JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b01217 • Publication Date (Web): 18 Aug 2015

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

One-pot Synthesis of β,β-Disubstituted α,β-Unsaturated Carbonyl Compounds

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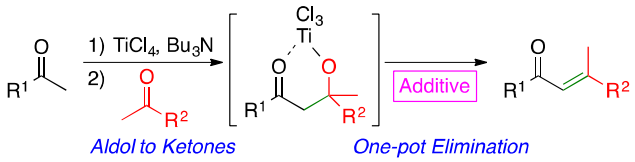


ABSTRACT: $TiCl_4$-promoted aldol reaction of ketones as aldol acceptors followed by elimination of the titanoxy group from the Ti-aldolates affords β,β-disubstituted α,β-unsaturated carbonyl compounds in a one-pot procedure; the use of additives, such as DMF, *N,N,N',N'*-tetramethylethylenediamine, and pyridine, in the elimination step was found to be important.

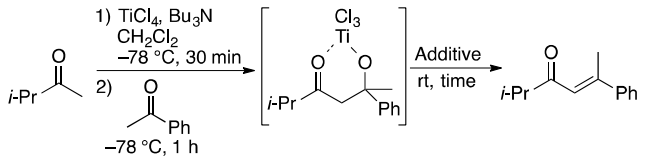
β,β-Disubstituted α,β-unsaturated carbonyl compounds are useful compounds themselves and as starting materials for the construction of tetra- or trisubstituted carbon stereogenic centers at the carbonyl β-position. The total syntheses of various natural products have been accomplished starting from these functional compounds.[1] We also reported the Lewis base-catalyzed enantioselective conjugate reduction of a β,β-disubstituted α,β-unsaturated ketone (enone) with trichlorosilane.[2]

The combination of the Horner–Wadsworth–Emmons reaction of ketones and subsequent transformation to enones via Weinreb amides is widely used to prepare *acyclic* β,β-disubstituted enones.[3] Sulfenylation/desulfenylation of ketones,[4] addition of organometallic reagents to β-amino-, β-alkylthio- or β-alkoxyenones,[5] conjugate addition of organometallic reagents to ynones,[6] rearrangement of tertiary propargylic alcohols or their acetates,[7] and oxidative rearrangement of tertiary allylic alcohols[8] have also been utilized. Recently, Donohoe and co-workers reported an efficient stereoselective method based on the Mizoroki–Heck reaction of vinyl Weinreb amides.[9] However, these precedents all require several reaction steps.

The aldol addition to simple ketones followed by dehydration (the aldol condensation) may offer a straightforward strategy for the preparation of β,β-disubstituted α,β-unsaturated carbonyl compounds from readily available starting materials; however, this has not yet been systematically studied because of the relatively low reactivity of ketones as electrophiles (aldol acceptors), its propensity for the retroaldol reaction, and generation of undesired self- and/or cross-aldol products. In one of the few examples, Tanabe and co-workers reported highly useful diastereoselective $TiCl_4$/Bu_3N-promoted aldol reactions between two ketones or between phenyl esters/*S*-phenyl thioesters and ketones.[10–13] They also reported the synthesis of a muscone precursor[10c] and dihydrojasmone[11b] by dehydration of the corresponding isolated aldol products. Inspired by their work, we envisaged that elimination of the titanoxy group directly from the Ti-aldolate intermediate (without isolation of the aldol product) might be feasible by optimizing the reaction conditions. Here, we report the one-pot synthesis of β,β-disubstituted α,β-unsaturated carbonyl compounds by using additives in the elimination step.

Initially, we investigated the reaction of methyl isopropyl ketone as the aldol donor and acetophenone as the aldol acceptor (Table 1). According to Tanabe's procedure with slight modification of the amounts of substrate and reagent,[10] methyl isopropyl ketone (1.0 equiv.) in dichloromethane was treated successively with $TiCl_4$ (1.1 equiv.) and Bu_3N (1.2 equiv.) at –78 °C, and acetophenone (1.0 equiv.) was added to the mixture. After 30 min, formation of the aldol product was confirmed by TLC analysis. If the reaction was quenched at this stage, the aldol product was obtained in 96% yield. However, when the temperature was increased to rt[14] without workup to facilitate the elimination, the desired enone was obtained only in 18% yield (Table 1, entry 1). A large amount of acetophenone was generated, which indicated progress of the retroaldol reaction. We reasoned that the Ti-enolate was regenerated because Ti strongly coordinated to the carbonyl oxygen atom in the Ti-aldolate intermediate. To cleave the coordinate bond, DMF was added as a ligand of titanium in the elimination step. As expected, the yield of the enone increased (Table 1, entries 2–4); DMF (5 equiv.) provided the best result. *N*-Methyl-2-pyrrolidone (NMP) and *N,N'*-dimethylpropyleneurea (DMPU) were inferior alternatives to DMF (Table 1, entries 5 and 6).[15] In addition to coordination to titanium, deprotonation of a carbonyl α-proton would facilitate the elimination step. Thus, tertiary amines were examined as additives. Monoamines were moderately effective (Table 1, entries 7–9),[16] whereas *N,N,N',N'*-tetramethylethylenediamine (TMEDA), which can bidentately coordinate to titanium, afforded a good yield (Table 1, entry 10). The use of larger amounts of TMEDA (2.0 equiv.) decreased the yield.[17] Next, pyridine and its derivatives were examined (Table 1, entries 11–14).[18] Unlike aliphatic amines, larger amounts (5.0 equiv.) of pyridine gave higher yield than lower amounts (3.0 equiv.) (entiries 11 and 12). Although the *E* selectivity was lowered, significant rate enhancement was observed with pyridine and α-picoline. Thus, we identified DMF, TMEDA, and pyridine as effective additives for the elimination step. It should also be noted that the titanium residue, which precipitates naturally or on addition of diethyl ether and hexane, can be removed by simple filtration through a Celite pad without aqueous workup. After evaporation, the filtrate can be directly purified by column chromatography on silica gel.

