Boron(III) Tribromide or Titanium(IV) Bromide and Lewis Base Promoted Baylis-Hillman Reaction

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It was found that, when the Baylis-Hillman reaction of arylaldehydes with methyl vinyl ketone was carried out at below −20 ℃ in the presence of boron(III) tribromide or titanium (IV) bromide using a catalytic amount of Lewis base such as amine, the brominated compounds and the Baylis-Hillman adducts could be obtained as the major products in good yields for various aryl aldehydes. But at room temperature, the elimination products were the major products. In addition, the palladium catalyzed allylic substitution reactions of the elimination products were also examined.

Keywords boron(III) tribromide, titanium(IV) bromide, Baylis-Hillman reaction, bromination, Lewis base, amine

Introduction

Recently, the Baylis-Hillman reaction has become a very hot field for synthetic chemists,[1-12] with a recent example of a catalytic asymmetric version.[13] It has been disclosed that the combination of a Lewis base such as chalcogenides, amines, phosphines or quaternary ammonium halides with Lewis acid $TiCl_4$ can significantly speed up this reaction and give the corresponding chlorinated products and elimination products in high yields at different temperatures.[14-15] As a result, it was found that amine (0.2 equiv.) and $TiCl_4$(1.4 equiv.) are the best combination for this reaction.[14-15] Based on those previous findings, it is further attempted to explore the use of Lewis acid BBr_3 or $TiBr_4$ and a Lewis base for this reaction because the corresponding brominated product **1** and bromination-elimination product **3** are the more useful compounds from the point view of synthetic chemistry because they can be more easily subjected to palladium catalyzed allylic substitution and the related transformations. Herein we wish to report the full details of BBr_3 or $TiBr_4$ and various Lewis bases promoted Baylis-Hillman reaction of aryl aldehyde with α,β-unsaturated enone, along with some results of the palladium catalyzed allylic substitutions.

Results and discussion

According to our previous results,[14-15] the reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone was initially attempted in the presence of BBr_3 or $TiBr_4$(1.0 equiv.) at −78 ℃. However, no reaction occurred (Scheme 1, Entries 1 and 2 in Table 1). After adding 20 mol% of Me_2S, *n*-Bu_3P or amine (Et_3N or 1, 8-diazabicyclo[5.4.0]undec-7-ene, DBU) as a Lewis base, the reaction took place to give the brominated product **1a** as a major product, along with the formation of **2a** (Scheme 1, Entries 3—10 in Table 1). Lewis acid $TiBr_4$ is more effective than Lewis acid BBr_3 for this reaction. In the reaction of an aryl aldehyde with methyl vinyl ketone in the presence of Lewis acid $TiCl_4$ and Lewis bases such as amines, chalcogenides or quaternary ammonium halides at low temperature, the chlorinated compound was obtained exclusively for various aldehydes.[13-15] The formation of Baylis-Hillman olefin **2a** sug-

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gested that the brominated compound **1a** more easily undergoes dehydrobromination to give **2a** during the reaction. Namely **1** is more labile than the corresponding chlorinated compound reported in the previous papers.[13-15] The amount of $TiBr_4$ was also crucial for this reaction since using a catalytic amount of $TiBr_4$, the reaction became very slow and gave low yields of **1a** and **2a**. The best reaction condition was found to utilize 0.2 equiv. of DBU as a Lewis base and 1.0 equiv. of $TiBr_4$ as a Lewis acid (Entry 9 in Table 1).

For *m*-nitrobenzaldehyde or *o*-nitrobenzaldehyde, the reaction proceeded quickly to give the corresponding **1b** and **2b** in good yields using $TiBr_4$ (1.0 equiv.) as a Lewis acid and a catalytic amount of DBU (0.2 equiv.) at −78 ℃ (Scheme 2, Entry 1 in Table 2). However, for other aryl aldehydes, the reactions proceeded slowly and needed higher temperature (−20 ℃) to give the corresponding brominated product **1** and the elimination product **3** in *Z* configuration in moderate yields (Scheme 2, Entries 2 and 3 in Table 2). Especially for *p*-ethylbenzaldehyde, only trace amount of **1** was formed and the major product was **3** (Entry 4 in Table 2). But using BBr_3 (1.0 equiv.) as a Lewis acid and Me_2S as a Lewis base for *p*-chlorobenzaldehyde, *p*-ethylbenzaldehyde or benzaldehyde under the same reaction conditions, the reaction was sluggish to afford the elimination compound **3** in moderate yields at −78—−20 ℃ (Scheme 3, Table 3).

