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Dimethyl sulfide–boron trihalide-mediated reactions of α,β-unsaturated ketones with aldehydes: one-pot synthesis of Baylis–Hillman adducts and α-halomethyl enones

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Abstract—The reactions of aldehydes with 3-buten-2-one (**2**) were conducted in the presence of $BBr_3{\cdot}Me_2S$ or $BCl_3{\cdot}Me_2S$ and then worked up with aqueous $NaHCO_3$, affording the α-methylene aldol **3**, α-halomethyl aldol **4** or **6**, and α-halomethyl enones **5** or **7**, respectively. In contrast, the reactions quenched with water gave the α-halomethyl enones **5** or **7** in high yields, while the work-up with an aqueous 10% trimethylamine gave the α-methylene aldol **3**. The phenol **15** and half-acetal **16** were obtained from the reaction of *p*-nitrobenzaldehyde (**1a**) with cyclohexenone (**10**). © 2001 Elsevier Science Ltd. All rights reserved.

Intense interest has recently been shown in the Baylis–Hillman reaction, and a great number of papers on this reaction has been published lately.[1] This reaction is quite slow; therefore, we developed the chalcogenide–$TiCl_4$-mediated reactions of electron-deficient alkenes with aldehydes in order to overcome this drawback.[2] We had deemed this reaction to be the chalcogen version of the Baylis–Hillman reaction because our reactions produced the Baylis–Hillman adducts after purification of the products by preparative TLC (PTLC) on silica gel. However, a detailed examination of the reactions revealed that the original products were α-chloromethyl aldols and that dehydrochlorination occurred during purification by PTLC on silica gel.[3,4] The reactions proceed via the Michael addition of a chloride ion and the successive nucleophilic attack of the resulting carbanion to an aldehyde. The chalcogenide used would play an important role in releasing the nucleophilic halide ion. Recently, similar reactions using $TiCl_4$ have been reported,[5] but the reactions of α,β-unsatureted esters using $TiCl_4$ only did not proceed.[5c] The asymmetric tandem conjugate addition–aldol reaction of α,β-unsaturated esters catalyzed by thiolates[6] or selenolates[7] has also been extensively studied.

When we examined the various kinds of Lewis acids for the chalcogenide-promoted tandem Michael addition–aldol reaction, BF_3 etherate was ineffective.[2] We anticipated that BBr_3 or BCl_3 would be reactive in this reaction because the bromide or chloride ion is more easily liberated in situ from the Lewis acid by the coordination of BBr_3 or BCl_3 with carbonyl oxygen than the fluoride ion. Since $BBr_3{\cdot}Me_2S$ and $BCl_3{\cdot}Me_2S$ are commercially available, the $BBr_3{\cdot}Me_2S$- or $BCl_3{\cdot}Me_2S$-mediated reactions of the α,β-unsaturated carbonyl compounds with aldehydes were examined.[8]

On the other hand, the Baylis–Hillman adducts are multifunctional molecules and have been used in a variety of stereoselective transformations, e.g. from secondary allyl alcohols to primary allyl alcohols,[9] allyl ethers,[10] nitro esters,[11] acetates,[12] and halides.[13] These compounds were utilized as the building blocks of natural products and biologically active compounds.[1] We found that the $BBr_3{\cdot}Me_2S$- or $BCl_3{\cdot}Me_2S$-mediated reactions gave the dehydrated products, α-halomethyl enones. This paper demonstrates that the above reactions are useful for the synthesis of 2-acylallyl halides (α-halomethyl enones).

We first treated *p*-nitrobenzaldehyde (**1a**) with 3 equiv. of 3-buten-2-one (**2**) in the presence of 1 equiv. of $BBr_3{\cdot}Me_2S$ in CH_2Cl_2 at 0°C. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution, and the raw product was separated by column chromatography on silica gel. The products were 3-(α-hydroxy-*p*-nitrobenzyl)but-3-en-2-one (**3a**), 3-bromomethyl-4-hydroxy-4-(*p*-nitrophenyl)butan-2-one (**4a**), and 3-bromomethyl-4-(*p*-nitrophenyl)but-3-en-2-one (**5a**) in 12, 53, and 30% yields, respectively. The product ratio was changed upon allowing the raw product to stand at room temperature. Therefore, the raw product was quickly and roughly chromatographed, and the product ratio was then determined by the ^1H NMR spectrum. No

Keywords: aldols; aldol reactions; Baylis–Hillman reactions; boron and compounds; dehydration; Micheal reactions.

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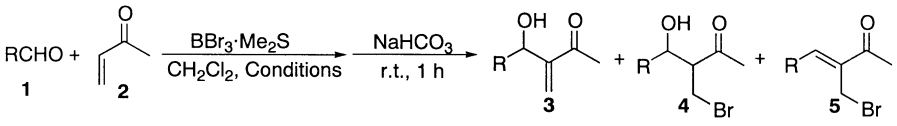
Table 1. Reaction of 3-buten-2-one and aldehydes using $BBr_3{\cdot}Me_2S$



Entry	RCHO	Conditions	Products (% yield)				
			Purification by CC[a]			Purification by PTLC[a]	
1	**1a** (R=*p*-$NO_2C_6H_4$)	0°C, 30 min	**3a** (12)	**4a** (53)	**5a** (30)	**3a** (68)	**5a** (28)
2	**1b** (R=*p*-ClC_6H_4)	0°C, 30 min	**3b** (trace)	**4b** (41)	**5b** (59)	**3b** (trace)	**5b** (59)
3	**1c** (R=*p*-$CF_3C_6H_4$)	0°C, 15 min	**3c** (7)	**4c** (65)	**5c** (28)	**3c** (70)	**5c** (13)
4	**1d** (R=C_6H_5)	0°C, 1 h then rt, 11 h	**3d** (2)	**4d** (12)	**5d** (86)	**3d** (trace)	**5d** (84)
5	**1e** (R=*p*-$CH_3C_6H_4$)	0°C, 1 h then rt, 11 h		**4e** (21)	**5e** (78)	**3e** (trace)	**5e** (92)
6	**1f** (R=$C_6H_5CH_2CH_2$)	0°C, 1 h then rt, 12 h	**3f** (trace)	**4f** (trace)	**5f** (78)	**3f** (trace)	**5f** (46)
7[b]	**1a** (R=*p*-$NO_2C_6H_4$)	0°C, 30 min	**3a** (trace)	**4a** (69)	**5a** (30)		
8[b]	**1b** (R=*p*-ClC_6H_4)	0°C, 30 min	**3b** (trace)	**4b** (45)	**5b** (46)		

[a] CC: column chromatography; PTLC: preparative TLC. The *syn*/*anti* isomer ratios of **4a–f** were not determined because of the overlapped signals.
[b] Me_2S (0.1 equiv.) was used.