Table 1. Screening of Additives[a]



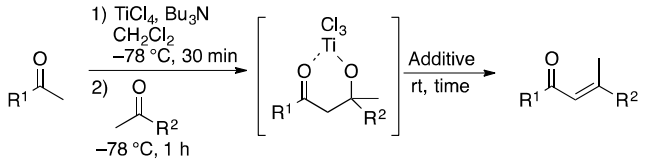
Entry	Additive (equiv.)	Time (h)	Yield (%)[b]	*E*/*Z*[c]
1	none	20	18	97:3
2	DMF (2.0)	20	58	96:4
3	DMF (5.0)	20	80	97:3
4	DMF (10)	20	74	98:2
5	NMP[d] (5.0)	21	19	97:3
6	DMPU[e] (5.0)	23	48	97:3
7	Bu_3N (1.0)	20	65	99:1
8	Et_3N (1.0)	20	48	97:3
9	*i*-Pr_2NEt (1.0)	20	39	97:3
10	TMEDA[f] (1.0)	20	72	97:3
11	pyridine (3.0)	1.5	63	87:13
12	pyridine (5.0)	5	87	86:14
13	α-picoline (5.0)	2	82	90:10
14	2,6-lutidine (5.0)	21	71	88:12

[a]The reaction was carried out by using methyl isopropyl ketone (1.0 mmol), $TiCl_4$ (1.1 mmol), Bu_3N (1.2 mmol), acetophenone (1.0 mmol), and additive in dichloromethane (2 mL). [b]Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d]*N*-methyl-2-pyrrolidone. [e]*N,N'*-Dimethylpropyleneurea. [f]*N,N,N',N'*-Tetramethylethylenediamine.

One-pot reactions of other substrates were investigated with these additives (Table 2). The reaction tolerated a variety of aromatic and aliphatic ketones. In most cases, pyridine resulted in a shorter reaction time and higher yield but lower *E* selectivity than DMF or TMEDA.[19,20] In most cases, high *E*/*Z* selectivity (>95:5) was observed with DMF and TMEDA additives. When propiophenone was used as aldol acceptor for the reaction with methyl isopropyl ketone, low *E*/*Z* selectivities were observed (Scheme 1).

Based on the above observation for the *E*/*Z* selectivity, we speculated that the stereochemical pathway would be different for the reaction with pyridine versus that with DMF or TMEDA. To verify this hypothesis, several control experiments were performed (Table 3). First, TMEDA or pyridine, and then (*E*)- or (*Z*)-enone (Ar = *p*-ClC_6H_4, isolated by chromatography after one-pot reaction) were added to a mixture of $TiCl_4$, Bu_3N and water in dichloromethane.[21] With TMEDA (Table 3, entries 1 and 2), the *E*/*Z* ratio became 97:3 irrespective of the geometry of the starting enone. However, with pyridine (Table 3, entries 3 and 4), the *E*/*Z* ratio of the starting enone was almost retained. Thus, the *E*/*Z* selectivity is controlled thermodynamically in the former case and kinetically in the latter case. Second, hydrogen chloride, a possible side product of the one-pot reaction, also caused isomerization (Table 3, entry 5), which suggested that the excess of pyridine (5.0 equiv.) trapped HCl and prevented the isomerization (equilibration).

