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Utilization of organogallium and organoindium compounds as alkylation reagents in organic synthesis: the addition of trialkylgallium and trialkylindium to aldehydes catalyzed by Lewis acids

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The utilization of organogallium and organoindium compounds as alkylation reagents to aldehydes was realized with titanium tetrachloride as the strong Lewis acid catalyst. Furthermore, 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. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: organogallium; organoindium; aldehydes; Lewis acid; asymmetric catalysis; chiral Lewis acid

INTRODUCTION

Although the first organogallium was synthesized in 1932, the synthetic potential of organogallium compounds has scarcely been explored, unlike their aluminum analogues, which have been widely used as alkylation reagents or catalysts in organic synthesis.[1,2] Utimoto *et al*.[3] reported that trimethylgallium could be used as a catalyst in the reaction of alkynyllithium with epoxide. Recently, our group presented the first example of enantioselective isocyanosilylation of meso epoxide using trimethylsilyl cyanide to form β-isocyanohydrins catalyzed by chiral organogallium and organoindium complexes with moderate to excellent enantioselectivities.[4,5] The only example of the utilization of trialkylgallium used as an alkylation reagent has been reported by Huang and coworkers[6] in the synthesis of ketones from acyl chlorides with the formation of lithium tetraorganogallates (Scheme 1). In the course of our continuing study on organogallium and organoindium chemistry, we present here the application of organogallium and organoindium compounds as alkylation reagents in their addition to aldehydes catalyzed by Lewis acid together with the asymmetric addition of organogallium to aldehydes using the chiral salan–titanium complex as catalyst.

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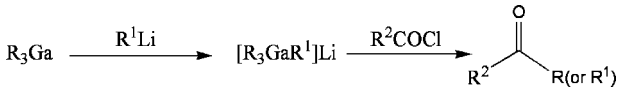
RESULTS AND DISCUSSION

Trialkylgallium addition to aldehydes with titanium tetrachloride as catalyst

As no reaction was found between trimethylgallium and aldehydes without any additives, we expected that the addition of a catalytic amount of Lewis acid could activate the electrophilic carbonyl group, and the addition of the nucleophilic methyl group to the carbonyl group could be realized. We examined the addition of a catalytic amount (10 mol%) of different Lewis acids to the mixture of trimethylgallium and benzaldehyde in tetrahydrofuran (THF). The results are collected in Table 1. We found



Scheme 1.

Table 1. The addition of trimethylgallium to benzaldehyde catalyzed by different Lewis acids[a]

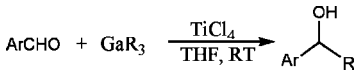
Entry	Catalyst	Solvent	Yield (%)[b]
1	None	THF	0
2	$Et_2O \cdot BF_3$	THF	0
3	$Yb(OTf)_3$	THF	10
4	$TiCl_4$	THF	80
5	$TiCl_4$	CH_2Cl_2	72
6	$TiCl_4$	Toluene	60
7[c]	$TiCl_4$	THF	73
8	$Ti(O^iPr)_4$	THF	0

[a] Unless specified otherwise, the reactions were all carried out with 10 mol% catalyst and three equivalents of trimethylgallium at room temperature for 24 h.
[b] Isolated yields.
[c] Two equivalents of trimethylgallium used.

that titanium tetrachloride was a good catalyst for the reaction and provided a high yield of the expected α-methylbenzyl alcohol, while $Ti(O^iPr)_4$ and $BF_3 \cdot Et_2O$ showed no catalytic activity in the reaction (Table 1, entries 2 and 8). $Yb(OTf)_3$ afforded only 10% yield of α-methylbenzyl alcohol (Table 1, entry 3). From Table 1, it is clear that the more dipolar THF was a good solvent and that the reaction in THF provides a higher yield, whereas the reactions in the less dipolar CH_2Cl_2 and toluene provided a lower chemical yield (Table 1, entries 5 and 6). A decrease in the amount of trimethylgallium used in the reaction caused a small decrease in yield (entry 7). These results reveal that only a very strong Lewis acid could efficiently catalyze the reaction between trimethylgallium and benzaldehyde.