change in the product ratio was observed before or after purification by column chromatography on silica gel. When the raw product was separated by PTLC on silica gel, α-bromomethyl aldol **4a** caused dehydrobromination to form butenone **3a** similar to the chloride **6a**,[2,4] and the Baylis–Hillman adduct **3a** and the α-bromomethyl enone **5a** were obtained in 68 and 28% yields, respectively. Other reactions of some aldehydes with **2** were similarly conducted; the products and their yields are shown in Table 1. The α-bromomethyl aldols **4** were obtained as a mixture of the *syn*- and *anti*-isomers, and the isomers were carefully separated by recycling preparative HPLC on polystyrene gel. The structures of *syn*- and *anti*-**4a** were determined by comparison of their ^1H NMR spectra with those of the corresponding chlorides **6a**, of which the *syn*-**6a** had been structurally well established by X-ray analysis.[4] However, the isomer ratios of the *syn*- and *anti*-isomers could not be determined from their ^1H NMR spectra because of the overlapping methylene peaks. The α-bromomethyl enones **5b**, **d**-**e** were identical with authentic samples.[13c] The (*Z*)-geometry of **5** was determined by observation of no NOE enhancement between a vinyl proton and the allylic methylene protons.

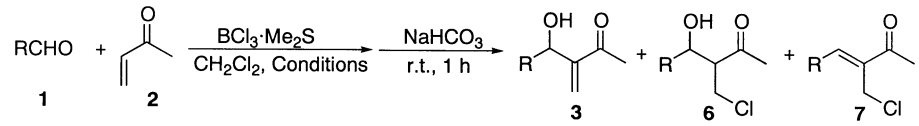
The reactions of aromatic aldehydes bearing an electron-withdrawing group smoothly proceeded (entries 1–3). The reactions of other aromatic aldehydes and an aliphatic aldehyde took longer but gave good yields (entries 4–6). The yields of the dehydrated products **5** were increased in the latter cases. The long reaction time seemed to cause the dehydration of **4**, and the reactions of **1d–f** were reexamined at 0°C for 1 h. However, the product ratios did not change, but the yields of the products decreased, and the starting materials were recovered. When 1 equiv. of BBr_3 and 0.1 equiv. of Me_2S were used, the product ratios of **4** were slightly increased, and no remarkable change was observed.

The reactions using a $BCl_3{\cdot}Me_2S$ complex were carried out, and these results are shown in Table 2. The products were the Baylis–Hillman adducts **3**, α-chloromethyl aldols **6**, and α-chloromethyl enones **7**, and the product ratios were determined by the ^1H NMR spectroscopy in a similar manner as the bromides. The reactions of the aromatic aldehydes with an electron-withdrawing group **1a–c** gave products **3** in higher yields than the reactions using $BBr_3{\cdot}Me_2S$.

The α-chloromethyl aldols **6** were obtained as a mixture of *syn*- and *anti*-diastereomers, but the exact isomer ratios of **6** were not determined because the signals due to the allylic methylene protons of the roughly purified reaction products had overlapped. Isomer separation of **6** and geometry determination of **5** were made in a similar manner as mentioned above for the bromides **4** and **5**, respectively.

Since chloromethyl aldol **6a** had been transformed into the Baylis–Hillman adduct **3a** and an enone **7a** upon standing in

Table 2. Reaction of 3-buten-2-one and aldehydes using $BCl_3{\cdot}Me_2S$



Entry	RCHO	Conditions	Products (% yield)[a]		
1	**1a** (R=*p*-$NO_2C_6H_4$)	0°C, 30 min	**3a** (28)	**6a** (52)	
2	**1b** (R=*p*-ClC_6H_4)	0°C, 30 min	**3b** (26)	**6b** (30)	**7b** (31)
3	**1c** (R=*p*-$CF_3C_6H_4$)	0°C, 30 min	**3c** (32)	**6c** (32)	**7c** (16)
4	**1d** (R=C_6H_5)	0°C, 1 h then rt, 11 h	**3d** (2)	**6d** (12)	**7d** (71)
5	**1e** (R=*p*-$CH_3C_6H_4$)	0°C, 1 h then rt, 11 h			**7e** (74)
6	**1f** (R=$C_6H_5CH_2CH_2$)	0°C, 1 h then rt, 11 h			**7f** (32)

[a] Purification by CC. The *syn*/*anti* isomer ratios of **6a–d** were not determined because of the overlapped signals.

Table 3. Self test and stability of **4**

Entry	Storage of time	Product ratios	
		3a/4a/5a	**3b/4b/5b**
1	Just after reaction	8:66:26	4:89:7
2	1 day (−50°C)	10:64:26	4:89:7
3	3 days	8:65:27	5:89:6
4	6 days	8:65:27	4:90:6
5	12 h (2°C)		5:89:6
6	2 days	8:65:27	5:88:7
7	12 h (20°C)	14:40:45	11:52:37
8	1 day	15:32:53	14:41:47
9	2.5 days	19:19:62	12:25:63

a $CDCl_3$ solution of **6a** at room temperature for 2 days,[4] we examined the stability of the products **3**–**5**; these results are summarized in Table 3.

When the product, which was rapidly and roughly purified as mentioned above, was kept in a freezer or a refrigerator, the isomer ratios did not change (entry 1). The dehydrobromination and dehydration of **4** took place upon storage at room temperature for 12 h to give **3** and **5**, respectively. These findings indicated that the aldol product-boron complex in situ formed could not be completely decomposed by the treatment of the reaction mixture with a saturated aqueous $NaHCO_3$ solution and that the acid formed by decomposition of the aldol–boron complex caused dehydration to form **5**. The enones **5** would also be formed by the reactions of **3** with hydrogen bromide in situ liberated because the chloro derivative **3a** had reacted with hydrogen chloride in the presence of $TiCl_4$ to form **7a**.[4]

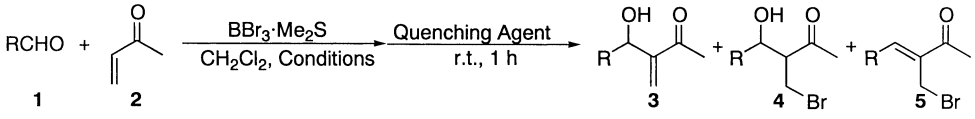
We next examined the work-up methods of a reaction mixture in order to selectively obtain the Baylis–Hillman adducts **3** and enones **5** and **7**. When the reaction mixture of **1a** and **2** was treated with a saturated aqueous K_2CO_3 solution, the methylene aldols **3a** and enone **5a** were obtained in 32 and 22% yields, respectively (Table 4, entry 1). Compound **3a** was quantitatively produced upon treatment with an aqueous 10% trimethylamine solution (entry 2), while enone **5a** was afforded in 88% yield by quenching the reaction mixture with water and allowing the raw product to stand for 12 h at room temperature (entry 3). Based on these findings, the dehydrated products **5b–f** (entries 9–13) and methylene aldols **3b**, **c** (entries 4 and 5) were selectively prepared. The aliphatic enone **5f** was obtained in 25% yield after a work up with water. No desired product was obtained by treatment of the reaction mixtures of **1d–f** with a 10% trimethylamine solution (entries 6–8).