Table 2. Substrate Scope[a]



Entry	R^1	R^2	Additive[c]	Time (h)	Yield (%)[b]	*E*/*Z*[d]
1	Ph	Ph	D	20	45	98:2
2	Ph	Ph	T	2	64	97:3
3	Ph	Ph	P	2	67	87:13
4	*p*-$MeOC_6H_4$	Ph	P	2	54	90:10
5	*p*-ClC_6H_4	Ph	P	2	68	92:8
6[e]	*p*-ClC_6H_4	Ph	P	2	87	92:8
7	Ph	*i*-Pr	D	24	45	86:14
8	Ph	*i*-Pr	T	1	86	87:13
9	Ph	*i*-Pr	P	2	73	88:12
10	*c*-Pr	Ph	D	7	19	95:5
11	*c*-Pr	Ph	T	20	38	95:5
12	*c*-Pr	Ph	P	1	77	89:11
13	*c*-Hex	Ph	D	20	73	97:3
14	*c*-Hex	Ph	T	20	72	97:3
15	*c*-Hex	Ph	P	1	86	85:15
16	*t*-Bu	Ph	D	20	38	98:2
17	*t*-Bu	Ph	T	20	78	98:2
18	*t*-Bu	Ph	P	1	87	86:14
19	*i*-Pr	*p*-$MeOC_6H_4$	D	4	70	>99:1
20	*i*-Pr	*p*-$MeOC_6H_4$	T	18	62	98:2
21	*i*-Pr	*p*-$MeOC_6H_4$	P	1	67	82:18
22	*i*-Pr	*p*-ClC_6H_4	D	20	38	96:4
23	*i*-Pr	*p*-ClC_6H_4	T	20	71	96:4
24	*i*-Pr	*p*-ClC_6H_4	P	1	67	73:27
25	*i*-Pr	*t*-Bu	P	2	99	73:27

[a]The reaction was carried out by using R^1COCH_3 (0.5 mmol), $TiCl_4$ (1.1 mmol), Bu_3N (1.2 mmol), R^2COCH_3 (0.5 mmol), and additive [DMF (2.5 mmol), TMEDA (0.5 mmol), or pyridine (2.5 mmol)] in dichloromethane (1 mL). [b]Isolated yield. [c]D: DMF (5.0 equiv.); T: TMEDA (1.0 equiv.); P: pyridine (5.0 equiv.). [d]Determined by ^1H NMR spectroscopic analysis of the crude product. [e]The aldol step was carried out at −45 °C for 1.0 h.

Scheme 1. Propiophenone as Aldol Acceptor

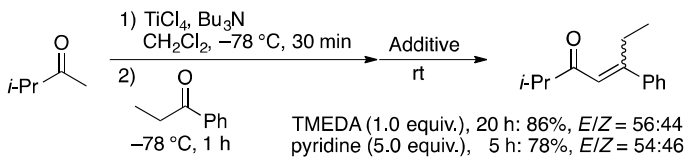
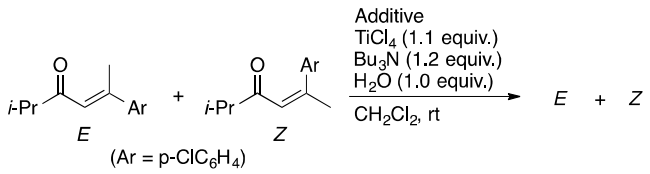


Table 3. Control Experiments[a]

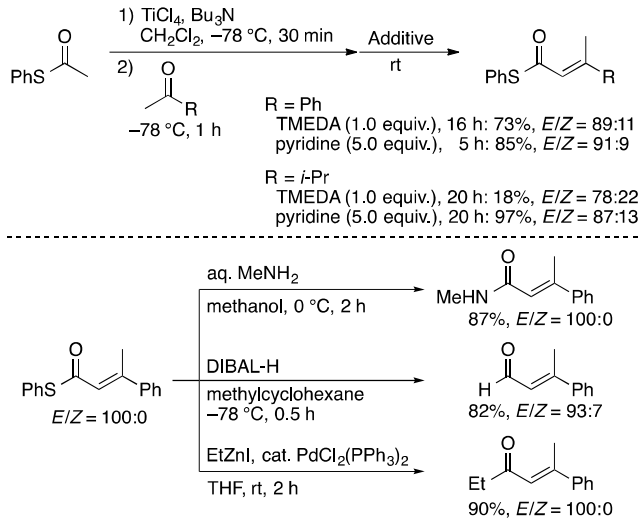


Entry	*E*/*Z* (start)	Additive (equiv.)	Time (h)	*E*/*Z* (end)[b]
1	98:2	TMEDA (1.0)	12	97:3
2	0:100	TMEDA (1.0)	12	97:3
3	98:2	pyridine (5.0)	1	98:2
4	0:100	pyridine (5.0)	1	3:97
5	0:100	HCl (1.0)[c]	1	97:3

[a]Additive and enone were successively added to a mixture of $TiCl_4$ (1.1 equiv.), Bu_3N (1.2 equiv.) and water (1.0 equiv.) in dichloromethane. [b]Determined by ^1H NMR spectroscopic analysis of the crude product. [c]Hydrogen chloride in Et_2O was used instead of a mixture of $TiCl_4$, Bu_3N, and water.