Scheme 1

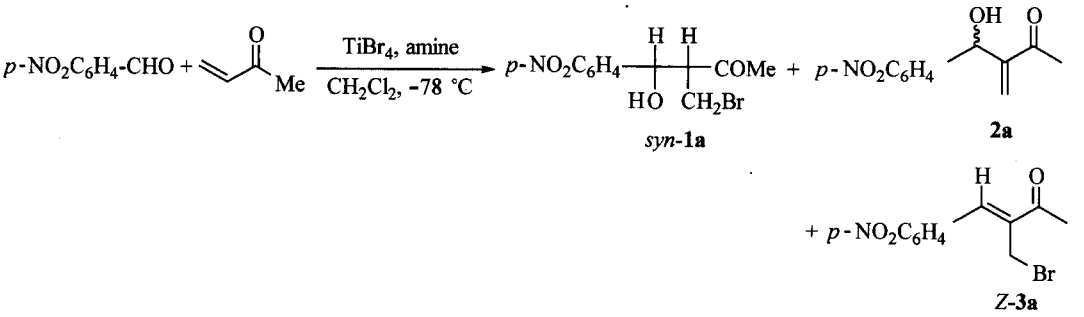
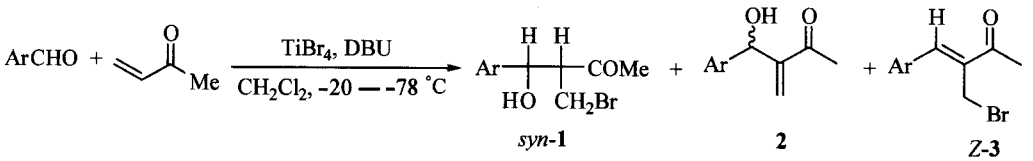


Table 1 Reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone in the presence of $TiBr_4$ (1.0 equiv.) and Lewis base (0.20 equiv.)

Entry	Lewis acid	Lewis base	Time (h)	Isolated yield (%)		
				syn-**1a**	**2a**	*Z*-**3a**
1	BBr_3	—	24	0	0	0
2	$TiBr_4$	—	24	0	0	0
3	BBr_3	Et_3N	24	32	12	0
4	BBr_3	Me_2S	24	32	12	0
5	BBr_3	DBU	24	44	22	0
6	$TiBr_4$	Me_2S	24	57	13	0
7	$TiBr_4$	$^nBu_3P$	24	60	28	0
8	$TiBr_4$	Et_3N	24	62	35	0
9	$TiBr_4$	DBU	24	66	23	0

Scheme 2



b: R = *m*-$NO_2C_6H_4$, **c**: R = *o*-$NO_2C_6H_4$,
d: R = *p*-ClC_6H_4, **e**: R = *p*-EtC_6H_4, **f**: R = C_6H_5

Table 2 Baylis-Hillman reaction of arylaldehydes with methyl vinyl ketone in the presence of $TiBr_4$ (1.0 equiv.) and DBU (0.20 equiv.) at low temperature

Entry	Ar	Temp.(℃)	Time (h)	Isolated yield (%)		
				syn-**1**	**2**	*Z*-**3**
1	*m*-$NO_2C_6H_4$ (**b**)	-78	30	52	30	0
2	*o*-$NO_2C_6H_4$ (**c**)	-78	30	45	20	0
3	*p*-ClC_6H_4 (**d**)	-20	50	34	trace	30
4	*p*-EtC_6H_4 (**e**)	-20	60	trace	trace	50
5	C_6H_5 (**f**)	-20	50	35	trace	20

Scheme 3

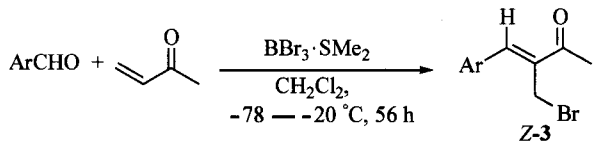
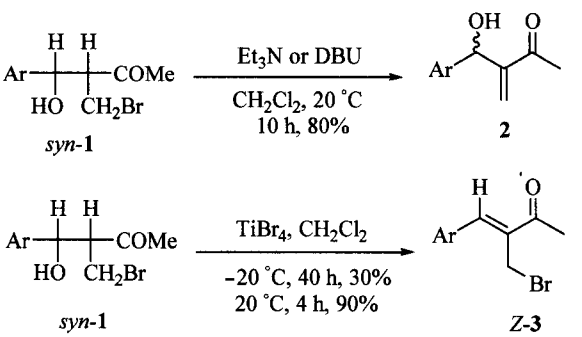


Table 3 Baylis-Hillman reaction of arylaldehydes with methyl vinyl ketone in the presence of BBr_3(1.0 equiv.) and Me_2S (0.20 equiv.) at low temperature

Entry	Ar	Temp.(℃)	Isolated yield (%)		
			syn-**1**	**2**	*Z*-**3**
1	*p*-ClC_6H_4 (**d**)	-78	trace	trace	63
2	*p*-EtC_6H_4 (**e**)	-20	trace	trace	61
3	C_6H_5 (**f**)	-20	trace	trace	56