Other electron-deficient alkenes **8**–**10** reacted with the *p*-nitrobenzaldehyde (**1a**) to give only the Baylis–Hillman products **11**, **12**, **14**, and allyl bromide **13** after work up with $NaHCO_3$, water, or trimethylamine (Table 5). The vinyl sulfone and *N*-tosylimine did not react with **1a** in the presence of $BBr_3{\cdot}Me_2S$ and $BCl_3{\cdot}Me_2S$.

The Baylis–Hillman adduct **11** was obtained in low yields after work-up of the reaction mixture of the acrylate **8** with **1a** (Table 1, entries 1–3). Treatment of the reaction mixture of the thioester **9**[3] and **1a** with a 10% trimethylamine solution gave a Baylis–Hillman adduct **12** in 80% yield (entry 4), while treatment with water afforded a dehydrated product **13** in 61% yield (entry 5). For the cyclohexenone (**10**), a Baylis–Hillman product **14** was obtained in high yields after work-up with a saturated aqueous $NaHCO_3$ solution or a 10% trimethylamine solution (entries 6 and 7). However, upon a work-up of the reaction mixture with water and then allowing the raw product to stand at room temperature for 12 h, *p*-nitrobenzylphenol (**15**) and a half-acetal **16** were isolated in 33 and 38% yields, respectively (Scheme 1).

Compound **15** showed a methylene peak at δ 4.08 as a singlet and aromatic signals at δ 6.76, 6.91 and 7.10–7.17 due to the *o*-substituted phenol in the ^1H NMR spectrum. The IR spectrum exhibited an absorption due to the phenolic hydroxy group at 3470 cm^{-1}. The MS and elemental analysis supported the composition formula of $C_{13}H_{11}NO_3$.

Table 4. Reaction of 3-buten-2-one and *p*-nitrobenzaldehy quenched with different agents

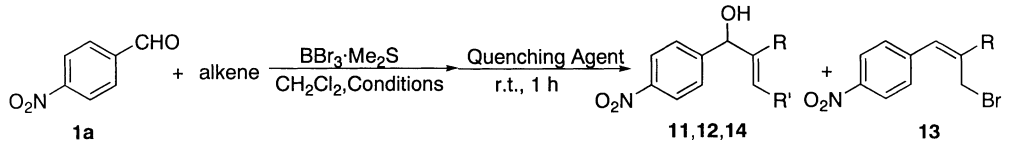


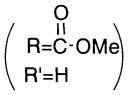
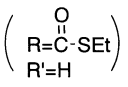
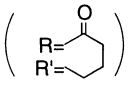
1 2 3 4 5

Entry	RCHO	Conditions	Quenching agent	Products (% yield)		
1	**1a** (R=*p*-$NO_2C_6H_4$)	0°C, 30 min	Sat. K_2CO_3	**3a** (32)[a]	**4a** (42)[a]	**5a** (22)[a]
2	**1a** (R=*p*-$NO_2C_6H_4$)	0°C, 30 min	10% NMe_3	**3a** (quant)		
3	**1a** (R=*p*-$NO_2C_6H_4$)	0°C, 30 min	H_2O			**5a** (88)
4	**1b** (R=*p*-ClC_6H_4)	0°C, 30 min	10% NMe_3	**3b** (85)		
5	**1c** (R=*p*-$CF_3C_4H_4$)	0°C, 30 min	10% NMe_3	**3c** (52)		
6	**1d** (R=C_6H_5)	0°C, 1 h–rt 11 h	10% NMe_3	Complex mixture		
7	**1e** (R=*p*-$CH_3C_6H_4$)	0°C, 1 h–rt 11 h	10% NMe_3	Complex mixture		
8	**1f** (R=$C_6H_5CH_2CH_2$)	0°C, 1 h–rt 11 h	10% NMe_3	Complex mixture		
9	**1b** (R=*p*-ClC_6H_4)	0°C, 30 min	H_2O			**5b** (89)
10	**1c** (R=*p*-$CF_3C_6H_4$)	0°C, 30 min	H_2O			**5c** (81)
11	**1d** (R=C_6H_5)	0°C, 1 h–rt 11 h		H_2O		**5b** (89)
12	**1e** (R=*p*-$CH_3C_6H_4$)	0°C, 1 h–rt 11 h	H_2O			**5e** (85)
13	**1f** (R=$C_6H_5CH_2CH_2$)	0°C, 1 h–rt 11 h	H_2O			**5f** (25)

[a] Purification by CC. Unless otherwise noted, purification by PTLC.

Table 5. Reaction of activated alkene and *p*-nitrobenzaldehyde using $BBr_3{\cdot}Me_2S$



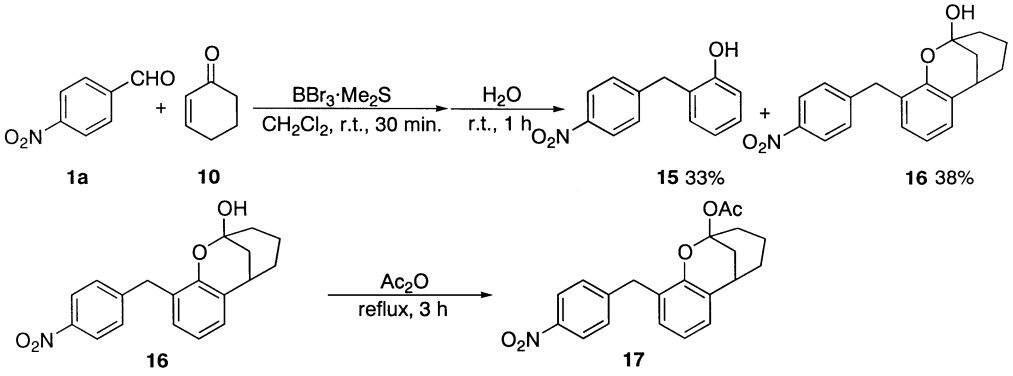
Entry	Alkene	Conditions	Quenching agent	Products (% yield)[a]
1	 **8**	rt, 3 days	Sat. $NaHCO_3$	 **11** (28)
2		rt, 3 days	10% NMe_3	**11** (16)
3		rt, 3 days	H_2O	**11** (9)
4	 **9**	rt, 4.5 h	10% NMe_3	 **12** (80)
5		rt, 4.5 h	H_2O	**13** (61)
6	 **10**	rt, 30 min	Sat. $NaHCO_3$	 **14** (70)
7		rt, 30 min	10% NMe_3	**14** (quant)

[a] Purification by PTLC.