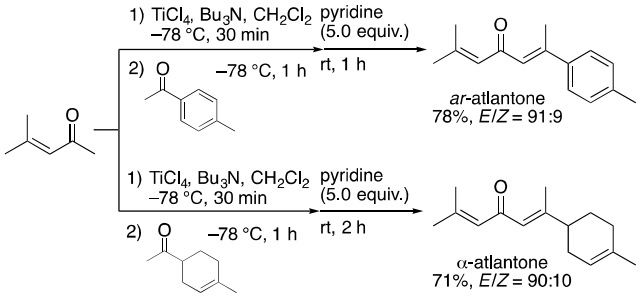
The one-pot reaction was also applicable to the preparation of β,β-disubstituted α,β-unsaturated carboxylic acid derivatives (Scheme 2). The reaction of *S*-phenyl thioacetate[22] with acetophenone using TMEDA or pyridine in the elimination step afforded the desired unsaturated thioester in good yield with good *E* selectivity. For the reaction with methyl isopropyl ketone, pyridine provided a much higher yield than TMEDA. In addition, the unsaturated thioester product (100% *E*, isolated by column chromatography) could be transformed to the corresponding *N*-methyl amide, aldehyde, or ethyl ketone by treatment with $MeNH_2$,[23] diisobutylaluminum hydride (DIBAL-H),[24] and EtZnI/palladium catalyst,[25] respectively.[26] It should be noted that these products are difficult to obtain from the one-pot reaction of the corresponding carbonyl compounds (i.e., *N*-methyl acetamide, acetaldehyde, and 2-butanone).

Scheme 2. Transformation of *S*-Phenyl Thioacetate



The one-pot method was applied to the one-pot synthesis of simple natural products, *ar*-atlantone[27] and α-atlantone[28] (Scheme 3). The Ti-aldol reaction of mesityl oxide with the required ketones followed by elimination with pyridine provided *ar*-atlantone and α-atlantone in good yield and *E* selectivity.

Scheme 3. Synthesis of Atlantones



In summary, we have demonstrated a one-pot method to synthesize β,β-disubstituted α,β-unsaturated carbonyl compounds by sequential $TiCl_4$-promoted aldol reaction to simple ketones and base-promoted elimination.

EXPERIMENTAL SECTION

General Methods. Dry dichloromethane (dehydrated) was stored over 4-Å MS prior to use. Titanium(IV) chloride was distilled under reduced pressure. Tributylamine, *N,N,N',N'*-Tetramethylethylenediamine (TMEDA), and pyridine were distilled from CaH_2. *N,N*-Dimethylformamide (DMF) was stored over 4Å MS prior to use. All other solvents and chemicals were purified based on standard procedures. Melting points (mp) were uncorrected. ^1H and $^{13}C\{^1H\}$ NMR spectra were measured in $CDCl_3$ with 400 or 600 MHz spectrometer. Tetramethylsilane (TMS) (δ = 0 ppm) and $CDCl_3$ (δ = 77.0 ppm) served as internal standards for ^1H and ^{13}C NMR, respectively. Infrared spectra were recorded on an FT-IR spectrometer. High-resolution mass spectra were recorded on a double-focusing magnetic-sector mass analyzer operating in a FAB mode. Thin-layer chromatography (TLC) was visualized with UV light, phosphomolybdic acid and/or anisaldehyde. Column chromatography was performed using sílica gel (spherical, neutral, 63-210 nm). The reactions under anhydrous conditions were carried out using oven- and heating gun-dried glassware with a rubber septum and a magnetic stirring bar under argon atmosphere.

Typical Procedure: One-pot Synthesis of β,β-Disubstituted Enone (Table 1, entry 12). $TiCl_4$ (2.82 M in CH_2Cl_2; 0.39 mL) and Bu_3N (0.29 mL, 1.2 mmol) were successively added to a stirred solution of methyl isopropyl ketone (87.0 mg, 1.0 mmol) in CH_2Cl_2 (2.0 mL) at –78 °C. After 30 min, acetophenone (119.7 mg, 1.0 mmol) was added to the mixture at –78 °C. Formation of the aldol product was detected by TLC analysis after 1 h. Then pyridine (0.40 mL, 5.0 mmol) was added at –78 °C and the reaction mixture was warmed to room temperature. After being stirred for 5 h, the reaction mixture was diluted with Et_2O (5 mL) and hexane (5 mL). The mixture was filtered through a Celite pad and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/acetone = 30:1) to give 2-methyl-5-phenylhex-4-en-3-one (163.8 mg, 87% yield, *E*/*Z* = 86:14).

