Titanium(IV) chloride, zirconium(IV) chloride or boron trichloride and phosphine-promoted Baylis–Hillman reaction of aldehydes with α,β-unsaturated ketone

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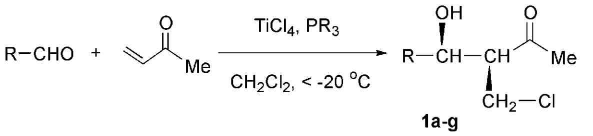
In the Baylis–Hillman reaction of aldehydes with an α,β-unsaturated ketone, the chlorinated compound **1** was obtained as the major product using tributylphosphine as a Lewis base in the presence of titanium(IV) chloride, zirconium(IV) chloride or boron trichloride in dichloromethane at <-20 °C. A plausible reaction mechanism has been proposed. Using (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as a chiral Lewis base, 10% ee could be achieved. We also found that, if the reaction was carried out at room temperature, the dehydrated compound **3** was obtained as the major product in the *Z*-configuration.

Introduction

Recently, the Baylis–Hillman reaction has become a very hot field for synthetic chemists.[1–11] The combination of a Lewis base such as SMe_2 or NEt_3 with the Lewis acid $TiCl_4$ can significantly speed up this reaction and give the corresponding chlorinated products.[12] Based on those previous results, we further attempt to explore new Lewis bases or Lewis acids and disclose the reaction mechanism of this interesting reaction. Herein we wish to report the full details of the $TiCl_4$, $ZrCl_4$ or BCl_3 and phosphine-promoted Baylis–Hillman reaction, along with a plausible mechanism based on the previous findings and our own results.

Results and discussion

Using procedures reported previously,[12b,c] we initially attempted the reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone in the presence of $TiCl_4$ (1.4 equiv.) and tributylphosphine (PBu_3) (0.2 equiv.) at −78 °C and found that the chlorinated product was also formed and the results were very similar to those using SMe_2 or NMe_3 as a Lewis base.[12b,c] For example, we carried out the reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone in the presence of $TiCl_4$ at −78 °C. No reactions occurred (Table 1, entry 1). After adding 20 mol% of tributylphosphine (PBu_3) as a Lewis base,[12b,c] the reaction took place smoothly to give the chlorinated product **1a**[12] as the major product (Scheme 1) (conditions B). At −78 °C, the reaction proceeded very well for aryl aldehydes having strong electron-withdrawing groups. The other aldehydes needed a higher temperature (−20 °C) for completion of the reaction. The results are summarized in Table 1. Triphenylphosphine can catalyze the reaction as well (Table 1, entry 9), but the reaction is relatively slow. In all cases, only one isomer was obtained and their relative configurations were confirmed as the *syn* form by comparison of their spectral data with those reported previously.[12b,c] For **1a**, we confirmed its configuration by X-ray analysis (Fig. 1).[13] Thus, the Lewis base did not affect the stereochemistry of the chlorinated products **1**. This is another novel system for producing *syn* form chlorinated products in the Baylis–Hillman reaction.



a: R = *p*-NO_2Ph, **b**: R = *m*-NO_2Ph, **c**: R = *p*-CF_3Ph,
d: R = *p*-EtPh, **e**: R = Ph, **f**: R = *p*-ClPh, **g**: R = $CH_3(CH_2)_3$

Scheme 1

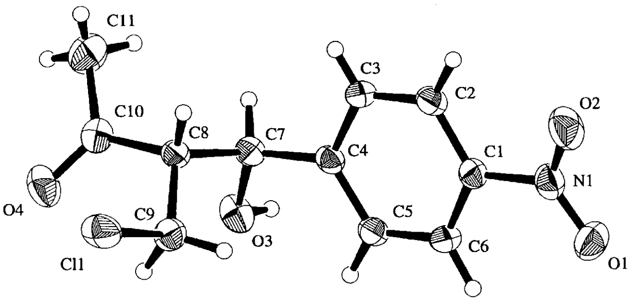
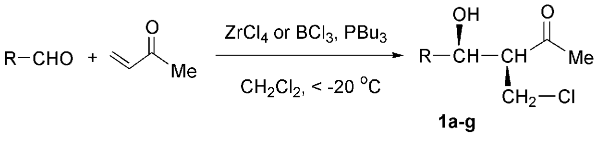


Fig. 1 The crystal structure of **1a**.