These data are identical with those of *p*-nitrobenzylphenol.[14] Compound **16** showed its *m/z* peak at 325 (M^+/base) in MS, and its formula was found to be $C_{19}H_{19}NO_4$ from high-resolution MS, which indicated that the product **16** resulted from the addition–substitution of **15** and cyclohexenone. The signals of eight aliphatic, one hydroxyl (δ=2.73, exchangeable), one benzylic methine (δ=3.19), and three adjacent aromatic protons were observed besides the signals of the *p*-nitrobenzyl moiety in the ^1H NMR spectrum. There was no absorption of the carbonyl group in the IR and ^{13}C NMR spectra of **16**.

For the confirmation of the structure of **16**, it was acetylated with acetic anhydride to give the acetate **17** in 59% yield. The structure of **17** was characterized as $C_{21}H_{21}NO_5$ by elemental analysis and MS and fully assigned by 2D NMR spectrometry (H–H COSY, C–H COSY, long-range C–H COSY) and NOE experiments, as shown in Fig. 1.

In order to elucidate the mechanism for the formation of the phenol **15** and half-acetal **16**, we conducted the reactions shown in Scheme 2.



Scheme 1.

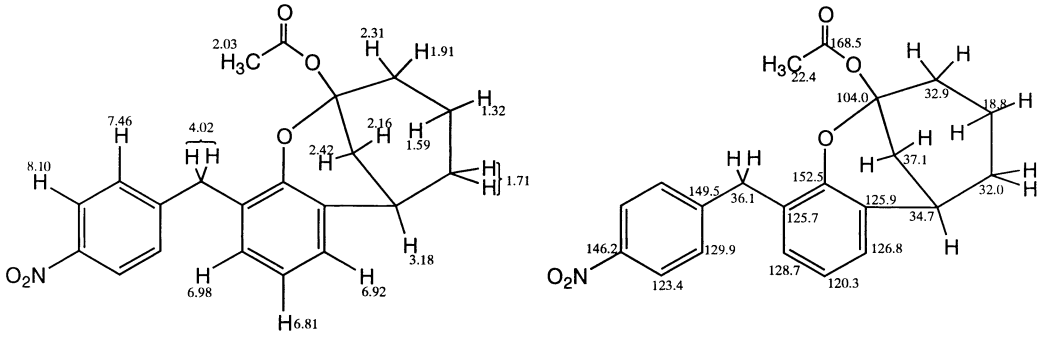
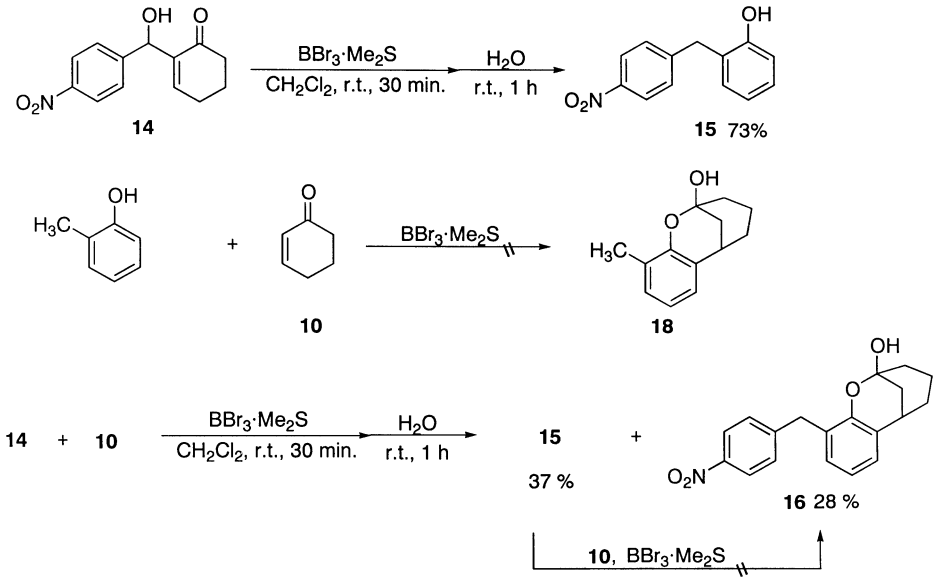


Figure 1. ^1H- and ^{13}C NMR spectral data of **17**.



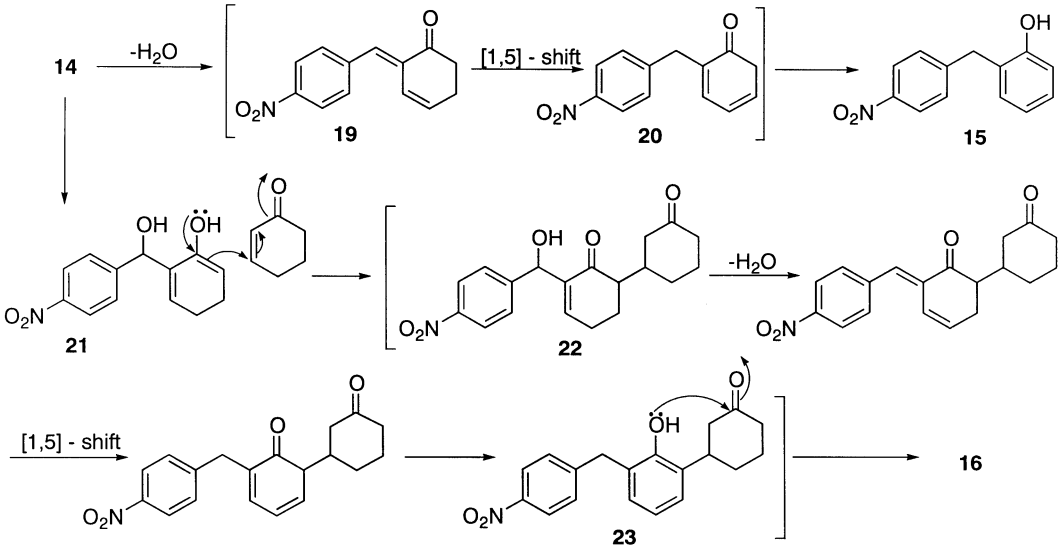
Scheme 2.