(*E*)-2-Methyl-5-phenylhex-4-en-3-one.[29] TLC: R_f 0.38 (hexane/acetone = 10:1, stained dark green with anisaldehyde).^1H NMR (400 MHz): δ = 1.17 (d, *J* = 7.0 H, 6H), 2.55 (s, 3H) 2.73 (sept, *J* = 7.0 H, 1H), 6.55 (s, 1H), 7.33-7.43 (m, 3H), 7.44-7.58 (m, 2H).

(*Z*)-2-Methyl-5-phenylhex-4-en-3-one.[29] TLC: R_f 0.35 (hexane/acetone = 10:1, stained dark green with anisaldehyde). ^1H NMR (400 MHz): δ = 0.99 (d, *J* = 6.9 Hz, 6H), 2.18 (d, *J* = 1.4 Hz, 3H), 2.45 (sept, *J* = 6.9 Hz, 1H), 6.20 (q, *J* = 1.4 Hz, 1H), 7.13-7.20 (m, 2H), 7.29-7.36 (m, 3H).

(*E*)-1,3-Diphenylbut-2-en-1-one.[3f] According to the typical procedure, the reaction of acetophenone (57.7 mg) and acetophenone (60.1 mg) at rt for 2 h gave 1,3-diphenylbut-2-en-1-one (75.1 mg, 67%, *E*/*Z* = 87:13). TLC: R_f 0.30 (hexane/AcOEt = 10:1, stained green with anisaldehyde). ^1H NMR (400 MHz): δ = 2.60 (d, *J* = 0.9 Hz, 3H), 7.17 (q, *J* = 0.9 Hz, 1H), 7.37-7.45 (m, 3H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.53-7.59 (m, 3H), 7.98-8.02 (m, 2H).

(*Z*)-1,3-Diphenylbut-2-en-1-one.[3f] TLC: R_f 0.24 (hexane/AcOEt = 10:1, stained green with anisaldehyde). ^{1}H NMR (400 MHz): δ = 2.32 (s, 3H), 6.69 (brs, 1H), 7.14-7.27 (m, 5H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 2H).

(*E*)-1-(4-Methoxyphenyl)-3-phenylbut-2-en-1-one.[3f] According to the typical procedure, the reaction of 4-methoxyacetophenone (150.2 mg) and acetophenone (123.2 mg) at rt for 2 h gave 1-(4-methoxyphenyl)-3-phenylbut-2-en-1-one (136.2 mg, 54%, *E*/*Z* = 90:10). TLC: R_f 0.36 (hexane/AcOEt = 7:1, stained yellow green with anisaldehyde). ^{1}H NMR (400 MHz): δ = 2.57 (d, *J* = 1.4 Hz, 3H), 3.88 (s, 3H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.12 (q, *J* = 1.4 Hz, 1H), 7.38-7.45 (m, 3H), 7.55-7.59 (m, 2H), 8.00 (d, *J* = 8.7 Hz, 2H).

(*E*)-1-(4-Chlorophenyl)-3-phenylbut-2-en-1-one. $TiCl_4$ (3.0 M CH_2Cl_2; 0.18 mL) and Bu_3N (0.14 mL, 0.6 mmol) were successively added to a stirred solution of 4-chloroacetophenone (71.2 mg, 0.46 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C. After 30 min, acetophenone (60.9 mg, 0.51 mmol) was added to the mixture at −78 °C. After being stirred at −45 °C for 1 h, pyridine (0.20 mL, 2.5 mmol) was added at −45 °C and the reaction mixture was warmed to room temperature. After being stirred for 2 h, the reaction mixture was diluted with Et_2O (5 mL) and hexane (5 mL). The mixture was filtered through a Celite pad and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 30/1) to give 1-(4-chlorophenyl)-3-phenylbut-2-en-1-one (102.7 mg, 87%, *E*/*Z* = 92:8). TLC: R_f 0.42 (hexane/AcOEt = 7:1, stained orange with anisaldehyde). IR (film): 3061, 1657, 1593, 1211, 1090, 762 cm^{-1}. ^{1}H NMR (400 MHz): δ = 2.60 (d, *J* = 1.4 Hz, 3H), 7.12 (q, *J* = 1.4 Hz, 1H), 7.40-7.47 (m, 5H), 7.55-7.59 (m, 2H), 7.93 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz): δ = 19.0, 121.4, 126.5, 128.6, 128.8, 129.3, 129.7, 137.6, 138.9, 142.6, 156.0, 190.4. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 257 ($M+H^+$, 100), 220 (M^+–Cl, 16), 139 ($ClC_6H_4CO^+$, 48). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{16}H_{14}OCl$ ($M+H^+$) 257.0733, found 257.0732.