In the mean time, it should be emphasized here that in all cases, only one diastereomer of **1** and the *Z* isomer of **3** were formed during the reaction process based on the ^1H NMR spectral data. Their relative configurations of **1** were confirmed as *syn*-form by comparison of their spectral data with those of the corresponding chlorinated products.[13] The *Z* isomer of **3** was also confirmed by comparison of their spectral data with those of the corresponding chlorinated products.[13] Compound **1** can be easily and completely transformed to compound **2** by treatment with the excess amount (2.0 equiv.) of triethylamine or DBU (Scheme 4). It was found that, at -20 ℃, **1** could be slowly transformed to **3** in the presence of $TiBr_4$, but at 20 ℃, this transformation was relatively fast (Scheme 4). Compound **3** is the most stable product in this reaction system. This is why **3** is always formed if the reaction is sluggish as shown in Scheme 3 and Scheme 4. The purification of **1** by preparative thin layer chromatography (TLC) would also cause the transformation of **1** to **2**. Thus, rapid flash column chromatography is necessary in order to obtain the pure product **1**. It is believed that the reaction mechanism of the formation of **1** is the same as that using $TiCl_4$ as a Lewis acid which has been disclosed in the previous papers.[13-15]

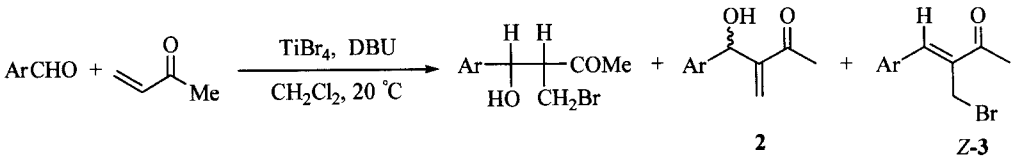
Scheme 4



If the same reaction was carried out at room temperature, the elimination product **3** was obtained exclusively with *Z* configuration in moderate yields (Scheme 5, Table 4). This is also because the formed brominated compound **1** could be more easily transformed to product **3** at room temperature in the presence of Lewis acid $TiBr_4$.

Besides methyl vinyl ketone, acrylonitrile underwent the same reaction to give the corresponding brominated product **4** in moderate yield in dichloromethane at 20 ℃ for 5 d. But at -78 ℃, no reaction occurred. Raising the reaction temperature to reflux (45 ℃) caused the decrease of the yield of **4**. Using methyl acrylate as a Michael acceptor, no reaction occurred (Scheme 6). These results are very similar to those of Baylis-Hillman reactions promoted by $TiCl_4$.[13-15]

Scheme 5

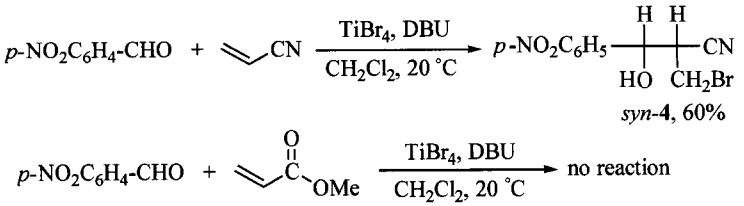


a: R = *p*-$NO_2C_6H_4$, **b**: R = *m*-$NO_2C_6H_4$, **c**: R = *o*-$NO_2C_6H_4$,
d: R = *p*-ClC_6H_4, **e**: R = *p*-EtC_6H_4, **f**: R = C_6H_5.

Table 4 Baylis-Hillman reaction of arylaldehydes with methyl vinyl ketone in the presence of $TiBr_4$ (1.0 equiv.) and DBU (0.20 equiv.) at room temperature (20 ℃)

Entry	Ar	Temp.(h)	Isolated yield (%)		
			syn-**1**	**2**	*Z*-**3**
1	*p*-$NO_2C_6H_4$ (**a**)	24	0	0	88
2	*m*-$NO_2C_6H_4$ (**b**)	24	0	0	62
3	*o*-$NO_2C_6H_4$ (**c**)	24	0	0	65
4	*p*-ClC_6H_4 (**d**)	48	0	0	55
5	*p*-EtC_6H_4 (**e**)	48	0	0	50
6	C_6H_5 (**f**)	48	0	0	53

Scheme 6



The palladium catalyzed allylic substitution of the *Z*-olefin **3a** with trimethylsilyl ketene acetal and diethyl malonate (Schemes 7 and 8) afforded the desired products **5/6** or **7/8** in moderate yields, respectively.[16,17] It is very surprising to find that the regioselectivities can be changed by using different bases for the palladium catalyzed substitution of allylic bromide with ketene silyl acetal (Scheme 7, Table 5). For allylic substitution by diethyl malonate, two regioisomers **7** and **8** were obtained in 10% and 43%, respectively (Scheme 8).[17]

In conclusion, a novel reaction system of Baylis-Hillman reaction has been discovered for the synthesis of brominated products using a catalytic amount of DBU as a Lewis base with excess amount of titanium(IV) bromide or boron(III) tribromide as a Lewis acid. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose the scope and limitations of this reaction.