Aldol **14** was treated with $BBr_3{\cdot}Me_2S$, and then the reaction mixture was decomposed with water. The ^1H NMR spectrum of the raw product did not show the presence of the phenol **15**. However, the transformation of **14** into **15** was observed after the sample was allowed to stand for 12 h at room temperature. This indicates that a contaminated acid would cause the conversion of the aldol **14** to the phenol **15**. The phenol **15** might be an intermediate of **16**; therefore, we conducted the reactions of *o*-cresol and benzylphenol **15** with cyclohexenone (**10**) in the presence of $BBr_3{\cdot}Me_2S$, but the expected products **18** and **16** were not obtained. In contrast, the reaction of **14** with **10** in the presence of $BBr_3{\cdot}Me_2S$ formed the half-acetal **16** in 28% yield together with benzylphenol **15**.

Based on these findings, the reaction mechanism for the formation of **15** and **16** is proposed in Scheme 3.

A contaminated acid dehydrates the Baylis–Hillman adduct **14** to form a cross-conjugated dienone **19**, which isomerizes into a conjugated dienone **20**. Successive aromatization by enolization forms the phenol **15**. Since *o*-cresol did not react with cyclohexenone, the phenol **15** would not be an intermediate of **16**, and the following pathway is more feasible. The dienol **21**, an enol isomer of **14**, undergoes the Michael addition to the cyclohexenone **10** to form the diketone **22**. The 2-(α-hydroxybenzyl)cyclohexenone moiety of **22** changes into the *o*-benzylphenol moiety of **23** in a similar way as **15**. The phenolic hydroxy group and the keto group of **23** intramolecularly forms the half-acetal moiety, and compound **16** is produced.

In conclusion, reactions of 3-buten-2-one with aldehydes in the presence of $BBr_3{\cdot}Me_2S$ or $BCl_3{\cdot}Me_2S$ proceeded in a similar manner to the $TiCl_4$–Me_2S-mediated reactions,



Scheme 3.

and the α-bromomethylene aldols were initially formed, but the aldol–boron complexes resulting in situ were more stable than the aldol–titanium complexes, and the boron complex could not be completely decomposed by the treatment with water or a saturated aqueous $NaHCO_3$ solution. The reactions treated with water or a saturated aqueous $NaHCO_3$ solution gave the α-halomethyl enones **5** and **7**, whereas the work-up with a 10% trimethylamine decomposed the boron–aldol complex and dehydrohalogenated the α-bromomethyl aldol **4** to give the Baylis–Hillman adducts **3**.

1. Experimental

Melting points were obtained with a Yanagimoto micro-melting-point apparatus and were uncorrected. The IR spectra of solids (KBr) and liquids (NaCl) were recorded on a JASCO FT/IR-230 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL EX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a JEOL EX-400 spectrometer. Mass spectra (MS) were recorded on a JEOL JMS-SX102A spectrometer with a direct-insertion probe at 70 eV. Elemental analyses of new compounds were performed by Yanaco CHN Corder MT-5. All chromatographic isolations were accomplished with BW-350 (Fuji Silysia) for column chromatography (CC) or with Kieselgel 60 PF_{254} with gypsum (Merck) for preparative TLC (PTLC). CH_2Cl_2 was washed with water, dried over $CaCl_2$, and freshly distilled. The recycling preparative HPLC was performed by LC-918 liquid chromatography (Japan Analytical Industry Co., Ltd.) equipped with JAIGEL-1H and -2H columns (polystyrene gels).

1.1. General procedure

To a stirred solution of *p*-nitrobenzaldehyde (**1a**) (76 mg, 0.5 mmol) and 3-buten-2-one (**2**) (105 mg, 1.5 mmol) in dry CH_2Cl_2 (1.5 ml) was added a boron tribromide–methyl sulfide complex (160 mg, 0.5 mmol) at 0°C. The mixture was stirred at the temperature described in the tables for 0.5 h, and the reaction mixture was worked up as follows:

Method A: A saturated aqueous $NaHCO_3$ (3 ml) was added to the reaction mixture, and the whole mixture was stirred for 1 h at room temperature. The precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure.

Method B: An aqueous 10% NMe_3 solution (3 ml) was added to the reaction mixture, and the whole mixture was stirred for 1 h at room temperature. The precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure.

Method C: Water (3 ml) was added to the reaction mixture, and the whole mixture was stirred for 1 h at room temperature. The precipitates were removed by filtration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was left for 12 h at room temperature. The residue was purified by PTLC on silica gel eluted with AcOEt–hexane (1:3 v/v) or column chromatography on silica gel eluted with AcOEt–hexane (1:10 v/v).

Compounds **3a**,[2] **3b**,[15] **3c**,[16] **3d–f**,[15] **5d–e**,[13c] **7a**,[4] **7b–f**,[13c] **11**,[2] **12**,[3] and **14**,[2] were identical to authentic samples by comparison of their spectral date.

1.1.1. (*R,*R**)-3-Bromomethyl-4-hydroxy-4-(4-nitrophenyl)butan-2-one (4a, *syn*).** Pale yellow prisms (ether–hexane), mp 87–89°C. Anal. Calcd for $C_{11}H_{12}BrNO_4$: C, 43.73; H, 4.00; N, 4.64. Found: C, 43.78; H, 4.00; N, 4.65. ^{1}H NMR ($CDCl_3$) δ: 2.24 (3H, s, CH_3), 3.22 (1H, d, *J*=2.4 Hz, OH), 3.46 (1H, ddd, *J*=3.9, 5.9, and 9.8 Hz, CH), 3.58 (1H, dd, *J*=3.9 and 10.3 Hz, CH_2Br), 3.78 (1H, dd, *J*=3.9 and 10.3 Hz, CH_2Br), 5.14 (1H, d, *J*=5.9 Hz, benzylic H), 7.62 (2H, d, *J*=8.8 Hz, ArH), 8.29 (2H, d, *J*=8.3, ArH). ^{13}C NMR ($CDCl_3$) δ: 27.9 (t), 32.0 (q), 60.5 (d), 72.6 (d), 123.8 (d), 127.1 (d), 147.6 (s), 148.1 (s), 208.8 (s). IR (KBr) ν_{max}/cm^{-1}: 3502 (OH), 1703 (C=O), 1509 and 1341 (NO_2). MS (FAB) *m*/*z* (rel. int. %): 304 (M^++H, 10%; ^{81}Br), 302 (M^++H, 10%; ^{79}Br), 154 (base).