On the other hand, we examined many metal halides, such as $PdCl_2$, $RhCl_3$, Cp_2ZrCl_2, $ZrCl_4$, $AlCl_3$, TMSCl, $SiCl_4$, BF_3, BCl_3, as Lewis acids and found that BCl_3 and $ZrCl_4$ also worked for this reaction, although they are not as effective as $TiCl_4$. For example, we carried out the Baylis–Hillman reaction using BCl_3 as a Lewis acid and PBu_3 as a Lewis base under the same reaction conditions as those shown in Scheme 1. The *syn* chlorinated products can be also obtained (Scheme 2, Table 2). For *p*-nitrobenzaldehyde, 80% yield of **1a** could be obtained, but needed a longer reaction time (40 h) at −78 °C. The results are summarized in Table 2.



a: R = *p*-NO_2Ph, **b**: R = *m*-NO_2Ph, **c**: R = *p*-CF_3Ph,
d: R = *p*-EtPh, **e**: R = Ph, **f**: R = *p*-ClPh, **g**: R = $CH_3(CH_2)_3$

Scheme 2

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Table 1 Baylis–Hillman reaction of aldehydes with methyl vinyl ketone in the presence of $TiCl_4$ and Lewis base

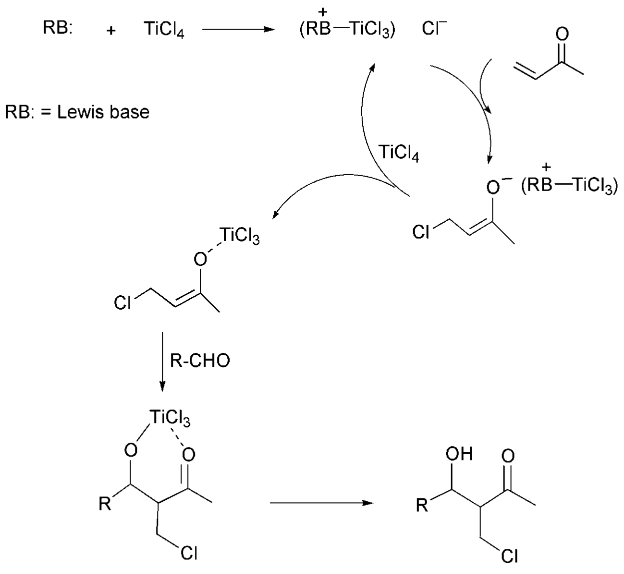
Entry	R	Lewis base	Conditions	Temp./°C	Time/h	Yield of **1** (%)[a]
1	*p*-NO_2Ph	None	A[b]	−78	12	—
2	*p*-NO_2Ph	PBu_3	B[c]	−78	12	80
3	*m*-NO_2Ph	PBu_3	B	−78	12	80
4	*p*-CF_3Ph	PBu_3	B	−78	48	81
5	*p*-EtPh	PBu_3	B	−20	72	51
6	Ph	PBu_3	B	−20	72	57
7	*p*-ClPh	PBu_3	B	−20	72	52
8	C_4H_9	PBu_3	B	−20	72	40
9	*p*-NO_2Ph	PBu_3	B	−78	24	40

[a] Isolated yields. [b] Aldehyde : $TiCl_4$ = 1 : 1.4. [c] Aldehyde : $TiCl_4$: Lewis base = 1 : 1.4 : 0.2.

Table 2 Baylis–Hillman reaction of aldehydes with methyl vinyl ketone in the presence of $ZrCl_4$, BCl_3 and PBu_3

Entry	R	Lewis acid	Conditions	Temp./°C	Time/h	Yield of **1** (%)[a]
1	*p*-NO_2Ph	$ZrCl_4$	B[b]	−78	40	50
2	*m*-NO_2Ph	$ZrCl_4$	B	−78	40	50
3	*p*-CF_3Ph	$ZrCl_4$	B	−78	48	41
4	*p*-NO_2Ph	BCl_3	B	−78	40	80
5	*m*-NO_2Ph	BCl_3	B	−78	40	60
6	*p*-CF_3Ph	BCl_3	B	−20	40	55
7	Ph	BCl_3	B	−20	80	45
8	*p*-EtPh	BCl_3	B	−20	80	25
9	*p*-ClPh	BCl_3	B	−20	80	26

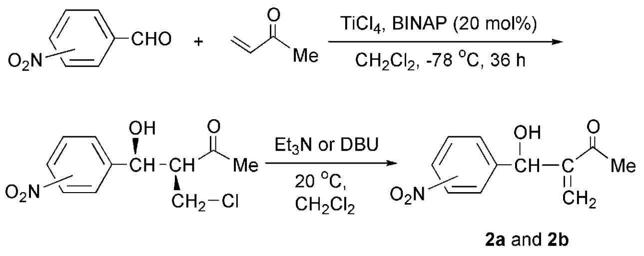
[a] Isolated yields. [b] Aldehyde : BCl_3 : Lewis base = 1 : 1.4 : 0.2.