Scheme 7

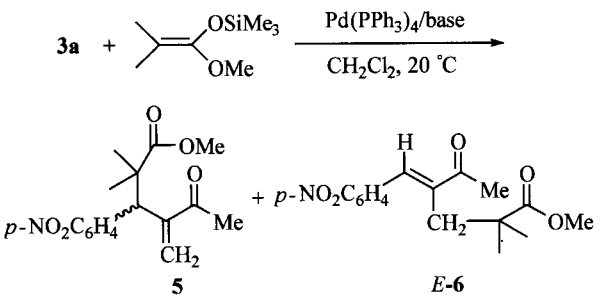
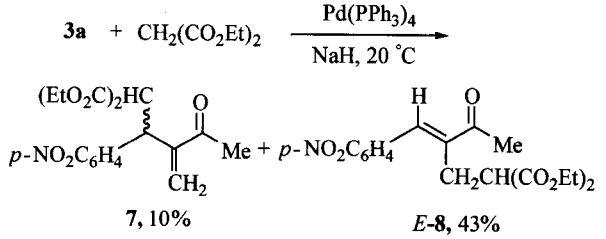


Table 5 The reaction of **3a** with 1-methoxy-2-methyl-1-(trimethylsiloxy) propene in the presence of Pd(0) catalyst

Entry	Base	Time (h)	Isolated yield (%)	
			5	*E*-**6**
1	no base	48	0	0
2	Et_3N	24	30	0
3	K_3PO_4	24	0	12
4	DBU	24	32	10

Scheme 8



Experimental

General

Melting points were obtained with a Yanagimoto micromelting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard and 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 GF254 silica gel coated plates. Flash column chromatography was carried out using 200—300 mesh silica gel.

Typical procedure for the reaction of arylaldehydes with methyl vinyl ketone in the presence of $TiBr_4$ *and* DBU *at low temperature*

syn-3-(*Bromomethyl*)-4-*hydroxy*-4-(*p-nitrophen-yl*)-2-*butanone* (**1a**) To a solution of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) was added titanium(VI) bromide (184 mg, 0.5 mmol), DBU (15.2 mg, 15 μL, 0.1 mmol) and methyl vinyl ketone (0.125 mL, 1.5 mmol) under an argon atmosphere at −78 ℃. The reaction mixture was stirred at −78 ℃ for 24 h. The reaction was quenched with $NaHCO_3$ (8.8%, 2.0 mL) and the mixture was extracted with dichloromethane (3 × 5.0 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatograph [eluent: petroleum ether (60—90 ℃)/EtOAc = 10/1] to give **1a** as a colorless oil (100 mg, 66%). IR (neat) ν: 3455 (O—H), 1677 (C = O) cm^{-1}. ^{1}H MMR (300 MHz, $CDCl_3$) δ: 2.20 (s, 3H, CH_3), 3.04 (s, 1H, OH), 3.37 (ddd, J = 10.3, 5.8, 3.8 Hz, 1H, CHC = O), 3.49 (dd, J = 10.3, 3.8 Hz, 1H, C**H**HBr), 3.71 (t, J = 10.3 Hz, 1H, CH**H**Br), 5.06 (d, J = 5.9 Hz, 1H, C**H**OH), 7.55 (d, J = 8.7 Hz, 2H, Ar), 8.23 (d, J = 8.7 Hz, 2H, Ar). MS (EI) m/z: 302, 304 (M^+) [HRMS (EI) found: 283.9915 (M^+ − 17), $C_{11}H_{11}BrNO_3$ requires 283.9922].

syn-3-(*Bromomethyl*)-4-*hydroxy*-4-(*m-nitrophenyl*)-2-*butanone* (**1b**) a colorless oil (79 mg, 52%). IR (neat) ν: 3455 (O—H), 1677 (C = O) cm^{-1}. ^{1}H MMR (300 MHz, $CDCl_3$) δ: 2.18 (s, 3H, CH_3), 3.20 (s, 1H, OH), 3.33—3.43 (m, 1H, CHC = O), 3.49 (dd, J = 9.2, 3.8 Hz, 1H, C**H**HBr), 3.72 (t, J = 9.2 Hz, 1H, CH**H**Br), 5.06 (d, J = 5.2 Hz, 1H, C**H**OH), 7.61 (t, J = 8.1 Hz, 1H, Ar), 7.69 (d, J = 7.8 Hz, 1H, Ar), 8.18 (dd, J = 8.0, 1.2 Hz, 1H, Ar), 8.25 (s, 1H, Ar). MS (EI) m/z: 302, 304 (M^+) [HRMS (EI) found: 282.9847 (M^+ − 18), $C_{11}H_{10}BrNO_3$ requires 282.9844].