1.1.2. (*R,*S**)-3-Bromomethyl-4-hydroxy-4-(4-nitrophenyl)butane-2-one (4a, *anti*).** White prisms (ether–hexane), mp 93–97°C. Anal. Calcd for $C_{11}H_{12}BrNO_4$: C, 43.73; H, 4.00; N, 4.64. Found: C, 43.63; H, 3.98; N, 4.65. ^{1}H NMR ($CDCl_3$) δ: 2.23 (3H, s, CH_3), 3.26–3.44 (4H, m, O*H*, C*H* and C*H*$_2$Br), 5.10 (1H, t, *J*=5.9 Hz, benzylic H), 7.56 (2H, d, *J*=8.8 Hz, ArH), 8.24 (2H, d, *J*=7.8 Hz, ArH). ^{13}C NMR ($CDCl_3$): 28.9 (t), 31.9 (q), 59.7 (d), 73.3 (d), 123.9 (d), 127.1 (d), 147.8 (s), 148.1 (s), 209.3 (s). IR (KBr) ν_{max}/cm^{-1}: 3493 (OH), 1701 (C=O), 1522 and 1342 (NO_2). MS (FAB) *m*/*z* (rel. int. %): 304 (M^++H, 7%; ^{81}Br), 302 (M^++H, 7%; ^{79}Br), 154 (base).

1.1.3. (3*Z*)-3-Bromomethyl-4-(4-nitrophenyl)but-3-en-2-one (5a). Yellow powders (AcOEt), mp 137°C. Anal. Calcd for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.55; H, 3.53; N, 4.92. ^{1}H NMR ($CDCl_3$) δ: 2.54 (3H, s, CH_3), 4.27 (2H, s, CH_2), 7.63 (1H, s, CH), 7.75 (2H, d, *J*=8.8 Hz, ArH), 8.33 (2H, d, *J*=8.8 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 23.8 (t), 26.0 (q), 124.1 (d), 130.1 (d), 139.2 (d), 140.0 (s), 140.1 (s), 147.9 (s), 196.5 (s). IR (KBr) ν_{max}/cm^{-1}: 1667 (C=O), 1511 and 1344 (NO_2). MS (EI) *m*/*z* (rel. int. %): 285 (M^+, 8%; ^{81}Br), 283 (M^+, 8%; ^{79}Br), 158 (base).

1.1.4. (3*Z*)-3-Bromomethyl-4-(4-chlorophenyl)but-3-en-2-one (5b).[13c] White prisms (ether–hexane), mp 99–100°C. Anal. Calcd for $C_{11}H_{10}ClBrO$: C, 48.30; H, 3.68. Found: C, 48.20; H, 3.78. ^{1}H NMR ($CDCl_3$) δ: 2.51 (3H, s, CH_3), 4.32 (2H, s, CH_2Br), 7.47 (2H, d, *J*=8.8 Hz, ArH), 7.56 (2H, d, *J*=8.3 Hz, ArH), 7.58 (1H, s, CH). ^{13}C NMR ($CDCl_3$) δ: 24.8 (t), 25.9 (q), 129.3 (d), 130.9 (d), 132.6 (s), 135.9 (s), 137.7 (s), 141.3 (d), 197.0 (s). IR (KBr) ν_{max}/cm^{-1}: 1670 (C=O). MS (EI) *m*/*z* (rel. int. %): 276 (M^+, 3%; ^{37}Cl, ^{81}Br), 274 (M^+, 15%), 272 (M^+, 10%; ^{35}Cl, ^{79}Br), 193 (base).

1.1.5. (3*Z*)-3-Bromomethyl-4-(4-trifluoromethylphenyl)-but-3-en-2-one (5c). White crystals (ether–hexane), mp

66°C. Anal. Calcd for $C_{12}H_{10}BrF_3O$: C, 46.93; H, 3.28. Found: C, 46.81; H, 3.42. ^{1}H NMR ($CDCl_3$) δ: 2.53 (3H, s, CH_3), 4.29 (2H, s, CH_2Br), 7.64 (1H, s, CH), 7.71 (2H, d,J=8.8 Hz, ArH), 7.75 (2H, d, J=8.3 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 24.3 (t), 26.1 (q), 122.4 (s), 125.1 (s), 125.9 (d), 129.6 (d), 137.8 (s), 139.1 (s), 140.6 (d), 196.9 (s). IR (KBr) ν_{max}/cm^{-1}: 1673 (C=O). MS (EI) m/z (rel. int. %): 308 (M^++2, 13%; ^{81}Br), 306 (M^+, 13%; ^{79}Br), 227 (base).

1.1.6. (3*Z*)-3-Bromomethyl-6-phenylhex-3-en-2-one (5f). Pale yellow oil. Anal. Calcd for $C_{13}H_{15}BrO$: C, 58.44; H, 5.66. Found: C, 58.30; H, 5.68. ^{1}H NMR ($CDCl_3$) δ: 2.33 (3H, s, CH_3), 2.67–2.72 (2H, m, $PhCH_2CH_2$), 2.88 (2H, m, $PhCH_2CH_2$), 4.13 (2H, s, CH_2Br), 6.83 (1H, t, J=7.3 Hz, olefinic H), 7.21–7.33 (5H, m, ArH). ^{13}C NMR ($CDCl_3$) δ: 22.4 (t), 25.5 (q), 31.4 (t), 34.2 (t), 126.5 (d), 128.3 (d), 128.6 (d), 138.9 (s), 140.3 (s), 147.0 (d), 196.5 (s). IR (NaCl) ν_{max}/cm^{-1}: 1672 (C=O). MS (FAB) m/z (rel. int. %): 269 (M^++H, 22%; ^{81}Br), 267 (M^++H, 25%; ^{79}Br), 187 (base).

1.1.7. (3*Z*)-3-Chloromethyl-4-(4-trifluoromethylphenyl)-but-3-en-2-one (7c). White powders (AcOEt), mp 50–54°C. Anal. Calcd for $C_{12}H_{10}ClF_3O$: C, 54.87; H, 3.84. Found: C, 54.64; H, 3.89. ^{1}H NMR ($CDCl_3$) δ: 2.54 (3H, s, CH_3), 4.40 (2H, s, CH_2Cl), 7.69 (1H, s, olefinic H), 7.69 (2H, d, J=8.3 Hz, ArH), 7.75 (2H, d, J=8.3 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 26.0 (q), 37.0 (t), 125.8 (s), 125.9 (d), 129.7 (d), 131.6 (s), 137.6 (s), 138.8 (s), 141.4 (d), 196.9 (s). IR (KBr) ν_{max}/cm^{-1}: 1673 (C=O). MS (EI) m/z (rel. int. %): 264 (M^+, 33%; ^{37}Cl), 262 (M^+, 92%; ^{35}Cl), 115 (base).