We then extended the reaction to other aldehydes and other trialkylgalliums. The reactions between trialkylgallium and aldehydes were carried out in THF with titanium tetrachloride (10 mol%) as catalyst at room temperature, and three equivalents of trialkylgallium were used in the reaction. The results, collected in Table 2, show that the nature of the aldehyde affects the yield of alcohols significantly. The aldehydes with an electron-withdrawing group on the aromatic ring showed better reactivity, whereas those aldehydes with an electron-donating group on the aromatic ring showed lower reactivity. One exception was 2-methoxybenzaldehyde, which could react with trimethylgallium even in the absence of the catalyst

Table 2. The addition of trialkylgallium to aldehydes with titanium tetrachloride as catalyst[a]



Entry	R	Aldehyde	Yield (%)[b]
1	Me	Benzaldehyde	80
2	Et	Benzaldehyde	75
3	Me	2-Methoxybenzaldehyde	90
4	Et	2-Methoxybenzaldehyde	70
5	Me	4-Methoxybenzaldehyde	65
6	Et	4-Methoxybenzaldehyde	60
7	Me	2-Chlorobenzaldehyde	72
8	Et	2-Chlorobenzaldehyde	70
9	Me	4-Chlorobenzaldehyde	75
10	Et	4-Chlorobenzaldehyde	74
11	Me	2-Nitrobenzaldehyde	82
12	Et	2-Nitrobenzaldehyde	80
13	Me	4-Nitrobenzaldehyde	84
14	Et	4-Nitrobenzaldehyde	84
15	Me	4-*tert*-Butylbenzaldehyde	64
16	Et	4-*tert*-Butylbenzaldehyde	62
17	Me	Phenylacetaldehyde	54
18	Et	Phenylacetaldehyde	55
19[c]	Me	2-Methoxybenzaldehyde	60

[a] Unless specified otherwise, the reactions were all carried out in THF with 10 mol% catalyst and three equivalents of trialkylgallium for 24 h.
[b] Isolated yields.
[c] No catalyst was used.

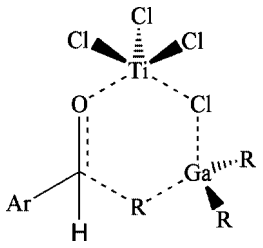


Figure 1. Possible transition state for the alkylation of aldehydes to triorganogallium compounds in the presence of titanium tetrachloride.

(entry 19); this may be due to the ortho methoxy participation effect. The sterically bulkier triethylgallium showed a slightly lower reactivity than trimethylgallium.

A possible working model for the catalytic process is depicted in Fig. 1. The titanium tetrachloride probably acts as a bifunctional catalyst in the reaction between trialkylgallium and aldehydes. It is likely that the titanium acts as a Lewis acid and activates the aldehyde; simultaneously, the trialkylgallium is activated by the interaction between chloride and the gallium atom.[2]

Trimethylindium addition to aldehydes with titanium tetrachloride as catalyst

As a congener of gallium, indium is similar in properties to gallium. For exploring the application of organoindium compounds as an alkylation reagent, we also studied the reaction between trimethylindium and aldehydes catalyzed by titanium tetrachloride. The reactions between trimethylindium and aldehydes were all carried out with titanium tetrachloride as catalyst in THF at room temperature. The results, collected in Table 3, indicate that trimethylindium shows a lower reactivity than trialkylgallium: the yields are lower than those for the reaction between trialkylgallium and aldehydes. The nature of the aldehyde also affects the reactivity greatly. The aldehydes with electron-withdrawing groups on the aromatic ring showed higher reactivities, whereas those aldehydes with electron-donating groups on the aromatic ring showed lower reactivities.

Asymmetric addition of trialkylgallium to aldehydes with chiral titanium complexes as catalysts

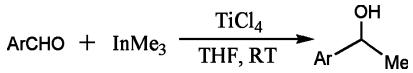
Having studied the reaction of trialkylgallium and benzaldehyde catalyzed by Lewis acid, we turned our attention to a catalytic asymmetric version of this reaction using chiral titanium complexes.