Scheme 3

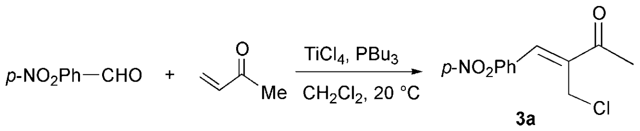
Concerning the reaction mechanism, Kataoka has reported a plausible reaction mechanism for the Baylis–Hillman reaction using SMe_2 as a Lewis base and $TiCl_4$ as a Lewis acid and explained why the *syn*-form chlorinated products could be formed predominantly.[12a] During our own investigation on the Baylis–Hillman reactions mentioned above, we always observed that, when $TiCl_4$ was combined with Lewis bases such as amines, phosphines or SMe_2 in dichloromethane, the solution immediately became dark red with some precipitation at low temperature. This phenomenon suggests that coordination of the Lewis base to $TiCl_4$ takes place and consequently changes the oxidation state of the Ti metal center. In fact, the previous studies on the reactions of phosphines with $TiCl_4$ have shown that many phosphines can coordinate to the Ti metal center. For example, the matrix-isolation technique and an infrared spectroscopy study have proved and characterized the 1 : 1 complexes of $TiCl_4$ with PH_3 or AsH_3.[14] In addition, in the normal reaction of $TiCl_4$ with phosphines, the formation of face-sharing ionic Ti(II) or Ti(III) clusters has been reported in which the molecular structures of $[PPh_4]_3[Cl_3Ti(\mu\text{-}Cl)_3(\mu\text{-}Cl)_3\text{-}TiCl_3]\cdot 2CH_2Cl_2$ and $[PPh_4]_3[Cl_3Ti(\mu\text{-}Cl)_3TiCl_3]\cdot 4CH_2Cl_2\cdot 0.5PhMe$ have been determined by X-ray analysis.[15] Furthermore, in the reactions of amines with $TiCl_4$, the formation of similar ionic Ti complexes having a chloride ion has been reported.[16] Based on these previous findings and our own investigation,[12c] we believe that, in the above Baylis–Hillman reactions, Lewis bases such as amines or phosphines first react with $TiCl_4$ to give an ionic Ti metal cluster having a chloride anion which then undergoes Michael attack on the α,β-unsaturated ketone to initiate the reaction (Scheme 3). Using BCl_3 or $ZrCl_4$ as a Lewis acid, the reaction proceeds by the same mechanism. If the Lewis bases can coordinate to Lewis acids such as $TiCl_4$, $ZrCl_4$ or BCl_3 and kick out the chloride ion, the reaction can take place to give the corresponding chlorinated product at low temperature. This finding obviously opens the way for achieving catalytic enantioselective Baylis–Hillman reactions by means of chiral phosphine ligands in a catalytic process.[17] However, as can be seen from Scheme 3, the chiral Lewis base obviously only forms an ion pair with the enolate and it does not participate in the attack on aldehydes in the last step. Thus it is very difficult to use this reaction process to achieve high enantioselectivity. As a matter of fact, we utilized a famous chiral ligand, (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), as a chiral ligand for this purpose.[18] Using 20 mol% of BINAP as a chiral Lewis base and *p*- or *m*-nitrobenzaldehyde as a substrate, Baylis–Hillman olefin **2a** or **2b** could be obtained in only 10% and 9% ee, respectively, after treating the chlorinated product **1a** or **1b** with triethylamine or DBU (Scheme 4). This result also partially supports the reaction mechanism shown in Scheme 3.

On the other hand, by carrying out this reaction at room temperature, we confirmed that the elimination product **3** was the only product (Scheme 5). This reaction was first disclosed by Li and co-workers. They reported that, in the presence of stoichiometric or nonstoichiometric TiX_4, compound **3** could be formed in the *Z*-configuration.[19] Later we also reported that **3** could be exclusively obtained in the $TiCl_4$ and chalcogenide-promoted Baylis–Hillman reaction at room temperature (20 °C).[12b] The *Z*-configuration has been disclosed by X-ray



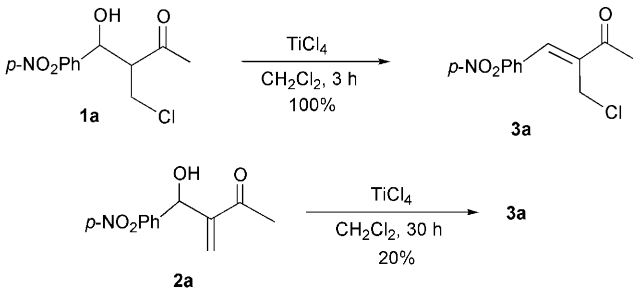
For **2a** (*p*-NO_2Ph): ee 10%, yield: 60%
For **2b** (*m*-NO_2Ph): ee 9%, yield: 70%

Scheme 4



Scheme 5

analysis.[12b] Based on Li's report,[19] compound **3** could be formed even in the absence of any Lewis base. In order to clarify the formation of **3**, we treated **1a** and **2a** directly with $TiCl_4$ in dichloromethane at room temperature. We found that **1a** can be transformed to **3a** within 3 h, whereas the reaction of **2a** was much slower (Scheme 6). These results strongly suggest that **3a** is derived directly from **1a** formed first in the reaction. Thus, we believe that, at room temperature, the chlorinated products **1** could be formed either in the absence or in the presence of Lewis base, but they are rapidly transformed to the elimination product **3** exclusively.



