Titanium(IV) Chloride and Quaternary Ammonium Salt Promoted Baylis−Hillman Reaction

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The Baylis−Hillman reaction of aldehydes with α,β-unsaturated ketones can be drastically affected by the reaction temperature and Lewis bases. When the reaction was carried out at −78 °C using catalytic amounts of quaternary ammonium salts ($R_4N^+X^-$, X = Cl, Br, I) as Lewis bases, in the presence of titanium(IV) chloride, the chlorinated aldol adduct **1** was obtained as the major product. Quaternary ammonium bromides and iodides ($R_4N^+X^-$, X = Br, I) have higher catalytic activity than corresponding chlorides ($R_4N^+Cl^-$). Quaternary ammonium fluorides ($R_4N^+F^-$) do not have activity at all. The amounts of Lewis acid and quaternary ammonium salts used affect the reaction rate and product. A plausible reaction mechanism is proposed. If the reaction was carried out at room temperature (about 20 °C) in the presence of titanium(IV) chloride and quaternary ammonium salts ($R_4N^+X^-$, X = Cl, Br, I), the elimination product **3**, derived from **1**, was formed as the major product.

Introduction

The Baylis−Hillman reaction and related processes, typically catalyzed by DABCO or tertiary phosphines, have become increasingly important in organic synthesis because the resulting adducts may have several functional groups available for numerous further transformations.[1−5] The major drawbacks of the Baylis−Hillman reaction are its slow reaction rate and limited range of substrates. To overcome these shortcomings, many efforts have been made, such as using Lewis acids or various other additives to activate carbonyl electrophiles.[6−10] Among those Lewis acids examined, $TiCl_4$ has been successfully utilized to promote the Baylis−Hillman reaction in the presence of Lewis base catalysts.[11] Recently, Li and co-workers reported new C═C bond formation via nonstoichiometric titanium(IV) halide mediated vicinal difunctionalization of α,β-unsaturated acyclic ketones in the presence of catalytic amounts of $Bu_4N^+I^-$.[12] We have also carried out similar but independent research and found different results. The reaction temperature, the anion of the quaternary ammonium salts, and the amount of Lewis acid or Lewis base can drastically affect the reaction. These effects have never been disclosed before. Herein we wish to report the full details of titanium(IV) chloride and quaternary ammonium salts promoted Baylis−Hillman reaction, along with a plausible reaction mechanism based on the previous findings and our own results.

Table 1. Reaction of *p*-Nitrobenzaldehyde with Methyl Vinyl Ketone in the Presence of $TiCl_4$ and Ammonium Salt at −78 °C

entry	ammonium salt (equiv)	$TiCl_4$ (equiv)	time (day)	yield (%)[a] 1a	2a
1		1.0	5		
2	$Bu_4N^+Br^-$ (0.0t)	0.5	5	82	0
3	$Bu_4N^+Br^-$ (0.25)	0.5	5	73	10
4	$Bu_4N^+Br^-$ (0.5)	0.5	5	71	16
5	$Bu_4N^+Br^-$ (1.0)	0.5	5	47	32
6	$Bu_4N^+Br^-$ (0.25)	1.0	3	82	trace
7	$Bu_4N^+Br^-$ (0.25)	1.4	1	85	7
8	$Bu_4N^+Br^-$ (0.05)	1.4	1	91	0
9	$Bu_4N^+I^-$ (0.25)	0.25	7	30	10
10	$Bu_4N^+I^-$ (0.25)	0.5	5	86	7
11	$Bu_4N^+I^-$ (0.25)	1.0	3	88	5
12	$Bu_4N^+I^-$ (0.05)	1.4	1	90	trace
13	$Bu_4N^+I^-$ (0.25)	1.4	1	87	6
14	$Bu_4N^+Cl^-$ (0.25)	1.4	3	65	trace
15	$PhCH_2Et_3N^+Cl^-$ (0.25)	1.4	3	70	trace
16	$Bu_4N^+F^-$ (0.25)	1.4	3		

[a] Isolated yields.

Results and Discussion

We initially attempted the reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone in the presence of $TiCl_4$ (1.0 equiv) at −78 °C. No reactions occurred (Table 1,

(1) For reviews, see: (a) Ciganek, E. *Org. React.* **1997**, *51*, 201. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

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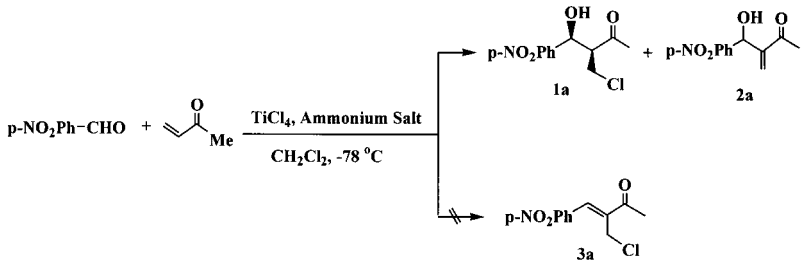
Scheme 1