Nitrogen-containing ligands are some of the most important types of chiral ligand which are becoming applicable for asymmetric synthesis.[7–9] It has been reported that such chiral ligands containing secondary and tertiary amino groups (sp^3-hybridized nitrogen atom) are superior in terms of reactivity and enantioselectivity compared with the imino analogues (sp^2-hybridized nitrogen atom).[10–12] We chose 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.[13–16] The reduction of the salen ligands **1a** and **1b** gave **2a** and **2b** respectively, and the subsequent methylation of **2a** gave the chiral tertiary amine **3** (Scheme 2). The salan ligand **3** has been employed in the formation and characterization of different metal complexes,[14,15] whereas, to our best knowledge, no example of their chemistry in asymmetric catalysis has been reported.

Treatment of the chiral ligands with an equal equivalent of titanium tetrachloride gave the catalysts. We studied the reactivity and enantioselectivity of the addition of trimethylgallium to benzaldehyde under different conditions (Scheme 3); the results are collected in Table 4.

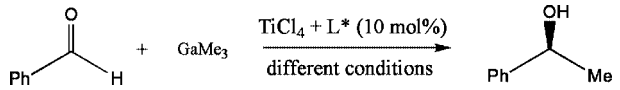
Of all the chiral ligands we investigated, we found that the catalysts formed from the reactions of titanium tetrachloride with one equivalent of the imine ligands **1a** and **1b** or the tertiary amine ligand **3** were effective catalysts for the addition of trimethylgallium to benzaldehyde, with moderate yields and mediocre to good enantioselectivity. Ligand **3** gave the best selectivity: up to 72% ee (Table 4, entry 8). We were surprised to find that the titanium complexes formed from 1 : 1 molar ratio of titanium tetrachloride and secondary amine ligands **2a** and **2b** were ineffective catalysts for the reaction, even at room temperature (Table 4, entries 3 and 4). This is probably due to the fact that all of the four chlorine atoms in titanium tetrachloride were replaced by phenoxy and amino groups in the ligands, the Lewis

Table 3. The addition of trimethylindium to aldehydes catalyzed by titanium tetrachloride[a]

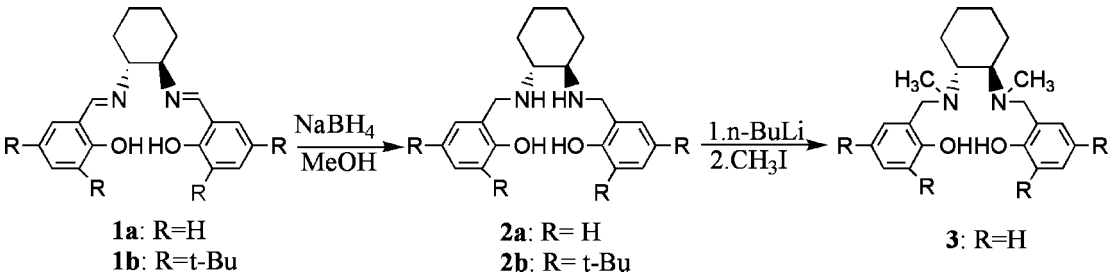


Entry	Aldehyde	Yield (%)[b]
1	Benzaldehyde	72
2	2-Methoxybenzaldehyde	56
3	4-Methoxybenzaldehyde	61
4	2-Chlorobenzaldehyde	68
5	4-Chlorobenzaldehyde	70
6	2-Nitrobenzaldehyde	77
7	4-Nitrobenzaldehyde	80
8	4-*tert*-Butylbenzaldehyde	56
9	Phenylacetaldehyde	50

[a] The reactions were all carried out with 10 mol% catalyst and three equivalents of trimethylindium in THF at room temperature for 24 h.
[b] Isolated yields.



Scheme 3.



Scheme 2.