syn-3-(*Bromomethyl*)-4-*hydroxy*-4-(*o-nitrophenyl*)-2-*butanone* (**1c**) a colorless oil (68 mg, 45%). IR (neat) ν: 3455 (O—H), 1671 (C = O) cm^{-1}. ^{1}H MMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3H, CH_3), 3.34 (dd, J = 10.1, 3.3 Hz, 1H, C**H**HBr), 3.40 (d, J = 2.1 Hz, 1H, OH), 3.58—3.66 (m, 1H, C**H**C = O), 3.77 (t, J = 10.1 Hz, 1H, CH**H**Br), 5.63 (s, 1H, C**H**OH), 7.53 (td, J = 7.3, 1.2 Hz, 1H, Ar), 7.70 (td, J = 7.3, 0.8 Hz, 1H, Ar), 7.88 (d, J = 8.1 Hz, 1H, Ar), 8.12 (dd, J = 8.1, 1.2 Hz, 1H, Ar). MS (EI) m/z: 302, 304 (M^+) [HRMS (EI) found: 283.9914 (M^+ − 17), $C_{11}H_{11}BrNO_3$ requires 283.9922].

syn-3-(*Bromomethyl*)-4-*hydroxy*-4-(*p-chlorophenyl*)-2-*butanone* (**1e**) a colorless oil (50 mg, 34%). IR (neat) ν: 3455 (O—H), 1673 (C = O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.02 (s, 3H, CH_3), 2.87 (s, 1H, OH), 3.31—3.38 (m, 1H, C**H**C = O), 3.56 (dd, J = 9.9, 3.8 Hz, 1H, C**H**HBr), 3.69 (t, J = 9.9 Hz, 1H, CH**H**Br), 4.81 (d, J = 6.8 Hz, 1H, C**H**OH), 7.25 (d, J = 8.4 Hz, 2H, Ar), 7.36 (d, J = 8.4 Hz, 2H, Ar). MS (EI) m/z: 291, 293 (M^+) [HRMS (EI) found: 271.9591 (M^+ − 18), $C_{11}H_{10}BrClO$ requires 271.9604].

syn-3-(*Bromomethyl*)-4-*hydroxy*-4-*phenyl*-2-*butanone* (**1f**) a colorless oil (43 mg, 35%). IR (neat) ν: 3455 (O—H), 1672 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.96 (s, 3H, CH_3), 3.02 (s, 1H, OH), 3.36—3.43 (m, 1H, CHC = O), 3.64 (dd, J = 9.8, 4.0 Hz, 1H, C**H**HBr), 3.70 (t, J = 9.8 Hz, 1H, CH**H**Br), 4.76 (d, J = 7.2 Hz, 1H, C**H**OH), 7.28—7.39 (m, 5H, Ar). MS (EI) m/z: 256, 258 (M^+) [HRMS (EI) found: 237.9970 (M^+ - 18), $C_{11}H_{11}BrO$ requires 237.9993].

3-[*Hydroxy*-(*p-nitrophenyl*)*methyl*]*but*-3-*en*-2-*one* (**2a**) a colorless solid (25 mg, 23%). m.p. 76—77 ℃. IR ($CHCl_3$) ν: 3483 (O—H), 1658 (C = O), 1604 (C = C), 3483 (O—H) cm^{-1}. ^1H MMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3H, CH_3), 3.35 (d, J = 5.3 Hz, 1H, OH), 5.68 (d, J = 5.3 Hz, 1H, C**H**Ar), 6.04 (s, 1H, C = C**H**H), 6.28 (s, 1H, C = CH**H**), 7.56 (d, J = 8.7 Hz, 2H, Ar), 8.20 (d, J = 8.7 Hz, 2H, Ar). MS (EI) m/z: 221 (M^+) [HRMS (EI) found: 221.0682 (M^+), $C_{11}H_{11}NO_4$ requires 221.0688].

3-[*Hydroxy*-(*m-nitrophenyl*)*methyl*]*but*-3-*en*-2-*one* (**2b**) a colorless solid (31 mg, 30%). m.p. 79—80 ℃. IR ($CHCl_3$) ν: 3492 (O—H), 1654 (C = O), 1628 (C = C), 3421 (O—H) cm^{-1}. ^1H MMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H, CH_3), 3.38 (d, J = 5.7 Hz, 1H, OH), 5.69 (d, J = 5.7 Hz, 1H, CHAr), 6.09 (s, 1H, C = C**H**H), 6.30 (s, 1H, C = CH**H**), 7.53 (t, J = 8.1 Hz, 1H, Ar), 7.75 (d, J = 7.8 Hz, 1H, Ar), 8.18 (dd, J = 8.0, 1.2 Hz, 1H, Ar), 8.25 (s, 1H, Ar). MS (EI) m/z: 204 (M^+ - 17) [HRMS (EI) found: 221.0685 (M^+), $C_{11}H_{11}NO_4$ requires 221.0688].