entry 1). However, after adding 5 mol % (0.05 equiv) of tetrabutylammonium bromide as a Lewis base, the reaction took place smoothly to give the chlorinated product **1a**, rather than **2a** and **3a** (which were usually considered as the Baylis−Hillman olefin and trisubstituted alkene) reported by Kataoka and Li,[9,12] respectively (Scheme 1, Table 1, entry 2). By careful investigation, we found that this reaction was very sensitive to the amounts of both $TiCl_4$ and quaternary ammonium salts present in the reaction mixture (Table 1). With 0.05 equiv of tetrabutylammonium bromide and 0.5 equiv of $TiCl_4$, the reaction required 5 days to provide **1a** in 82% yield (Table 1, entry 2). Increasing the amount of $TiCl_4$ in the presence of catalytic amounts of quaternary ammonium salt could significantly speed up the reaction and gave higher yields of **1a** (Table 1, entries 3, 6, and 7). Increasing the amount of quaternary ammonium salt reduced the selectivity of the reaction with the yield of the Baylis−Hillman olefin **2a** remarkably increased (Table 1, entries 3−5). The reaction using $Bu_4N^+Cl^-$ or $PhCH_2Et_3N^+Cl^-$ as a promoter was slower than those using $Bu_4N^+I^-$ and $Bu_4N^+Br^-$ under the same reaction conditions (Table 1, entries 14 and 15), whereas $Bu_4N^+F^-$ could not promote the reaction at all under the same conditions (Table 1, entry 16). These results suggested that the anion of quaternary ammonium salts played a very important role in this reaction. The tetrabutylammonium bromide ($Bu_4N^+Br^-$) showed the highest catalytic activity. Thus, the best reaction conditions were shown by entry 8, with 0.05 equiv (5 mol %) of $Bu_4N^+Br^-$ as Lewis base and 1.4 equiv of $TiCl_4$ as Lewis acid at −78 °C (Table 1, entry 8). In all those cases, only chlorinated compound was formed. It is interesting to note that neither brominated nor iodinated product was detected when using the bromide or iodide as promoter. This means that only chloride ions from $TiCl_4$ takes part in the reaction.

Next we examined other aldehydes using the optimized reaction conditions. We found that, for aryl aldehydes having a strong electron-withdrawing group on the phenyl ring, the reaction proceeded quickly at −78 °C to give **1** in high yields (Scheme 2, Table 2, entry 1). However, other aryl aldehydes or aliphatic aldehydes needed higher temperatures (−20 °C) to produce **1** in moderate to high yields (Table 2, entries 3−8). Aryl aldehydes can also react with acrylonitrile under similar reaction conditions to give the corresponding elimination product **2i** in moderate yields (in dichloromethane at 10 °C for 5 days). At −78 °C, no reaction occurred. Raising the reaction temperature to reflux (45 °C) led to a decrease in the yield of **2i** (Scheme 3). No reactions occurred with methyl acrylate as Michael acceptor (Scheme 3).

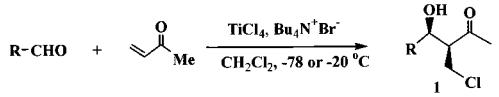
The ^1H NMR spectroscopic data and HPLC analyses showed that only one diastereoisomer (syn/anti) was

Table 2. Baylis−Hillman Reaction of Aldehydes with Methyl Vinyl Ketone in the Presence of $TiCl_4$ (1.4 equiv) and $Bu_4N^+Br^-$ (0.05 equiv) at Low Temperature

entry	R	temp/°C	time/h	yield (%)[a] of **1**
1	*o*-NO_2Ph	−78	36	92
2	*p*-CF_3Ph	−78	72	40
3	*p*-CF_3Ph	−20	36	90
4	*p*-ClPh	−20	36	52
5	*m*-FPh	−20	36	80
6	*p*-EtPh	−20	36	52
7	Ph	−20	36	67
8	$CH_3(CH_2)_8$	−20	36	29

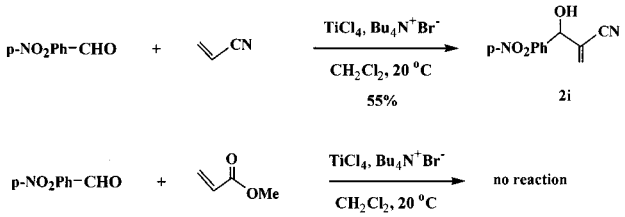
[a] Isolated yield.

Scheme 2

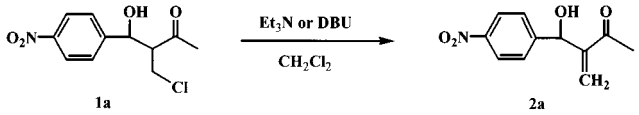


b:R= o-NO_2Ph, c: R= *p*-CF_3Ph, d: R= *p*-ClPh, e: R= *m*-FPh; f: R= *p*-EtPh; g: R= Ph, h: R= $CH_3(CH_2)_8$.