Table 4. 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	**3**	CH_2Cl_2	Rt	72	30
10	**3**	THF	−60	70	50
11	**3**	Toluene	−60	41	56

[a] 10 mol% of $TiCl_4$ and chiral ligands, and three equivalents of $GaMe_3$ were used, based on the benzaldehyde, and the reactions were carried out for 72 h.
[b] All the yields were isolated yields.
[c] Enantiomeric excess values were determined by high-performance liquid chromatography (HPLC) analysis using a Daicel Chiral OD-H column.

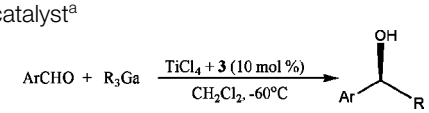
acidity of the titanium being drastically decreased. Thus, chiral ligand **3** was chosen as the optimal ligand in the reaction.

The influence of the temperature has 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 of the ee value to 30% with CH_2Cl_2 as solvent (Table 4, entry 9). The reaction was sluggish when the temperature decreased to −78 °C. So −60 °C was chosen as the optimal temperature.

The effect of the solvent on the enantioselectivity and chemical yield was also examined. Among the solvents investigated, CH_2Cl_2 gave the highest enantioselectivity and good chemical yield. When THF was used as solvent, the best chemical yield but moderate ee values were obtained (Table 4, entry 10). Toluene gave both lower chemical yield and ee values (Table 4, entry 11). So, CH_2Cl_2 was proven to be the best solvent in terms of selectivity.

We thus used **3** as the chiral ligand for enantioselective addition of trialkylgallium to a variety of aldehydes. The reactions were carried out at −60 °C in CH_2Cl_2 with three equivalents of trialkylgallium as optimal conditions. The results are summarized in Table 5. Moderate to good chemical yields of isolated products, in the range 50–84%, were obtained. All the predominant enantiomeric products obtained were of (*S*) configuration. The enantioselectivity varied from 20 to 84%, depending on the nature of the aldehyde. The addition of sterically bulkier triethylgallium to 4-nitrobenzaldehyde and 2-nitrobenzaldehyde provided the products with the best enantioselectivities, 81% (Table 5, entry 10) and 84% ee (Table 5, entry 11) respectively. The

Table 5. The addition of trialkylgallium to aldehydes with chiral titanium catalyst[a]



Entry	R	Aldehydes	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	Me	4-*tert*-Butylbenzaldehyde	64	70	(*S*)
2	Me	4-Methoxybenzaldehyde	65	50	(*S*)
3	Me	4-Nitrobenzaldehyde	84	40	(*S*)
4	Me	2-Nitrobenzaldehyde	78	25	(*S*)
5	Me	4-Chlorobenzaldehyde	55	44	(*S*)
6	Me	2-Chlorobenzaldehyde	62	45	(*S*)
7	Me	Phenylacetaldehyde	50	55	(*S*)
8	Me	Benzaldehyde	52	72	(*S*)
9	Et	Benzaldehyde	55	54	(*S*)
10	Et	4-Nitrobenzaldehyde	75	81	(*S*)
11	Et	2-Nitrobenzaldehyde	70	84	(*S*)
12	Et	4-Chlorobenzaldehyde	60	54	(*S*)
13	Et	2-Chlorobenzaldehyde	60	45	(*S*)
14	Et	4-Methoxybenzaldehyde	52	47	(*S*)
15	Et	4-*tert*-Butylbenzaldehyde	54	50	(*S*)
16	Et	Phenylacetaldehyde	50	40	(*S*)

[a] 10 mol% of $TiCl_4$ and chiral ligand, and three equivalents 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 excess values were determined by HPLC analysis using a Daicel Chiral OD-H column.
[d] The absolute configurations were determined by comparing the optical rotations with the literature values.[17,18]

change of the substituent group on the aromatic ring of the aldehydes to probe electronic effects displayed no regular trends in the enantioselectivity.

Conclusions

The utilization of organogallium and organoindium compounds as alkylation reagents in the addition to aldehydes was realized by using titanium tetrachloride as a strong Lewis acid catalyst. Furthermore, the catalytic asymmetric addition of organogallium to aldehydes was investigated with chiral titanium complexes, which was formed from titanium tetrachloride and the salan ligand, with moderate to good chemical yields and enantioselectivities up to 84% ee. Further work is under way in our laboratory to understand the mechanism and improve the enantioselectivity of this reaction.