(*E*)-3,4-Dimethyl-1-phenylpent-2-en-1-one.[6] According to the typical procedure, the reaction of acetophenone (115.4 mg) and methyl isopropyl ketone (88.9 mg) at −78 °C for 2 h gave 3,4-dimethyl-1-phenyl-2-penten-1-one (131.9 mg, 73%, *E*/*Z* = 88:12). TLC: R_f 0.18 (hexane/CH_2Cl_2 = 2:1, stained orange with anisaldehyde). ^{1}H NMR (400 MHz): δ = 1.15 (d, *J* = 7.2 Hz, 6H), 2.17 (s, 3H), 2.49 (sept, *J* = 7.2 Hz, 1H), 6.74 (s, 1H) , 7.43-7.47 (m, 2H), 7.47-7,56 (m, 1H), 7.92 (d, *J* = 7.2 Hz, 2H).

(*Z*)-3,4-Dimethyl-1-phenyl-2-penten-1-one.[6] TLC: R_f 0.24 (hexane/CH_2Cl_2 = 2:1, stained orange with anisaldehyde).^{1}H NMR (400 MHz): δ = 1.08 (d, *J* = 7.0 Hz, 6H), 1.92 (s, 3H), 3.78 (sept, 1H), 6.61 (s, 1H), 7.40-7.50 (m, 2H), 7.50-7.56 (m, 1H), 7.93 (d, *J* = 7.3 Hz, 2H).

(*E*)-1-Cyclopropyl-3-phenylbut-2-en-1-one. According to the typical procedure, the reaction of cyclopropyl methyl ketone (46.2 mg) and acetophenone (60.7 mg) at rt for 1 h gave 1-cyclopropyl-3-phenylbut-2-en-1-one (71.7 mg, 77%, *E*/*Z* = 89:11). TLC: R_f 0.49 (hexane/AcOEt = 10:1, stained dark green with anisaldehyde). IR (ATR): 3008, 1668, 1597, 1574, 1381, 1102, 1094, 974, 895, 760, 693 cm^{-1}. ^{1}H NMR (600 MHz): δ = 0.89-0.94 (m, 2H), 1.09-1.13 (m, 2H), 2.03-2.08 (m, 1H), 2.54 (d, *J* = 1.3 Hz, 3H), 6.66 (q, *J* = 1.3 Hz, 3H), 7.34-7.41 (m, 3H), 7.49-7.52 (m, 2H). ^{13}C NMR (150 MHz): δ = 11.2, 18.5, 22.8, 124.9, 126.5, 128.5, 128.9, 142.7, 152.9, 201.0. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 187 ($M+H^+$, 100), 145 ($PhMeC{=}CHCO^+$, 33). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{13}H_{15}O$ ($M+H^+$) 187.1123, found 187.1119.

(*E*)-1-Cyclohexyl-3-phenylbut-2-en-1-one. According to the typical procedure, the reaction of cyclohexyl methyl ketone (60.5 mg) and methyl acetophenone (61.0 mg) at rt for 1 h gave 1-cyclohexyl-3-phenylbut-2-en-1-one (94.1 mg, 86%, *E*/*Z* = 85:15). TLC: R_f 0.59 (hexane/acetone = 10:1, stained dark green with anisaldehyde). IR (ATR): 2926, 2852, 1678, 1598, 1573, 1446, 1145, 966, 757, 694 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.15-1.46 (m, 5H), 1.60-1.72 (m, 1H), 1.77-1.85 (m, 2H), 1.86-1.94 (m, 2H), 2.40-2.49 (m, 1H), 2.53 (d, *J* = 1.4 Hz, 3H), 6.54 (q, *J* = 1.4 Hz, 1H), 7.34-7.42 (m, 3H), 7.46-7.51 (m, 2H). ^{13}C NMR (100 MHz): δ = 18.4, 25.8, 25.9, 28.6, 52.1, 123.6, 126.4 128.5, 128.9, 142.8, 154.0, 204.6. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 229 ($M+H^+$, 96), 145 ($PhMeC{=}CHCO^+$, 100). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{16}H_{21}O$ ($M+H^+$) 229.1592, found 229.1591.

(*E*)-2,2-Dimethyl-5-phenylhex-4-en-3-one. According to the typical procedure, the reaction of *tert*-butyl methyl ketone (49.4 mg) and acetophenone (60.0 mg) at rt for 1 h gave 2,2-dimethyl-5-phenylhex-4-en-3-one (86.3 mg, 87%, *E*/*Z* = 86:14). TLC: R_f 0.47 (hexane/acetone = 10:1, stained black with anisaldehyde). IR (ATR): 2966, 1674, 1597, 1573, 1446, 1088, 958, 764, 694 cm^{-1}. ^1H NMR (400 MHz): δ = 1.21 (s, 9H), 2.50 (d, *J* = 1.4 Hz, 3H), 6.74 (q, *J* = 1.4 Hz, 1H), 7.34-7.42 (m, 3H), 7.46-7.51 (m, 2H). ^{13}C NMR (100 MHz): δ = 18.6, 26.6, 44.2, 120.8, 126,4 128.5, 128.8, 143.2, 154.1, 206.7. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 203 ($M+H^+$, 61), 145 ($PhMeC=CHCO^+$, 100). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{14}H_{19}O$ ($M+H^+$) 203.1436, found 203.1433.