Scheme 3

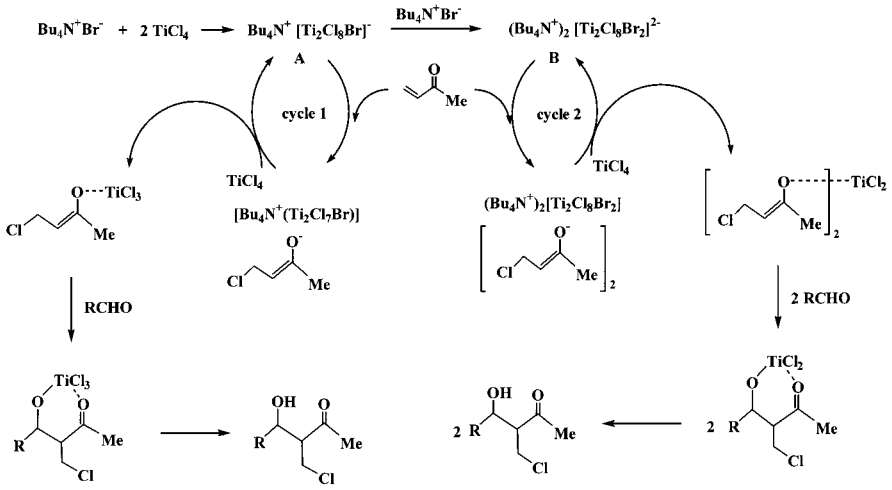


Scheme 4



formed from aldehydes in the reaction. Their relative configurations were assigned as syn-form on the basis of X-ray analysis of the crystal structure of **1a**[13] (Figure 1, Supporting Information). The HPLC analysis also supported our results. Compound **1** could be transformed to compound **2**[9d] by treatment with an excess (2.0 equiv) of triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature (Scheme 4). Purification of **1** by preparative TLC also caused the transformation of **1** to **2**. Thus, rapid flash column chromatography was necessary to obtain pure **1**. However, when the reaction was carried out at higher temperatures (0 °C), we found that both syn and anti isomers could be formed at the same time, along with **2** and **3**. For example, in the reaction of *o*-nitrobenzaldehyde with methyl vinyl ketone at 0 °C using 1.4 equiv of $TiCl_4$ and 0.05 equiv of $Bu_4N^+Br^-$ for 6 h, syn-**1a** and anti-**1a** were produced in a ratio of 4:1. Thus, to obtain **1** in one isomer with high yield, the

Scheme 5



reaction should be strictly kept at lower temperature. Recently Kataoka and co-workers reexamined his chalcogen−Baylis-Hillman reaction at 0 °C and disclosed the plausible mechanism for the formation of syn- and anti-**1a**.[14]

In fact, the reaction of quaternary ammonium bromide or chloride with methyltitanium chloride had been investigated by Clark and Coles previously.[15] The resulting complex was quite complicated. Two different series of binuclear anionic complex salts could be formed depending on the molar ratios of the reactants (type A, $R[Me_2Ti_2X_6Y]$; type B, $[R]_2[MeTiX_3Y_2]$, X = Cl, Y = Cl, Br).[16] In our experiments, we found that mixing $TiCl_4$ with quaternary ammonium salt gave a dark red solution, which was very similar to that reported by Clark and Coles in the reaction of quaternary ammonium bromide or chloride with methyltitanium chloride. We believe that similar binuclear anionic chemical species exist in the reaction system involving quaternary ammonium salts with $TiCl_4$, which are the true active catalysts for this reaction. In Scheme 5 we propose a mechanism for the formation of **1** on the basis of these previous findings and the results of our own investigations (Table 1). The quaternary ammonium salt first reacted with $TiCl_4$ to form intermediate A, which further reacted with the quaternary ammonium salt to give intermediate B if the reaction system contained sufficient quaternary ammonium salt (Scheme 5). The anionic complex A acted as the key activator by chloride ion attacking at methyl vinyl ketone to carry out cycle 1. If the system contains a large amount of quaternary ammonium salt, the anionic complex B would become the major activator of cycle 2 by carrying two chloride ions to initiate the chlorinated aldol reaction. The reaction in cycle 1 was fast, but cycle 2, which would give two chloride ions from binuclear anionic titanium, was slow. Thus, 0.05 equiv of quaternary ammonium salt and 1.4 equiv of $TiCl_4$ produced a high yield of **1** in a short time. With 0.25 equiv of quaternary ammonium salt and 0.5 equiv of $TiCl_4$, the yield of **1** could reach about 80%, but the reaction required 5 days. We tried to isolate the proposed anionic complexes, but did not succeed so far. In fact, the formation of chlorinated compound **1** is a major reaction process in the $TiCl_4$ and Lewis base promoted Baylis−Hillman reaction. However, it is not understood yet why the yield of Baylis−Hillman olefin **2a** can be increased by using a large amount of quaternary ammonium salt as a Lewis base and why at low temperature only one isomer was formed.