3-[*Hydroxy*-(*o-nitrophenyl*)*methyl*]*but*-3-*en*-2-*one* (**2c**) a colorless oil (22 mg, 20%). IR ($CHCl_3$) ν: 3362 (O—H), 1665 (C = O), 1625 (C = C) cm^{-1}. ^1H MMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 3.52 (d, 1H, J = 4.1 Hz, OH), 5.80 (s, 1H, C = C**H**H), 6.17 (s, 1H, C = CH**H**), 6.22 (d, 1H, J = 4.1 Hz, CHAr), 7.46 (td, 1H, J = 8.2, 1.2 Hz, Ar), 7.65 (td, 1H, J = 7.6, 0.8 Hz, Ar), 7.78 (dd, 1H, J = 7.0, 0.8 Hz, Ar), 7.97 (d, 1H, J = 8.2 Hz, Ar). MS (EI) m/z: 204 (M^+ - 17) [HRMS (EI) found: 221.0687 (M^+), $C_{11}H_{11}NO_4$ requires 221.0688].

Typical procedure for the reaction of arylaldehydes with methyl vinyl ketone in the presence of $TiBr_4$ *and* DBU *at room temperature*

Z-3-(*Bromomethyl*)-4-(*p-nitrophenyl*)-3-*buten*-2-*one* (**3a**) To a solution of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) was added titanium(VI) bromide (184 mg, 0.5 mmol), DBU (15.2 mg, 15 μL, 0.1 mmol) and methyl vinyl ketone (0.125 mL, 1.5 mmol) under argon atmosphere at 20 ℃. The reaction mixture was stirred at 20 ℃ for 24 h. The reaction was quenched with $NaHCO_3$ (8.8%, 2.0 mL) and the mixture was extracted with dichloromethane (3 × 5.0 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica-gel column chromatograph [eluent: petroleum ether (60—90 ℃)/EtOAc = 10/1] to give **3a** as a white solid (125 mg, 88%). m.p. 95—96 ℃. IR ($CHCl_3$) ν: 1670 (C = O), 1620 (C = C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.55 (s, 3H, CH_3), 4.28 (s, 2H, CH_2Br), 7.65 (s, 1H, CH), 7.77 (d, J = 8.6 Hz, 2H, Ar), 8.35 (d, J = 8.7 Hz, 2H, Ar). MS (EI) m/z: 283, 285 (M^+) [HRMS (EI) found: 282.9835 (M^+), $C_{11}H_{10}BrNO_3$ requires 282.9844] (Seheme 5 and Table 4).

Z-3-(*Bromomethyl*)-4-(*m-nitrophenyl*)-3-*buten*-2-*one* (**3b**) a white solid (88 mg, 62%). m.p. 108—110 ℃. IR ($CHCl_3$) ν: 1670 (C = O), 1620 (C = C) cm^{-1}. ^1H NMR(300 MHz, $CDCl_3$) δ: 2.54 (s, 3H, CH_3), 4.28 (s, 2H, CH_2Br), 7.65 (s, 1H, CH), 7.68 (t, J = 8.0 Hz, 1H, Ar), 7.97 (d, J = 7.8 Hz, 1H, Ar), 8.31 (dd, J = 8.0, 1.0 Hz, 1H, Ar), 8.46 (s, 1H, Ar). MS (EI) m/z: 283, 285 (M^+) [HRMS (EI) found: 282.9838 (M^+), $C_{11}H_{10}BrNO_3$ requires 282.9844].

Z-3-(*Bromomethyl*)-4-(*o-nitrophenyl*)-3-*buten*-2-*one* (**3c**) white solid (95 mg, 65%). m.p. 97—98 ℃. IR ($CHCl_3$) ν: 1673 (C = O), 1620 (C = C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3H, CH_3), 4.10 (s, 2H, CH_2Br), 7.65 (s, 1H, CH), 7.68 (t, J = 8.0 Hz, 1H, Ar), 7.97 (d, J = 7.8 Hz, 1H, Ar), 8.31 (dd, J = 8.0, 1.0 Hz, 1H, Ar), 8.46 (s, 1H, Ar). MS (EI) m/z: 283, 285 (M^+) [HRMS (EI) found: 283.9919 (M^+ + 1), $C_{11}H_{11}BrNO_3$ requires 283.9922].

Z-3-(*Bromomethyl*)-4-(*p-chlorophenyl*)-3-*buten*-2-*one* (**3d**) a colorless oil (78 mg, 55%). IR ($CHCl_3$) ν: 1654 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3H, CH_3), 4.30 (s, 2H, CH_2Br), 7.45 (d, J = 8.5 Hz, 2H, Ar), 7.56 (d, J = 8.5 Hz, 2H, Ar), 7.58 (s, 1H, CH). MS (EI) m/z: 273, 275 (M^+) [HRMS (EI) found: 271.9604 (M^+), $C_{11}H_{10}BrClO$ requires 271.9604].

