the imine ligands **1a** and **1b** and tertiary amine ligand **3**, respectively, were effective catalysts for the addition of trimethylgallium to benzaldehyde, with moderate yields and mediocre to good enantioselectivities. Ligand **3** gave the best selectivity up to 72% ee (entry 8). Surprisingly, the titanium complexes formed from a 1:1 molar ratio of titanium tetrachloride and secondary amine ligands **2a** and **2b** were ineffective catalysts for the reaction, even at room temperature (entries 3 and 4). This is probably due to all four chlorines in titanium tetrachloride being replaced by phenoxy and amino groups in the ligands, the Lewis acidity of the titanium is hence decreased by a large margin, and thus cannot catalyze the reaction.



Scheme 2.

Table 1. The asymmetric addition of trimethylgallium to benzaldehyde catalyzed by chiral titanium complexes with various ligands under different conditions[a]

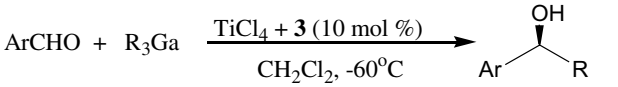
Entry	Ligand	Solvent	Temperature (°C)	Yield[b] (%)	Ee[c] (%)
1	**1a**	CH_2Cl_2	−60	52	53
2	**1b**	CH_2Cl_2	−60	58	48
3	**2a**	CH_2Cl_2	rt	0	nd
4	**2b**	CH_2Cl_2	rt	0	nd
5	**3**	CH_2Cl_2	0	64	40
6	**3**	CH_2Cl_2	−20	60	45
7	**3**	CH_2Cl_2	−40	56	62
8	**3**	CH_2Cl_2	−60	52	72
9[d]	**3**	CH_2Cl_2	−60	50	70
10[e]	**3**	CH_2Cl_2	−60	40	55
11	**3**	CH_2Cl_2	rt	72	30
12	**3**	THF	−60	70	50
13	**3**	Toluene	−60	41	56

[a] 10 mol % of $TiCl_4$ and chiral ligands, and 3 equiv of $GaMe_3$ were used based on the benzaldehyde, and the reactions carried out for 72 h.
[b] All the yields are isolated yields.
[c] Enantiomeric excesses were determined by HPLC analysis using a DAICEL CHIRAL OD-H column.
[d] 2 equiv of Me_3Ga were used.
[e] 1 equiv of Me_3Ga was used.

The influence of the temperature and the effect of the solvent have been examined in the use of **3** as chiral ligand. A variation of the reaction temperature from −60 °C to room temperature caused a sharp decrease in the ee value to 30% with CH_2Cl_2 as solvent (entry 11). The reaction proved sluggish when the temperature was decreased to −78 °C. The nature of the solvent was revealed to have a remarkable effect upon the enantioselectivity and chemical yield. Of all the solvents investigated, CH_2Cl_2 gave the highest enantioselectivity and good chemical yield. When THF was used as solvent, moderate ee values and the best chemical yield were obtained (entry 12). Toluene gave both lower chemical yield and ee value (entries 12 and 13). Thus, CH_2Cl_2 proved to be the best solvent in terms of selectivity. Moreover, there was a slight decrease of the chemical yield and enantioselectivity when the quantity of trimethylgallium used dropped to 2 equiv (entry 9) and 1 equiv (entry 10).

We thus used **3** as the chiral ligand for the enantioselective addition of trimethylgallium and triethylgallium to a variety of aldehydes.[9] The reactions were carried out at −60 °C in CH_2Cl_2 with 3 equiv of trialkylgallium as optimal conditions. The results are summarized in Table 2. Moderate to good chemical yields of the isolated products, in the range of 52–84%, were obtained. The substituents on the aromatic ring affected the chemical yields of the reactions significantly. The aldehydes with electron-withdrawing groups showed better reactivity, while those with electron-donating groups provided the products with lower chemical yields. All of the predominant enantiomeric products obtained were of an (*S*)-configuration. The enantioselectivity varied from 20% to 84% depending on the nature of the aldehyde. The addition of steric bulkier triethylgallium to 4-nitro-

Table 2. The addition of trialkylgallium to different aldehydes with chiral titanium catalyst[a]



Entry	R	Aldehydes	Yield[b] (%)	Ee[c] (%)	Config[d]
1	Me	4-*tert*-Butylbenzaldehyde	64	70	(*S*)
2	Me	4-Methoxybenzaldehyde	65	50	(*S*)
3	Me	2-Methoxybenzaldehyde	80	20	(*S*)
4	Me	4-Nitrobenzaldehyde	84	40	(*S*)
5	Me	2-Nitrobenzaldehyde	78	25	(*S*)
6	Me	4-Chlorobenzaldehyde	55	44	(*S*)
7	Me	2-Chlorobenzaldehyde	62	45	(*S*)
8	Et	Benzaldehyde	55	54	(*S*)
9	Et	4-Nitrobenzaldehyde	75	81	(*S*)
10	Et	2-Nitrobenzaldehyde	70	84	(*S*)
11	Et	4-Chlorobenzaldehyde	60	54	(*S*)

[a] 10 mol % of $TiCl_4$ and chiral ligand, and 3 equiv of trialkylgallium were used based on the aldehydes, and the reactions were carried out at −60 °C for 72 h.
[b] All the yields were isolated yields.
[c] Enantiomeric excesses were determined by HPLC analysis using a DAICEL CHIRAL OD-H column.
[d] The absolute configurations were determined by comparing the specific rotations with the literature values.[10]

benzaldehyde and 2-nitrobenzaldehyde provided the products with the best enantioselectivities 81% (entry 9) and 84% ee (entry 10). The change of the substituent group on the aromatic ring of aldehydes to probe the electronic effects displayed no regular trends in the enantioselectivity. It is interesting to note that the reaction between 2-methoxybenzaldehyde and trimethylgallium could occur even in the absence of a Lewis acid (60% yield, 24 h at room temperature), due to the *ortho*-methoxy participation effect. This is the reason why entry 3 in Table 2 gave the best chemical yield but with very low ee value.