Scheme 6

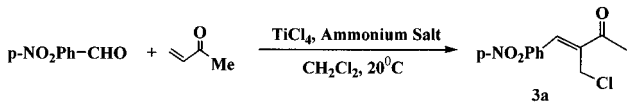


Table 3. Reaction of *p*-Nitrobenzaldehyde with Methyl Vinyl Ketone in the Presence of $TiCl_4$ and 0.26 equiv of Ammonium Salt at Room Temperature

entry	ammonium salt	$TiCl_4$/equiv	time/day	yield (%)[a] of **3a**
1	$Bu_4N^+F^-$	0.26	5	
2	$PhCH_2Et_3N^+Cl^-$	0.26	5	20
3	$PhCH_2Et_3N^+Cl^-$	0.5	4	70
4	$Bu_4N^+Br^-$	0.26	5	71
5	$Bu_4N^+Br^-$	0.5	4	80
6	$Bu_4N^+Br^-$	1.0	1	92
7	$Bu_4N^+I^-$	0.26	5	60
8	$Bu_4N^+I^-$	0.5	4	73
9	$Bu_4N^+I^-$	1.0	1	84

[a] Isolated yield.

By carrying out this reaction at room temperature, we confirmed that elimination product **3** was the only product, as reported by Li and co-workers (Scheme 6).[12] However, we found that the yield of **3** could also be affected drastically by the amount of $TiCl_4$. Some of our results were in conflict with those reported by Li. Using *p*-nitrobenzaldehyde as the substrate in the presence of 0.26 equiv of $TiCl_4$ and 0.26 equiv of $Bu_4N^+Br^-$ or $Bu_4N^+I^-$, **3a** could be obtained in 71 and 60%, respectively, after 5 days (Scheme 6, Table 3, entries 4 and 7). The yields of **3a** were slightly lower, but the reaction time was much longer than the 24 h reported by Li. $Bu_4N^+F^-$ showed no catalytic activity for this reaction. $Bu_4N^+Cl^-$ (quaternary ammonium chloride) was less effective than either $Bu_4N^+Br^-$ (quaternary ammonium bromide) or

(13) Crystal data for **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) Å, b = 14.277(1) Å, c = 7.838(1) Å, V = 1187.8(3) Å^3; space group: $P2_12_12_1$ (No. 19); Z_{value} = 4; D_{clalc} = 1.441 g/cm^3; F_{000} = 536.00; μ(Mo Kα) = 3.23 cm^{-1}; residuals R, R_w = 0.065, 0.052.

(14) Kataoka, T.; Kinoshita, H.; Iwama, T.; Tsujiyama, S.-I.; Iwamura, T.; Watanabe, S.-I.; Muraoka, O.; Tanabe, G. *Tetrahedron* **2000**, *56*, 4725.

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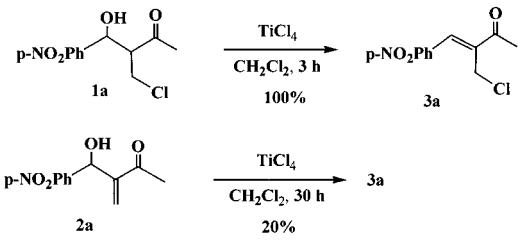
Table 4. Baylis-Hillman Reaction of Aldehydes with Methyl Vinyl Ketone in the Presence of 1.0 Eq of $TiCl_4$ and 0.25 Eq of $Bu_4N^+Br^-$ at Room Temperature

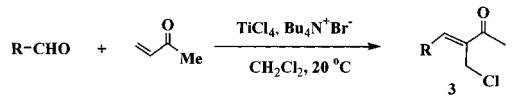
entry	R	time/h	yield (%)[a] of **3**
1	*o*-NO_2Ph	24	91
2	*p*-CF_3Ph	24	86
3	*p*-ClPh	24	60
4	*m*-FPh	24	78
5	*p*-EtPh	36	50
6	Ph	24	71
7	$Me(CH_2)_8$	24	30

[a] Isolated yield.

Scheme 7



Scheme 8



b:R= *m*-NO_2Ph, c: R= *p*-CF_3Ph, d: R= *p*-ClPh, e: R= *m*-FPh; f: R= *p*-EtPh; g: R= Ph; h: R= $Me(CH_2)_8$.

$Bu_4N^+I^-$ (quaternary ammonium iodide) (Table 3, entries 1−3). We also found that increasing the amount of $TiCl_4$ could enhance the reaction rate and give a higher yield of **3a** in a shorter time (Table 3, entries 5, 6, 8, and 9). By using 1.0 equiv of $TiCl_4$ and 0.26 equiv of $Bu_4N^+Br^-$, the reaction could be completed in 1 day (24 h); these was found to be the best reaction conditions for the preparation of **3a**. The amount of quaternary ammonium salt did not affect the reaction product or the yield of **3a** because, using 0.05 equiv or 0.5 equiv of $Bu_4N^+Br^-$ in the presence of 1.0 equiv of $TiCl_4$, **3a** was obtained in the 90 and 91%, respectively, very similar to the yields obtained using 0.26 equiv of $Bu_4N^+Br^-$ (Table 4, entry 6).