Scheme 6

Conclusion

We found that the titanium(IV) chloride and phosphine-promoted Baylis–Hillman reaction is a very efficient reaction system for producing chlorinated compound **1**. Phosphine compounds are good Lewis bases for this reaction. BCl_3 and $ZrCl_4$ are good Lewis acids for this reaction as well. In comparison with the previous results,[12b,c] the activities of Lewis acids for this reaction are $TiCl_4 > BCl_3 > ZrCl_4$ and the activities of Lewis bases are $NEt_3 > PBu_3 > SMe_2$. The best combination of Lewis acid and Lewis base for this reaction is $TiCl_4$ (1.4 equiv.) with NEt_3 (0.2 equiv.). The relative configuration of **1** was not affected at all by the Lewis bases (SMe_2, NEt_3, PBu_3) or Lewis acids ($TiCl_4$, BCl_3, $ZrCl_4$) used. This reaction was initiated by chloride ion attacking at the α,β-unsaturated ketone Michael acceptor. The chloride ion was produced by coordination of Lewis bases (SMe_2, NEt_3, PBu_3) to Lewis acids such as $TiCl_4$, BCl_3, and $ZrCl_4$. In this reaction system, it is very difficult to achieve high enantioselectivity just by using catalytic amounts of chiral Lewis bases. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose its scope and limitations. Studies along these lines are currently in progress.

Experimental

General

Mps were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. Mass spectra were recorded with an HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. Organic solvents were dried by standard methods when necessary. Some of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo-Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai $60F_{254}$ silica gel-coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure.

The physical data and spectral data of **1a**–**g** are the same as those reported previously.[12]

Typical reaction procedure for the preparation of *syn*-3-(chloromethyl)-4-hydroxy-4-(4′-nitrophenyl)butan-2-one 1a

To a solution of tributylphosphine (5.05 mg, 0.025 mmol) in dichloromethane (1.3 mL) was added 1.4 M titanium tetrachloride in dichloromethane (0.7 mL, 0.7 mmol) at −78 °C. After stirring for 5 min, a solution of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) and methyl vinyl ketone (105 mg, 1.5 mmol, 123 μL) were added. The reaction mixture was kept for 24 h at −78 °C. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (1.0 mL). After filtration, the filtrate was extracted with dichloromethane (5.0 mL × 2) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography to give compound **1a** (102 mg, 80%) as a colorless solid (eluent: ethyl acetate–petroleum ether = 1 : 4); mp 90–91 °C; IR (KBr) ν 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20 (3H, s, Me), 2.93 (1H, br s, OH), 3.22–3.38 (1H, m), 3.67 (1H, dd, *J* 11.3, 4.0 Hz), 3.89 (1H, dd, *J* 11.3, 9.2 Hz), 5.11 (1H, d, *J* 5.6 Hz), 7.56 (2H, d, *J* 8.6 Hz, Ar), 8.25 (2H, d, *J* 8.6 Hz, Ar); MS (EI) *m/z* 258 (MH^+, 0.60), 208 ($M^+ - 49$, 60), 71 ($M^+ - 186$, 100) [Found: C, 51.64; H, 4.94; N, 5.35%. $C_{11}H_{12}ClNO_4$ requires C, 51.27; H, 4.69; N, 5.44%].

Acknowledgements

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13 The crystal data of **1a**:† empirical formula: $C_{11}H_{12}ClNO_4$; formula weight: 257.67; crystal color, habit: colorless, column; crystal dimensions: 0.28 × 0.30 × 0.18 mm; crystal system: orthorhombic; lattice type: primitive; lattice parameters: $a = 10.615(1)$, $b = 14.277(1)$, $c = 7.838(1)$ Å, $V = 1187.8(3)$ Å^3; space group: $P2_12_12_1$ (#19); $Z_{\text{value}} = 4$; $D_{\text{calc}} = 1.441$ g cm^{-3}; $F_{000} = 536.00$; μ(Mo-Kα) = 3.23 cm^{-1}; temperature of data collection: 24 °C; residuals: R; $R_w = 0.065$; 0.052; residuals: $R1 = 0.033$; no. of reflections to calc. $R1$: 1108.

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