Z-3-(*Bromomethyl*)-4-(*p-ethylphenyl*)-2-*butanone* (**3e**) a colorless oil (67 mg, 50%). IR ($CHCl_3$) ν: 1671 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, J = 7.6 Hz, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.69 (q, J = 7.6 Hz, 2H, CH_2), 4.38 (s, 2H, CH_2Br), 7.33 (d, J = 8.2 Hz, 2H, Ar), 7.58 (d, J = 8.2 Hz, 2H, Ar), 7.64 (s, 1H, CH). MS (EI) m/z: 267, 269 (M^+) [HRMS (EI) found: 266.0299 (M^+), $C_{13}H_{15}BrO$ requires 266.0306].

Z-3-(*Bromomethyl*)-4-*phenyl*-3-*buten*-2-*one* (**3f**) a colorless oil (65 mg, 55%). IR ($CHCl_3$) ν: 1672 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.51 (s, 3H, CH_3), 4.38 (s, 2H, CH_2Br), 7.43—7.55 (m, 3H, Ar), 7.58—7.67 (m, 2H, Ar), 7.68 (s, 1H, CH). MS (EI) m/z: 239, 241 (M^+) [HRMS (EI) found: 237.9988 (M^+), $C_{11}H_{11}BrO$ requires 237.9993].

Typical procedure for the reaction of arylaldehydes with methyl vinyl ketone in the presence of $BBr_3 \cdot Me_2S$ *at low temperature*

To a solution of *p*-chlorobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) was added boron(III) bromide. Me_2S (188 mg, 0.6 mmol), and methyl vinyl ketone (0.125 mL, 1.5 mmol) under an argon atmosphere at 20 ℃. The reaction mixture was stirred at −78—−20 ℃ for 56 h. The reaction was quenched with $NaHCO_3$ (8.8%, 2.0 mL) and the mixture was extracted with dichloromethane (3 × 5.0 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica-gel column chromatograph [eluent: petroleum ether (60—90 ℃)/EtOAc = 10/1] to give **3d** as a colorless oil (86 mg, 63%) (Scheme 3 and Table 3).

Formation of syn-2-bromomethyl-3-hydroxy-3-(p-nitrophenyl)propionitrile (**4**)

To a solution of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) was added titanium (VI) bromide (184 mg, 0.5 mmol), DBU (15.2 mg, 15 μL, 0.1 mmol) and acrylonitrile (0.098 mL, 1.5 mmol) under argon atmosphere at 20 ℃. The reaction mixture was stirred at 20 ℃ for 48 h. The reaction was quenched with $NaHCO_3$ (8.8%, 2.0 mL) and the mixture was extracted with dichloromethane (3 × 5.0 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica-gel column chromatograph [eluent: petroleum ether (60—90 ℃)/EtOAc = 10/1] to give **4** as a colorless oil (86 mg, 60%). IR ($CHCl_3$) ν: 2240 (C≡N), 1606 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.27—3.34 (m, 1H, CHCN), 3.38 (d, J = 4.0 Hz, 1H, OH), 3.51 (dd, J = 10.6, 4.3 Hz, 1H, C**H**HBr), 3.72 (dd, J = 7.3, 4.3 Hz, 1H, CH**H**Br), 5.14 (dd, J = 7.5, 4.0 Hz, 1H, C**H**OH), 7.65 (d, J = 8.7 Hz, 2H, Ar), 8.25 (d, J = 8.7 Hz, 2H, Ar). MS (EI) m/z: 285, 287 (M^+) [HRMS (EI) found: 284.9863 ($M^+ + 1$), $C_{10}H_{10}BrN_2O_3$ requires 284.9875].

Transformation of **1** *to the Baylis-Hillman product* **2** *in the presence of triethylamine*

To a solution of **1a** (302 mg, 1.0 mmol) in dichloromethane (10 mL) was added triethylamine (202 mg, 2.0 mmol) and the reaction mixture was stirred at room temperature (20 ℃) for 10 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography [eluent: petroleum ether (60—90 ℃)/EtOAc = 5/1] to give **2a** as a colorless solid (177 mg, 80%).

Transformation of **1** *to the elimination product* **3** *in the presence of* $TiBr_4$

To a solution of **1a** (302 mg, 1.0 mmol) in dichloromethane (10 mL) was added $TiBr_4$ (368 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with $NaHCO_3$ (8.8%, 2.0 mL) and the mixture was extracted with dichloromethane (3 × 5.0 mL). The com-

bined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography [eluent: petroleum ether (60—90 ℃)/EtOAc = 15/1] to give *Z*-**3a** as a white solid (255 mg, 90%).