To gain a better insight into this catalytic reaction, the catalyst was also isolated and identified. Reaction of ligand **3** with $TiCl_4$ in CH_2Cl_2 at room temperature for 2 h followed by evaporation of the solvent in vacuo and washing of the solid with Et_2O and Et_2O–hexane (1:1) gave a deep red solid of structure **4** (Scheme 3), which was identified by ^1H NMR, IR, MS, and element analysis.[11] No absorbance above 3300 cm^{-1} was found in the IR spectra of **4**, thus indicating that phenoxy hydrogens do not exist in the catalyst. Considering the monomeric feature of the complex formed from ligand **1b** and $TiCl_4$, which has been proven by X-ray structure analysis,[12] the structure of **4** should be monomeric.

3. Conclusion

In summary, the utilization of organogallium as an alkylation reagent in the addition to aldehydes was realized by using titanium tetrachloride as a strong Lewis acid catalyst. For the first time, the catalytic asymmetric addition of organogallium to aldehydes was investigated with chiral titanium complexes, which was formed from titanium tetrachloride and salan ligand, with moderate to good chemical yields and enantioselectivities up to 84% ee. Further work is underway in our group to understand the mechanism and improve the enantioselectivity of this reaction.

Acknowledgements

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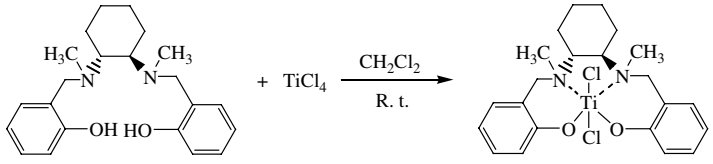

3 **4**

Scheme 3.

Cawley, A.; Thornton-Pett, M.; Wantz, L.; Warne, J. N. D.; Greatrex, R.; Brown, D.; Kee, T. *Tetrahedron Lett.* **1999**, *40*, 4403–4406.

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7. Ligand **3** (see Ref. 6a) was synthesized by a new method: Under an argon atmosphere, 7.2 mL of *n*-BuLi (2.5 M solution in *n*-hexane, 18 mmol) was added dropwise to a solution of **2a** (1.3 g, 4 mmol) in 30 mL of THF at 0 °C. After being stirred for 1.5 h, the mixture was allowed to warm to ambient temperature. Iodomethane (1.17 mL, 18 mmol) was added slowly and stirring continued for another 6 h. Water (30 mL) was then added to quench the reaction and the aqueous layer separated and extracted with CH_2Cl_2 (5×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was further purified by flash chromatography (petroleum ether–ethyl acetate = 4:1) to give **3** (0.9 g, 60% yield) as a white solid, mp: 120 °C; $[\alpha]_D^{25} = -6.7$ (*c* 0.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.22–7.17 (m, 2H), 7.02–7.00 (m, 2H), 6.87–6.78 (m, 4H), 3.87 (d, 2H, $J = 13.5$ Hz), 3.66 (d, 2H, $J = 13.5$ Hz), 2.75–2.72 (m, 2H), 2.25 (s, 6H), 2.06–2.02 (m, 2H), 1.85–1.83 (m, 2H), 1.27–1.17 (m, 4H); IR (KBr): 3422, 2988, 1612, 1588, 1488, 1284, 1256, 761, 722 cm^{-1}.
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9. A typical procedure for the asymmetric addition of trimethylgallium to benzaldehyde is described below. In a 20 mL reaction tube, ligand **3** (35.4 mg, 0.1 mmol) was dissolved in dichloromethane (3 mL) under an argon atmosphere followed by the slow addition of titanium tetrachloride (0.22 mL, 0.1 mmol, 1 mL in 19 mL of dichloromethane) at −60 °C and the mixture stirred for 2 h at this temperature. Trimethylgallium (0.3 mL, 3 mmol, in 2.7 mL of dichloromethane) was then added dropwise and the mixture stirred for an hour at −60 °C followed by the addition of benzaldehyde (0.1 mL, 1 mmol). After the mixture was stirred at this temperature for another 72 h, water (6 mL) was added to quench the reaction. The aqueous layer was separated and further extracted with dichloromethane (4×25 mL); the organic layer was combined, washed with water, and dried. Evaporation of the solvent gave the crude product, which was further purified by preparative TLC (petroleum ether–ethyl acetate = 5:1) to give 63 mg (52% yield) of α-methylbenzyl alcohol.
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11. Identification of complex **4**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.17 (m, 4H), 6.96–6.75 (m, 4H), 3.98 (d, 2H, $J = 11.90$ Hz), 3.84 (d, 2H, $J = 11.87$ Hz), 2.84 (m, 2H), 2.03 (s, 6H), 1.75 (m, 4H), 1.24 (m, 4H); IR (KBr): 3211, 2988, 1672, 1488, 1284, 761 cm^{-1}; MS (EI): *m/z* (%) = 354 (40), 276 (50), 247 (60), 141 (60), 110 (100); Anal. Calcd for $C_{22}H_{28}N_2O_2TiCl_2$: C, 56.05; H, 5.98; N, 5.97. Found: C, 55.87; H, 5.81; N, 5.75.
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