Concerning the formation of **3a**, we treated **1a** and **2a** directly with $TiCl_4$ in dichloromethane at room temperature. We found that **1a** was transformed to **3a** within 6 h, whereas the reaction of **2a** was much slower (Scheme 7). These results strongly suggest that **3a** is derived directly from **1a** formed first in the reaction. The *Z*-configuration of **3a** has been confirmed by X-ray analysis in our previous paper (Figure 2, Supporting Information).[17]

Using the optimized reaction conditions, we carried out this reaction using various aldehydes (Scheme 8, Table 4). Aryl aldehydes with a strongly electron-withdrawing group on the phenyl ring gave higher yields of **3** (Table 4, entries 1 and 2); 70−80% yields of **3** could be achieved for many aryl aldehydes. For aliphatic aldehydes, the yield of **3** was only moderate (Table 4, entry 7).

Conclusions

We have found that titanium(IV) chloride and quaternary ammonium salt promoted the Baylis−Hillman reaction and that the reaction was not as simple as previously reported. The reaction temperature, the amount of Lewis acid, and the amount of Lewis base can drastically affect the reaction product and reaction rate. We propose that two catalytic cycles work together at low temperatures: cycle 1 is based on the active catalyst A and cycle 2 is based on the active catalyst B (Scheme 5). In the reaction system with a large excess of $TiCl_4$ (1.4 equiv) and a catalytic amount of quaternary ammonium salt (0.05 equiv), cycle 1 plays a major role in the formation of the chlorinated compound **1** because catalyst A is formed predominantly and it catalyzes a fast reaction. Using a smaller amount of $TiCl_4$ (0.5 equiv) and a catalytic amount of quaternary ammonium salt (0.25 equiv), cycle 2 plays a major role in the formation of the chlorinated compound **1**, because catalyst B is formed predominantly and it catalyzes a slow reaction. Thus, the ratio of $TiCl_4$ to quaternary ammonium salt is crucial for this reaction. Undoubtedly compound **3** was derived mainly from **1**. If a quaternary ammonium salt is used as the Lewis base, the counterion is also important. Efforts are underway to elucidate the mechanistic details of this reaction and to define the scope and limitations of this reaction. In addition, we are planning to synthesize chiral quaternary ammonium salts for use as chiral Lewis bases to accomplish enantioselective Baylis−Hillman reactions.

Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI method and HRMS was measured on a Finnigan MA+ mass spectrometer. Organic solvents used were dried by standard methods when necessary. Commercially available reagents were used without further purification. HPLC analysis was carried out by column: Kromasil 4.6 × 150 mm and LUNA C_{18} 4.6 × 150 mm, respectively. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 300−400 mesh silica gel.

Typical Reaction Procedure for the Preparation of *syn*-3-(Chloromethyl)-4-hydroxy-4-(4′-nitrophenyl)-2-butanone (1a). To a solution of tetrabutylammonium bromide (8.06 mg, 0.025 mmol) in dichloromethane (1.3 mL) was added 1.4 N titanium tetrachloride in dichloromethane (0.7 mL, 0.7 mmol) at −78 °C. After beibg stirred 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 uL) were added. The reaction mixture was kept for 24 h at −78 °C. The reaction was quenched by addition of a 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** (117 mg, 91%) 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/e* 258 (MH^+, 0.60), 208

(17) Shi, M.; Jiang, J.-K. Tetrahedron, **2000**, *56*, 4793. The crystal data of **3a**: empirical formula $C_{22}H_{20}N_2O_6Cl_2$; formula weight 479.32; crystal color, habit - colorless, prismatic; crystal dimensions 0.20 × 0.20 × 0.30 mm; crystal system monoclinic; lattice type: primitive; lattice parameters: a = 7.524(2) Å, b = 17.541(3) Å, c = 17.07(1) Å, β = 98.64(4)°, V = 2227(1) Å^3; space group: $P2_1/n$ (No. 14); Z value = 4; D_{calc} = 1.429 g/cm^3; F_{000} = 992.00; μ(Mo Kα) = 3.33 cm^{-1}; R = 0.066, R_w = 0.061. TEXSAN, Crystal Structure Analysis Package, Molecular Structure Corporation, Houston, TX, 1985 and 1992.

($M^+ - 49$, 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.

Preparation of *syn*-3-(Chloromethyl)-4-hydroxy-4-(2′-nitrophenyl)-2-butanone (1b). This compound was prepared in the same manner as that described above: white solid, mp 70−71 °C; 118 mg, 92%; IR (KBr) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (3H, s, Me), 3.45 (1H, br s, OH), 3.46−3.60 (2H, m, CH_2), 3.95 (1H, ddd, J = 12.1 12.1 2.1 Hz, CH), 5.67 (1H, s, CH), 7.52 (1H, t, J = 7.5 Hz, Ar), 7.71 (1H, t, J = 7.5 Hz, Ar), 7.87 (1H, d, J = 7.7 Hz, Ar), 8.10 (1H, d, J = 8.1 Hz, Ar); MS (EI) *m/e* 257 (M^+, 0.60), 208 ($M^+ - 49$, 60), 71 ($M^+ - 186$, 100); HRMS (EI) *m/z* 239.0353 ($M^+ - H_2O$), $C_{11}H_{10}O_3NCl$ requires M − H_2O, 239.0349.