(*E*)-5-(4-Methoxyphenyl)-2-methylhex-4-en-3-one. According to the typical procedure, the reaction of methyl isopropyl ketone (40.7 mg) and *p*-methoxyacetophenone (74.1 mg) at rt for 1 h gave 5-(4-methoxyphenyl)-2-methylhex-4-en-3-one (68.7 mg, 67%, *E*/*Z* = 82:18). TLC: R_f 0.47 (hexane/AcOEt = 7:1, stained dark green with anisaldehyde). IR (film): 2966, 1680, 1593, 1512, 1252, 1180, 829 cm^{-1}. ^1H NMR (400 MHz): δ = 1.16 (d, *J* = 6.9 Hz, 6H), 2.54 (d, *J* = 1.4 Hz, 3H), 2.71 (sept, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 6.53 (q, *J* = 1.4 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz): δ = 18.2, 18.5, 42.0, 55.3, 113.8, 121,6 127.8, 134.8, 153.8, 160.4, 205.0. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 219 ($M+H^+$, 75), 175 ($ArMeC=CHCO^+$, 100). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{14}H_{19}O_2$ ($M+H^+$) 219.1385, found 219.1384.

(*E*)-5-(4-Chlorophenyl)-2-methylhex-4-en-3-one. According to the typical procedure, the reaction of methyl isopropyl ketone (41.3 mg) and *p*-chloroacetophenone (72.8 mg) at rt for 1 h gave 5-(4-chlorophenyl)-2-methylhex-4-en-3-one (70.1 mg, 67%, *E*/*Z* = 73:27). TLC: R_f 0.57 (hexane/AcOEt = 10:1, stained dark green with anisaldehyde). IR (ATR): 2968, 1682, 1600, 1562, 1489, 1071, 1063, 1011, 967, 821, 770 cm^{-1}. ^1H NMR (400 MHz): δ = 1.15 (d, *J* = 6.9 Hz, 6H), 2.51 (d, *J* = 1.4 Hz, 3H), 2.71 (sept, *J* = 6.9 Hz, 1H), 6.52 (q, *J* = 1.4 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz): δ = 18.1, 18.2, 41.9, 123.3, 127.6, 128,5 134.8, 141.0, 152.5, 204.7. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 223 ($M+H^+$, 97), 179 ($ArMeC=CHCO^+$, 100). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{13}H_{16}OCl$ ($M+H^+$) 223.0890, found 223.0895.

(*Z*)-5-(4-Chlorophenyl)-2-methylhex-4-en-3-one. TLC: R_f 0.49 (hexane/AcOEt = 10:1, stained dark green with anisaldehyde). IR (ATR): 2970, 1689, 1616, 1594, 1490, 1092, 1013, 843, 823, 765 cm^{-1}. ^1H NMR (600 MHz): δ = 1.02 (d, *J* = 6.9 Hz, 6H), 2.15 (d, *J* = 1.4 Hz, 3H), 2.51 (sept, *J* = 6.9 Hz, 1H), 6.24 (q, *J* = 1.4 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz): δ = 18.2, 27.0, 40.8, 125.4, 128.3, 128.4, 133.8, 139.4, 151.2, 204.6. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 223 ($M+H^+$, 100), 179 ($ArMeC=CHCO^+$, 95). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{13}H_{16}OCl$ ($M+H^+$) 223.0890, found 223.0892.

(*E*)-2,5,6,6-Tetramethylhept-4-en-3-one.[5b] According to the typical procedure, the reaction of methyl isopropyl ketone (40.5 mg) and *tert*-butyl methyl ketone (48.3 mg) at rt for 2 h gave 2,5,6,6-tetramethylhept-4-en-3-one (79.1mg, 99%, *E*/*Z* = 73:27). TLC: R_f 0.50 (hexane/AcOEt = 10:1, stained black with anisaldehyde). ^1H NMR (400 MHz): δ = 1.09 (s, 9H), 1.12 (d, *J* = 6.9 Hz, 6H), 2.12 (s, 3H), 2.63 (sept, *J* = 6.9 Hz, 1H), 6.17 (s, 1H).