Reaction of **3a** *with* 1-*methoxy*-2-*methyl*-1-(*trimethylsiloxy*)*propene in the presence of* $Pd(PPh_3)_4$ *and base*

The formation of 2,2-*dimethyl*-4-*methylene*-3-(*p-nitrophenyl*)-5-*oxo-hexanoic acid methyl ester* (**5**) *and E*-2,2-*dimethyl*-4-(*p-nitrobenzylidene*)-5-*oxo-hexanoic acid methyl ester* (**6**) To a dichloromethane solution of **3a** (120 mg, 0.40 mmol), 1-methoxy-2-methyl-1-(trimethylsiloxy) propene (70 mg, 0.40 mmol) and DBU (80 mg, 0.40 mmol) was added $Pd(PPh_3)_4$ (5.0 mg, 0.0040 mmol) under argon atmosphere at room temperature and the reaction mixture was stirred for 24 h. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography [eluent: petroleum ether (60—90 ℃)/EtOAc = 10/1] to give **5** and **6** as a colorless oil, respectively.

5, 39 mg, 32%. IR ($CHCl_3$) ν: 1725, 1679 (C=O), 1605 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 4.66 (s, 1H, CH), 6.18 (s, 1H), 6.32 (s, 1H), 7.38 (d, J = 8.7 Hz, 2H, Ar), 8.12 (d, J = 8.7 Hz, 2H, Ar). MS (EI) m/z: 290 ($M^+ - CH_3$) [HRMS (EI) found: 305.1266 (M^+), $C_{16}H_{19}NO_5$ requires 305.1263].

6, 12 mg, 10%. IR ($CHCl_3$) ν: 1725, 1677 (C=O), 1604 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.99 (s, 6H, $2\times CH_3$), 2.47 (s, 3H, CH_3), 2.90 (s, 2H, CH_2), 3.48 (s, 3H, OCH_3), 7.50 (d, J = 8.7 Hz, 2H, Ar), 7.52 (s, 1H, CH), 8.28 (d, J = 8.7 Hz, 2H, Ar). MS (EI) m/z: 305 (M^+) [HRMS (EI) found: 305.1256 (M^+), $C_{16}H_{19}NO_5$ requires 305.1263].

Reaction of **3a** *with sodium dimethyl malonate in the presence of* $Pd(OAc)_2$ *and base*

The formation of diethyl 2-[2-*methylene*-1-(*p-nitrophenyl*)-3-*oxo-butyl*]*malonate* (**7**) *and diethyl E*-2-[2-(*p-nitrobenzylidene*)-3-*oxo-butyl*] *malonate* (**8**): To a THF solution of **3a** (130 mg, 0.46 mmol), palladium acetate (2.2 mg, 0.010 mmol) and triphenylphosphine (10.5 mg, 0.040 mmol) was added a freshly prepared sodium dimethyl malonate from dimethyl malonate (96.4 mg, 0.73 mmol) and sodium hydride (50% NaH, 33.6 mg, 0.70 mmol) in THF (5 mL) under argon atmosphere at room temperature and the reaction mixture was stirred for 20 h. The reaction was quenched with an aqueous $NaHCO_3$ solution (8.8%, 2.0 mL) and the mixture was extracted with dichloromethane (3×5.0 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography [eluent: petroleum ether (60—90 ℃)/EtOAc = 10/1] to give **7** and **8** as a colorless oil, respectively.

7, 70 mg, 43%. IR ($CHCl_3$) ν: 1731, 1677 (C=O), 1605 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.99 (t, J = 7.1 Hz, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.94 (q, J = 7.1 Hz, 2H, CH_2), 4.14 (q, J = 7.1 Hz, 2H, CH_2), 4.20 (d, J = 12.4 Hz, 1H, CH), 4.84 (d, J = 12.4 Hz, 1H, CH), 6.04 (s, 1H), 6.20 (s, 1H), 7.45 (d, J = 8.7 Hz, 2H, Ar), 8.07 (d, J = 8.7 Hz, 2H, Ar). MS (EI) m/z: 364 (M^+) [HRMS (EI) found: 363.1323 (M^+), $C_{18}H_{21}NO_7$ requires 363.1318].

8, 16 mg, 10%. IR ($CHCl_3$) ν: 1731, 1677 (C=O), 1605 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.15 (t, J = 7.1 Hz, 6H, CH_3), 2.44 (s, 3H, CH_3), 3.05 (d, J = 7.9 Hz, 2H, CH_2), 3.68 (t, J = 7.9 Hz, 1H, CH), 4.06 (q, J = 7.1 Hz, 2H, CH_2O), 4.10 (q, J = 7.1 Hz, 2H, CH_2O), 7.56 (d, J = 8.7 Hz, 2H, Ar), 7.57 (s, 1H, CH), 8.24 (d, J = 8.7 Hz, 2H, Ar). MS (EI) m/z: 364 (M^+) [HRMS (EI) found: 363.1314 (M^+), $C_{18}H_{21}NO_7$ requires 363.1318].

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