Preparation of *anti*-3-(Chloromethyl)-4-hydroxy-4-(2′-nitrophenyl)-2-butanone (1b′). This compound was prepared in the same manner as that described above: white solid, mp 70−71 °C; 27 mg, 23%; IR (KBr) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.14 (3H, s, Me), 3.48 (1H, br s, OH), 3.50−3.65 (2H, m, CH_2), 3.86 (1H, dd, J = 9.4 9.4 Hz, CH), 5.57 (1H, d, J = 3.5 Hz, CH), 7.52 (1H, t, J = 7.5 Hz, Ar), 7.69 (2H, t, J = 7.5 Hz, Ar), 8.02 (1H, d, J = 8.1 Hz, Ar); MS (EI) *m/e* 257 (M^+, 0.60), 208 ($M^+ - 49$, 60), 71 ($M^+ - 186$, 100); HRMS (EI) *m/z* 239.0353 ($M^+ - H_2O$), $C_{11}H_{10}O_3NCl$ requires M − H_2O, 239.0349.

Preparation of *syn*-3-(Chloromethyl)-4-hydroxy-4-(4′-trifluoromethylphenyl)-2-butanone (1c). This compound was prepared in the same manner as that described above, but at −20 °C: 126 mg, 90%; a colorless oil; IR (KBr) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.13 (3H, s, Me), 2.65 (1H, br s, OH), 3.22−3.37 (1H, m), 3.70 (1H, dd, J = 10.2, 3.9 Hz), 3.89 (1H, dd, J = 10.2, 10.2 Hz), 5.02 (1H, d, J = 6.1 Hz), 7.37 (2H, d, J = 8.0 Hz, Ar), 7.64 (2H, d, J = 8.0 Hz, Ar); MS (EI) *m/e* 280 (M^+, 0.45), 243 ($M^+ - 37$, 40), 43 ($M^+ - 237$, 100); HRMS (EI) *m/z* 262.0377 ($M^+ - H_2O$), $C_{12}H_{10}OClF_3$ requires M − H_2O, 262.0372.

Preparation of *syn*-3-(Chloromethyl)-4-hydroxy-4-(4′-chlorophenyl)-2-butanone (1d). This compound was prepared in the same manner as that described above, but at −20 °C: 64 mg, 52%; a colorless oil; IR (KBr) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.0 (3H, s, Me), 2.50 (1H, br s, OH), 3.20−3.32 (1H, m), 3.75 (1H, dd, J = 10.7, 3.8 Hz), 3.87 (1H, dd, J = 10.7, 10.7 Hz), 4.82 (1H, d, J = 6.7 Hz), 7.10−7.32 (4H, m, Ar); MS (EI) *m/e* 246 (M^+, 1.20), 121 ($M^+ - 125$, 20), 91 ($M^+ - 155$, 100); HRMS (EI) *m/z* 246.0210 (M^+), $C_{11}H_{12}O_2Cl_2$ requires M, 246.0214.

Preparation of *syn*-3-(Chloromethyl)-4-hydroxy-4-(3′-fluorophenyl)-2-butanone (1e). This compound was prepared in the same manner as that described above, but at −20 °C: 92 mg, 80%; a colorless oil; IR (KBr) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.0 (3H, s, Me), 2.50 (1H, br s, OH), 3.20−3.32 (1H, m), 3.75 (1H, dd, J = 10.7, 3.8 Hz), 3.87 (1H, dd, J = 10.7, 10.7 Hz), 4.82 (1H, d, J = 6.7 Hz), 7.10−7.50 (4H, m, Ar); MS (EI) *m/e* 230 (M^+, 1.60), 105 ($M^+ - 125$, 20), 75 ($M^+ - 155$, 100); HRMS (EI) *m/z* 230.0512 (M^+), $C_{11}H_{12}O_2ClF$ requires *M*, 230.0510.

Preparation of *syn*-3-(Chloromethyl)-4-hydroxy-4-(4′-ethylphenyl)-2-butanone (1f). This compound was prepared in the same manner as that described above, but at −20 °C: 63 mg, 52%; a colorless solid; mp 69−71 °C; IR (KBr) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (3H, t, J = 7.7 Hz), 2.02 (3H, s, Me), 2.15 (1H, br s, OH), 2.63 (2H, q, J = 7.7 Hz), 3.22−3.37 (1H, m), 3.80 (1H, dd, J = 10.7, 3.8 Hz), 3.90 (1H, dd, J = 10.7, 10.7 Hz), 4.82 (1H, d, J = 7.2 Hz), 7.10−7.32 (4H, m, Ar); MS (EI) *m/e* 222 ($M^+ - 18$, 1.20), 191 ($M^+ - 49$, 20), 135 ($M^+ - 105$, 100); HRMS (EI) *m/z* 240.0908 (M^+), $C_{13}H_{17}O_2Cl$ requires M, 240.0917.