1.1.8. (3*Z*)-3-Chloromethyl-6-phenylhex-3-en-2-one (7f). Pale yellow oil. Anal. Calcd for $C_{13}H_{15}ClO$: C, 70.11; H, 6.79. Found: C, 69.88; H, 6.90. ^{1}H NMR ($CDCl_3$) δ: 2.31 (3H, s, CH_3), 2.68–2.73 (2H, m, $PhCH_2CH_2$), 2.83–2.87 (2H, m, $PhCH_2CH_2$), 4.23 (2H, s, CH_2Cl), 6.84 (1H, t, J=7.3 Hz, benzylic H), 7.19–7.33 (5H, m, ArH). ^{13}C NMR ($CDCl_3$) δ: 25.4 (q), 30.9 (t), 34.5 (t), 35.3 (t), 126.4 (d), 128.4 (d), 128.6 (d), 138.7 (s), 140.2 (s), 147.4 (d), 196.7 (s). IR (NaCl) ν_{max}/cm^{-1}: 1673 (C=O). MS (EI) m/z (rel. int. %): 224 (M^+, 16%; ^{37}Cl), 222 (M^+, 47%; ^{35}Cl), 91 (base).

1.1.9. *S*-Ethyl (*Z*)-2-bromomethyl-3-(4-nitrophenyl)-thioacrylate (13). Pale yellow crystals (ether–hexane), mp 96–98°C. Anal. Calcd for $C_{12}H_{12}BrNO_3S$: C, 43.65; H, 3.66; N, 4.24. Found: C, 43.57; H, 3.72; N, 4.16. ^{1}H NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.3 Hz, CH_2CH_3), 3.07 (2H, q, J=7.3 Hz, CH_2CH_3), 4.31 (2H, s, CH_2Br), 7.73 (1H, s, olefinic H), 7.74 (2H, d, J=8.8 Hz, ArH), 8.33 (2H, d, J=8.8 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.5 (q), 24.1 (t), 24.5 (t), 124.1 (d), 130.2 (d), 137.0 (d), 139.4 (s), 140.3 (s), 147.9 (s), 191.6 (s). IR (KBr) ν_{max}/cm^{-1}: 1650 (C=O), 1521 and 1340 (NO_2). MS (EI) m/z (rel. int. %): 331 (M^+, 47%; ^{81}Br), 329 (M^+, 45%; ^{79}Br), 268 (base).

1.2. Reaction of *p*-nitrobenzaldehyde (1a) and cyclohexenone (10): formation of 15 and 16

To a stirred solution of *p*-nitrobenzaldehyde (**1a**) (76 mg, 0.5 mmol) and cyclohexenone (**10**) (144 mg, 1.5 mmol) in dry CH_2Cl_2 was added a boron tribromide–methyl sulfide complex (160 mg, 0.5 mmol) at 0°C. The mixture was stirred at the temperature for 0.5 h, and the reaction was worked up by the addition of water (3 ml). The whole mixture was stirred for 1 h at room temperature. The precipitates were removed by filtaration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was left for 12 h at room temperature and then purified by PTLC on silica gel, eluted with AcOEt–hexane (1:3 v/v) to give 2-(4-nitrobenzyl)-phenol (**15**) (37 mg, 33%) and 10-(4-nitrobenzyl)-1,2,3,4,5,6-hexahydro-2,6-methano-1-benzoxacine-2-ol (**16**) (61 mg, 38%).

1.2.1. 2-(4-Nitrobenzyl)phenol (15). Pale yellow powders (ether), mp 112–113°C. Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.99; H, 4.99; N, 6.08. ^{1}H NMR ($CDCl_3$) δ: 4.08 (2H, s, CH_2), 4.83 (1H, s, OH), 6.76 (1H, d, J=7.8 Hz, ArH), 6.91 (1H, t, J=7.3 Hz, ArH), 7.10–7.17 (2H, m, ArH), 7.38 (2H, d, J=8.3 Hz, ArH), 8.12 (2H, d, J=8.7 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 36.1 (t), 115.6 (d), 121.2 (d), 123.6 (d), 125.8 (s), 128.3 (d), 129.5 (d), 131.0 (d), 146.4 (s), 148.7 (s), 1535 (s). IR (KBr) ν_{max}/cm^{-1}: 3470 (OH), 1505 and 1339 (NO_2). MS (EI) m/z (rel. int. %): 229 (M^+, base).

1.2.2. 10-(4-Nitrobenzyl)-1,2,3,4,5,6-hexahydro-2,6-methano-1-benzoxacine-2-ol (16). Pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.19–1.30 (1H, m, CH_2), 1.53–1.78 (4H, m, CH_2), 1.91 (2H, d, J=14.1 Hz, CH_2), 2.03 (1H, dd, J=2.4 and 11.7 Hz, CH_2), 2.73 (1H, brs, OH), 3.19 (1H, s, CH), 3.98 and 4.08 (each 1H, d, J=15.1 Hz benzylic CH_2), 6.79 (1H, t, J=7.3 Hz, ArH), 6.92–6.97 (2H, m, ArH), 7.38 (2H, d, J=8.8 Hz, ArH), 8.16 (2H, d, J=8.3 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 18.7 (t), 32.0 (t), 35.2 (d), 36.1 (t), 36.2 (t), 39.0 (t), 98.8 (s), 119.9 (d), 123.4 (d), 125.2 (d), 125.6 (s), 126.8 (d), 128.7 (d), 129.5 (d), 146.2 (s), 149.4 (s), 153.2 (s). HRMS. Calcd for $C_{19}H_{19}NO_4$: 325.1314. Found 325.1317. IR (NaCl) ν_{max}/cm^{-1}: 3437 (OH), 1516 and 1344 (NO_2). MS (EI) m/z (rel. int. %): 325 (M^+, base).

1.2.3. Acetylation of 16. Compound **16** (325 mg, 1.0 mmol) and acetic anhydride (133 mg, 1.3 mmol) were refluxed for 3 h. The reaction mixture was evaporated under reduced pressure to remove acetic anhydride. The residue was purified by PTLC on silica gel eluted with AcOEt–hexane (1:4 v/v) to give 2-acetoxy-10-(4-nitrobenzyl)-1,2,3,4,5,6-hexahydro-2,6-methano-1-benzoxacine (**17**) (217 mg, 59%).