EXPERIMENTAL

General

All reactions were performed in a glove box or using standard Schlenk techniques under an argon atmosphere. The solvents were refluxed with sodium benzophenone and

distilled under nitrogen prior to use. Trialkylgallium and trimethylindium were provided by the National 863 Program Advanced Material MO Precursors R&D Center of China (>98% purity). ^{1}H NMR data were collected on a Bruker ARX-300 spectrometer, with chemical shifts referenced to $SiMe_4$ as internal standard. IR spectra were obtained as KBr pellets with a 5DX-FT-2 spectrometer. Elemental analyses were performed on a Perkin–Elmer 240 C elemental analyzer. HPLC analyses were performed on a chiral column (Daicel Chiralcel OD-H column, Chromatography Interface 600 Series Link and Series 200 pump), with Series 200 UV–VIS detection at 254 nm.

Typical procedure of trialkylgallium or trialkylindium addition to aldehydes

In a 20 ml reaction tube, titanium tetrachloride (0.11 ml, 0.1 mmol) was dissolved in 2 ml of THF at room temperature, then trimethylgallium (0.3 ml, 3 mmol, in 2.7 ml of THF) was added dropwise, the mixture was stirred for 1 h at room temperature, followed by the addition of benzaldehyde (0.1 ml, 1 mmol). After the mixture was stirred at this temperature for another 23 h, water (3 ml) was added to quench the reaction. The aqueous layer was separated and further extracted with dichloromethane (25 × 4 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 thin-layer chromatography (TLC; petroleum ether : ethyl acetate, 5 : 1) to give 97 mg of α-methylbenzyl alcohol (80% yield).

Synthesis of ligand 3

Under argon atmosphere, 7.2 ml of *n*-BuLi (2.5 M solution in *n*-hexane, 18 mmol) was added to a solution of **2a** (1.3 g, 4 mmol) in 30 ml of THF dropwise at 0 °C. After 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 was continued for another 6 h. Then, water (30 ml) was added to quench the reaction, the aqueous layer was separated and extracted with CH_2Cl_2 (30 × 5 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, m.p.: 120 °C; $[\alpha_D^{25}]$ −6.7 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 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). ^{13}C NMR (300 MHz, $CDCl_3$), δ ppm: 158.247, 129.467, 129.400, 122.743, 119.423, 116.854, 62.346, 57.384, 35.947, 25.679, 22.681. Anal. Found: C, 74.03; H, 8.06; N, 7.72; Calc. for $C_{22}H_{30}N_2O_2$: C, 74.58; H, 8.53; N, 7.74%. MS: 354.0, 276.0, 247.1, 219.1, 141.0, 110.0 (100%), 70.0, 44.0. IR (KBr, cm^{-1}): 3422m, 2998s, 2945s, 2862m, 1612m, 1588s, 1488s, 1456s, 1373m, 1348s, 1284s, 1256s, 1243m, 1027m, 761m. MS (EI) *m*/*z* (100): 354 (40), 276 (54), 247 (62), 141 (64), 110 (100).

Typical procedure for the asymmetric addition of trimethylgallium to benzaldehyde

In a 20 ml reaction tube, ligand **3** (35.4 mg, 0.1 mmol) was dissolved in dichloromethane (3 ml) under 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 was stirred for 2 h at this temperature. Then, trimethylgallium (0.3 ml, 3 mmol, in 2.7 ml of dichloromethane) was added dropwise, the mixture was stirred for 1 h 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 (25 × 4 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 of α-methylbenzyl alcohol (52% yield). HPLC (Daicel Chiracel OD-H, hexane : isopropanol, 95: 5, flow rate 0.5 ml min^{-1}, $\lambda = 254$ nm): $t_r = 18.82$ min (major, *S*), $t_r = 22.77$ min (minor, *R*).

Acknowledgments

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