Preparation of *syn*-3-(Chloromethyl)-4-hydroxy-4-phenyl-2-butanone (1g). This compound was prepared in the same manner as that described above, but at −20 °C: 71 mg, 67%; a colorless oil; IR (KBr) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (3H, s, Me), 2.45 (1H, br s, OH), 3.22−3.37 (1H, m), 3.78 (1H, dd, J = 10.7, 3.8 Hz), 3.90 (1H, dd, J = 10.4, 10.4 Hz), 4.84 (1H, d, J = 6.9 Hz), 7.10−7.32 (5H, m, Ar); MS (EI) *m/e* 212 (M^+, 1.05), 163 ($M^+ - 49$, 60), 107 ($M^+ - 105$, 100); HRMS (EI) *m/z* 212.0594 (M^+), $C_{11}H_{13}O_2Cl$ requires M, 212.0604.

Preparation of *syn*-3-(Chloromethyl)-4-hydroxy-4-butyl-2-butanone (1h). This compound was prepared in the same manner as that described above, but at −20 °C: 28 mg, 29%; a colorless oil; IR (KBr) ν 1720 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3H, t, J = 7.1 Hz), 1.10−1.60 (6H, m), 2.08 (1H, s, OH), 2.34 (3H, s, Me), 3.0−3.10 (1H, m), 3.60−3.85 (3H, m); MS (EI) *m/e* 192 (M^+, 0.80), 155 ($M^+ - 37$, 30), 43 ($M^+ - 149$, 100); HRMS (EI) *m/z* 192.0908 (M^+), $C_9H_{17}O_2Cl$ requires M, 192.0917.

The physical data of the known product 3-[(4′-nitrophenyl)hydroxymethyl]-3-buten-2-one (2a):[9,16] mp 66−68 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (3H, s, Me), 3.26 (1H, br s, OH), 5.68 (1H, s), 6.05 (1H, s), 6.28 (1H, s), 7.56 (2H, d, J = 8.6 Hz, Ar), 8.19 (2H, d, J = 8.6 Hz, Ar).

Preparation of 2-[(4′-Nitrophenyl)hydroxymethyl]-acrylonitrile (2i): a yellow solid; mp 60−62 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.26 (1H, br s, OH), 5.45 (1H, s), 6.10 (1H, s), 6.19 (1H, s), 7.60 (2H, d, J = 8.4 Hz, Ar), 8.24 (2H, d, J = 8.4 Hz, Ar); MS (EI) *m/e* 204 (M^+, 0.80), 155 ($M^+ - 37$, 30), 43 ($M^+ - 149$, 100); HRMS (EI) *m/z* 204.0530 (M^+), $C_{10}H_8N_2O_3$ requires M, 204.0535.

Typical Reaction Procedure for the Preparation of 3-(Chloromethyl)-4-(4′-nitrophenyl)-3-buten-2-one (3a). To a solution of tetramethylammonium bromide (8.06 mg, 0.025 mmol) in dichloromethane (1.3 mL) was added 1.0 N titanium tetrachloride in dichloromethane (0.5 mL, 0.5 mmol) at room temperature. After beibg stirred 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 uL) were added into the reaction at room temperature. The reaction mixture was kept for 24 h at room temperature. The reaction was quenched by addition of a 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 **3a** (110 mg, 92%) as a colorless solid (eluent: ethyl acetate/petroleum ether = 1/8): mp 134−136 °C; IR (KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 Hz) δ 2.55 (3H, s, Me), 4.38 (2H, s, CH_2), 7.69 (1H, s), 7.75 (2H, d, J = 8.6 Hz, Ar), 8.35 (2H, d, J = 8.6 Hz, Ar); MS (EI) *m/e* 239 (M^+, 0.40), 222 ($M^+ - 17$, 40), 115 ($M^+ - 124$, 100). Found: C, 54.94; H, 3.92; N, 5.87. $C_{11}H_{10}ClNO_3$ requires C, 55.13; H, 4.21; N, 5.84.

Preparation of 3-(Chloromethyl)-4-(2′-nitrophenyl)-3-buten-2-one (3b). This compound was prepared in the same manner as that described above: 109 mg, 91%; a colorless solid; mp 120−122 °C; IR (KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.52 (3H, s, Me), 4.23 (2H, s, CH_2), 7.64 (1H, td, J = 6.4, 1.5 Hz, Ar), 7.72 (1H, d, J = 6.7 Hz, Ar), 7.80 (1H, t, J = 7.5 Hz, Ar), 8.02 (1H, s), 8.27 (1H, d, J = 7.5 Hz, Ar); MS (EI) *m/e* 239 (M^+, 60), 222 ($M^+ - 17$, 50), 115 ($M^+ - 124$, 50), 43 ($M^+ - 196$, 100); HRMS (EI) *m/z* 239.0351 (M^+), $C_{11}H_{10}ClNO_3$ requires M, 239.0349.