Colorless oil. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.45; H, 5.87; N, 3.74. ^{1}H NMR ($CDCl_3$) δ: 1.26–1.39 (1H, m, CH_2), 1.57–1.61 (1H, m, CH_2), 1.68–1.75 (2H, m, CH_2), 1.87–1.95 (1H, m, CH_2), 2.03 (3H, s, CH_3), 2.16 (1H, dd, J=2.9 and 12.2 Hz, CH_2), 2.28–2.33 (1H, m, CH_2), 2.39–2.44 (1H, m, CH_2), 3.18 (1H, brs, CH), 4.02 (2H, s, benzylic H), 6.81 (1H, t,J=7.3 Hz, ArH), 6.92 (1H, dd, J=1.5 and 7.8 Hz, ArH), 6.98 (1H, dd, J=1.5 and 7.8 Hz, ArH), 7.46 (2H, d, J=8.8 Hz, ArH), 8.10 (2H, d, J=8.8 Hz, ArH). ^{13}C NMR ($CDCl_3$) δ: 18.8 (t), 22.4 (q), 32.0 (t), 32.9 (t), 34.7 (d), 36.1 (t), 37.1 (t), 104.0 (s), 120.3 (d), 123.4 (d), 125.7 (s), 125.9 (s), 126.8 (d), 128.7 (d), 129.9 (d), 146.2 (s), 149.3 (s), 152.5 (s), 168.5 (s). IR

(NaCl) ν_{max}/cm^{-1}: 1748 and 1077 (COO), 1519 and 1345 (NO_2). MS (EI) *m/z* (rel. int. %): 367 (M^+, 50%), 325 (base).

1.3. Reaction of 14 with cyclohexenone (10)

To a stirred solution of compound **14** (115 mg, 0.47 mmol) and cyclohexenone (**10**) (90 mg, 0.94 mmol) in dry CH_2Cl_2 was added a boron tribromide–methyl sulfide complex (150 mg, 0.47 mmol) at 0°C. The mixture was stirred at that temperature for 0.5 h, and the reaction was worked up by the addition of water (3 ml). The whole mixture was stirred for 1 h at room temperature. The precipitates were removed by filtaration through Celite™ and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was left for 12 h at room temperature and then purified by PTLC on silica gel, eluted with AcOEt–hexane (1:3 v/v) to give 2-(4-nitrobenzyl)phenol (**15**) (40 mg, 37%) and 10-(4-nitrobenzyl)-1,2,3,4,5,6-hexahydro-2,6-methano-1-benzoxacine-2-ol (**16**) (43 mg, 28%).

1.4. Treatment of 14 with boron tribromide–methyl sulfide complex

To a stirred solution of compound **14** (56 mg, 0.23 mmol) in dry CH_2Cl_2 was added a boron tribromide–methyl sulfide complex (74 mg, 0.23 mmol) at 0°C. The mixture was stirred at that temperature for 0.5 h, and the reaction was worked up by the addition of water (3 ml). The whole mixture was stirred for 1 h at room temperature. The precipitates were removed by filtaration through Celite™, and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was left for 12 h at room temperature and then purified by PTLC on silica gel, eluted with AcOEt–hexane (1:2 v/v) to give 2-(4-nitrobenzyl)-phenol (**15**) (38 mg, 73%).

References

1. For reviews (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062. (c) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 51, Chapter 2. (d) Langer, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3049–3052.
2. (a) Kataoka, T.; Iwama, T.; Tsujiyama, S. *Chem. Commun.* **1998**, 197–198. (b) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S. *Tetrahedron* **1998**, *54*, 11813–11824.
3. (a) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Tsurukami, Y.; Iwamura, T.; Watanabe, S. *Synlett* **1999**, 197–198. (b) Kataoka, T.; Iwama, T.; Kinoshita, H.; Tsurukami, Y.; Tsujiyama, S.; Fujita, M.; Honda, E.; Iwamura, T.; Watanabe, S. *J. Organomet. Chem.* **2000**, *611*, 455–462.
4. Kataoka, T.; Kinoshita, H.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S.; Muraoka, O.; Tanabe, G. *Tetrahedron* **2000**, *56*, 4725–4731.
5. (a) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, 1383–1385. (b) Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1–5. (c) Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett.* **2000**, 617–620. (d) Shi, M.; Jiang, J.-K. *Tetrahedron* **2000**, *56*, 4793–4797. (e) Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* **2000**, 2397–2400.
6. (a) Kamimura, A.; Mitsudera, H.; Asano, S.; Kakei, A.; Noguchi, M. *Chem. Commun.* **1998**, 1095–1096. (b) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509–1512 and 6979–6982. (c) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakei, A. *J. Org. Chem.* **1999**, *64*, 6353–6360.
7. (a) Mitsudera, H.; Kakehi, A.; Kamimura, A. *Tetrahedron Lett.* **1999**, *40*, 7389–7392. (b) Jauch, J. *Synlett* **1999**, 1325–1327. (c) Jauch, J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2764–2765. (d) Jauch, J. *J. Org. Chem.* **2001**, *66*, 609–611.
8. Very recently, Shi and his coworkers reported the reactions using BCl_3–phosphine: Shi, M.; Jiang, J.-K.; Cui, S.-C.; Feng, Y.-S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390–393. Independently, we have studied the reactions using $BBr_3{\cdot}Me_2S$ or $BCl_3{\cdot}Me_2S$. A part of this work was presented at the Eighth International Conference on New Aspects of Organic Chemistry, July 11–15, 2000, Kyoto, Japan (Abstract p 201) and at the 121st Annual Meeting of the Pharmaceutical Society of Japan, March 28–30, 2001, Sapporo, Japan (Abstract II p 18).
9. Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613–2616.
10. (a) Basavaiah, D.; Kumaragurubaran, N.; Padmaja, K. *Synlett* **1999**, 1630–1632. (b) Basavaiah, D.; Hyma, R. S.; Muthukumaran, K.; Kumaragurubaran, N. *Synthesis* **2000**, 217–219.
11. Basavaiah, D.; Hyma, R. S.; Muthukumaran, K.; Kumaragurubaran, N. *Tetrahedron* **2000**, *56*, 5905–5907.
12. Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981–984.
13. (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795–797. (b) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213–1220. (c) Basavaiah, D.; Hyma, R. S.; Padmaja, K.; Krishnamacharyulu, M. *Tetrahedron* **1999**, *55*, 6971–6976.
14. Keum, G.; Lim, H. J.; Kang, S. B.; Chung, B. Y. *Bull. Korean Chem. Soc.* **2000**, *21*, 809–812.
15. (a) Basavaiah, D.; Gowriswari, V. V. L.; Rao, P. D.; Bharathi, T. K. *J. Chem. Res. (S)* **1995**, 267. (b) Basavaiah, D.; Gowriswari, V. V. L.; Rao, P. D.; Bharathi, T. K. *J. Chem. Res. (M)* **1995**, 1656–1673.
16. Iwama, T.; Tsujiyama, S.; Kinoshita, H.; Kanematu, K.; Tsurukami, Y.; Iwamura, T.; Watanabe, S.; Kataoka, T. *Chem. Pharm. Bull.* **1999**, *47*, 956–961.