Preparation of 3-(Chloromethyl)-4-(4′-trifluoromethylphenyl)-3-buten-2-one (3c). This compound was prepared in the same manner as that described above: 113 mg, 86%; a colorless solid; mp 43−45 °C; IR (KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.54 (3H, s, Me), 4.39 (2H, s, CH_2), 7.70 (1H, s), 7.60−7.76 (4H, m, Ar); MS (EI) *m/e* 262 (M^+, 100), 193 ($M^+ - 69$, 70), 183 ($M^+ - 79$, 50), 115 ($M^+ - 147$, 40); HRMS (EI) *m/z* 262.0381 (M^+), $C_{12}H_{10}ClF_3O$ requires M, 262.0372.

Preparation of 3-(Chloromethyl)-4-(4′-chlorophenyl)-3-buten-2-one (3d). This compound was prepared in the same manner as that described above: 69 mg, 60%; a colorless solid; mp 87−89 °C; IR (KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.51 (3H, s, Me), 4.42 (2H, s, CH_2), 7.46 (2H, d, J = 8.6 Hz), 7.54 (2H, d, J = 8.6 Hz), 7.69 (1H, s); MS (EI) *m/e* 228 (M^+, 20), 193 ($M^+ - 35$, 40), 149 ($M^+ - 79$, 40), 115 ($M^+ - 113$, 40), 43 ($M^+ - 185$, 100); HRMS (EI) *m/z* 228.0110 (M^+), $C_{11}H_{10}Cl_2O$ requires M, 228.0109.

Preparation of 3-(Chloromethyl)-4-(3′-fluorophenyl)-3-buten-2-one (3e). This compound was prepared in the same manner as that described above: 83 mg, 78%; a colorless solid; mp 63−64 °C; IR (KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.51 (3H, s, Me), 4.42 (2H, s, CH_2), 7.10−7.50 (4H, m, Ar), 7.69 (1H, s); MS (EI) *m/e* 212 (M^+, 15), 177 (M^+− 35, 40), 99 (M^+ − 113, 40), 43 (M^+ − 169, 100); HRMS (EI) *m/z* 212.0411 (M^+), $C_{11}H_{10}ClFO$ requires M, 212.0404.

Preparation of 3-(Chloromethyl)-4-(4′-ethylphenyl)-3-buten-2-one (3f). This compound was prepared in the same manner as that described above: 56 mg, 50%; a colorless oil; IR (KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (3H, t, J = 7.1 Hz), 2.51 (3H, s, Me), 2.67 (2H, q, J = 7.1 Hz), 4.48 (2H, s, CH_2), 7.31 (2H, d, J = 8.0 Hz), 7.55 (2H, d, J = 8.0 Hz), 7.69 (1H, s); MS (EI) *m/e* 222 (M^+, 30), 193 (M^+ − 29, 100), 128 (M^+ − 94, 40); HRMS (EI) *m/z* 222.0809 (M^+), $C_{13}H_{15}ClO$ requires M, 222.0811.

Preparation of 3-(Chloromethyl)-4-phenyl-3-buten-2-one (3g). This compound was prepared in the same manner as that described above: 69 mg, 71%; a colorless oil; IR (KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.52 (3H, s, Me), 4.46 (2H, s, CH_2), 7.31−7.50 (3H, m, Ar), 7.51−7.61 (2H, m, Ar), 7.71 (1H, s); MS (EI) *m/e* 194 (M^+, 100), 115 (M^+ − 79, 40), 43 (M^+ − 151, 40); HRMS (EI) *m/z* 194.0498 (M^+), $C_{11}H_{11}ClO$ requires M, 194.0492.

Preparation of 3-(Chloromethyl)-4-nonyl-3-buten-2-one (3h). This compound was prepared in the same manner as that described above: 37 mg, 30%; a colorless oil; IR (KBr) ν 1640 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (3H, t, J = 7.1 Hz, Me), 1.10−1.40 (12H, m, CH_2), 1.40−1.60 (2H, m, CH_2), 2.36 (3H, s, Me), 2.34 (2H, td, J = 7.6, 7.6 Hz), 4.32 (2H, s, CH_2), 6.85 (1H, t, J = 7.6 Hz); MS (EI) *m/e* 244 (M^+, 20), 209 (M^+ − 35, 40), 109 (M^+ − 135, 70), 43 (M^+ − 201, 100); HRMS (EI) *m/z* 244.1596 (M^+), $C_{14}H_{25}ClO$ requires M, 244.1594.

Crystallography. A suitable single crystal was mounted at the top of a glass capillary. Data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo Kα radition, λ = 0.71069 Å, using the ω−2θ technique at 20 °C. The data were collected for Lorentz polarization effects. The structure was solved by direct methods and expanded using Fourier techniques.[16] The non-hydrogen atoms were refined anisotropically by full-matrix least squares. All hydrogen atoms were included in calculated position. All calculations were performed using the TEXSAN crystallographic software package. Their crystal structures have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition numbers CCDC 144817 for **1a** and CCDC 142973 for **3a**.

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Supporting Information Available: The ^1H NMR charts of **1a**−**h**, **3a**−**h**, HPLC charts of **1a** and **1h**, X-ray data of **1a** and **3a**, and ortep drawings for **1a** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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