(*E*)-2-Methyl-5-phenylhept-4-en-3-one. According to the typical procedure, the reaction of methyl isopropyl ketone (44.1 mg) and propiophenone (69.0 mg) with TMEDA (150 μL) at rt for 24 h gave 2-methyl-5-phenylhept-4-en-3-one (88.8 mg, 86%, *E*/*Z* = 56:44). TLC: R_f 0.52 (hexane/AcOEt = 10:1, stained dark green with anisaldehyde). IR (ATR) 2968, 1682, 1595, 1574, 1463, 1445, 1068, 1056, 764, 695. ^1H NMR (600 MHz): δ = 1.06 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 7.2 Hz, 6H), 2.70 (sept, *J* = 7.2 Hz, 1H), 3.04 (q, *J* = 7.2 Hz, 2H), 6.42 (s, 1H), 7.37-7.39 (m, 3H) 7.44-7.46 (m, 2H). ^{13}C NMR (100 MHz): δ = 13.6, 18.4, 24.7, 42.0, 123.0, 126.8, 128.5, 128.8, 141.7, 160.7, 204.8. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 203 ($M+H^+$, 69), 159 ($PhEtC=CHCO^+$, 100), 77 (Ph^+, 87). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{14}H_{19}O$ ($M+H^+$) 203.1436, found 203.1427.

(*Z*)-2-Methyl-5-phenylhept-4-en-3-one. R_f 0.45 (hexane/AcOEt = 10:1, stained dark green with anisaldehyde). IR (ATR): 2968, 1693, 1672, 1618, 1598, 1464, 1442, 1381, 1092, 1013, 832, 765, 697. ^{1}H NMR (400 MHz): δ = 0.97 (d, *J* = 7.2 Hz, 6H), 1.05 (d, *J* = 7.8 Hz, 3H), 2.38-2.52 (m, 3H), 6.15 (s, 1H), 7.10-7.16 (m, 2H) 7.26-7.38 (m, 3H). ^{13}C NMR (100 MHz): δ = 12.3, 18.3, 33.2, 40.4, 124.0, 127.2, 127.7, 128.1, 140.5, 157.6, 206.2. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 203 ($M+H^+$, 100), 159 (PhEtC=CHCO$^+$, 100), 77 (Ph^+, 90), 71 (^{i}PrCO$^+$, 85). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{14}H_{19}O$ ($M+H^+$) 203.1436, found 203.1442.

S-Phenyl (*E*)-3-phenylbut-2-enethioate. According to the typical procedure, the reaction of *S*-phenyl thioacetate (76.3 mg) and acetophenone (67.2 mg) at rt for 5 h gave *S*-phenyl 3-phenylbut-2-enethioate (108.3 mg, 85%, *E*/*Z* = 91:9). TLC: R_f 0.57 (hexane/AcOEt = 10:1, stained pale red with anisaldehyde). mp 63–64 °C. IR (ATR): 3056, 1682, 1597, 1572, 1438, 1047, 936, 833, 735, 690, 566 cm^{-1}. ^{1}H NMR (400 MHz): δ = 2.55 (d, *J* = 1.4 Hz, 3H), 6.49 (q, *J* = 1.4 Hz, 1H), 7.37-7.54 (m, 10H). ^{13}C NMR (100 MHz): δ = 18.9, 122.6, 126.6, 128,3 128.6, 129.1, 129.3, 129.5, 134.6, 141.5, 154.1, 187.7. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 255 ($M+H^+$, 19), 145 (PhMeC=CHCO$^+$, 100). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{16}H_{15}OS$ ($M+H^+$) 255.0844, found 255.0847.

S-Phenyl (*E*)-3,4-dimethylpent-2-enethioate. According to the typical procedure, the reaction of *S*-phenyl thioacetate (79.0 mg) and methyl isopropyl ketone (41.0 mg) at rt for 20 h gave *S*-phenyl 3,4-dimethylpent-2-enethioate (102.5 mg, 97%, *E*/*Z* = 87:13). TLC: R_f 0.62 (hexane/CH_2Cl_2 = 1:1, stained pale red with anisaldehyde). IR (ATR): 2964, 1683, 1616, 1440, 1031, 1023, 883, 830, 729, 688 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.09 (d, *J* = 6.9 Hz, 6H), 2.11 (s, 3H), 2.38 (sept, *J* = 6.9 Hz, 1H), 6.07 (s, 1H), 7.38-7.46 (m, 5H). ^{13}C NMR (100 MHz): δ = 17.6, 20.8, 38.2, 119.7, 128.5, 129.0, 129.1, 134.7, 164.8, 187.7. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 221 ($M+H^+$, 23), 111 (^{i}PrMeC=CHCO$^+$, 100). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{13}H_{17}OS$ ($M+H^+$) 221.1000, found 221.1003.

Control Experiments for *E*/*Z* Isomerization. Table 3, entry 1 (from *E* isomer): $TiCl_4$ (3.00 M in CH_2Cl_2; 0.12 mL) was added to a stirred solution of H_2O (6.1 μL, 0.34 mmol) and Bu_3N (0.1 mL, 0.41 mmol) in CH_2Cl_2 (0.68 mL) at –78 °C. After 0.5 h, TMEDA (0.05 mL, 0.34 mmol) was added at –78 °C and the reaction mixture was warmed to room temperature. After 0.5 h, (*E*)-5-(4-chlorophenyl)-2-methylhex-4-en-3-one (76.7 mg, 0.34 mmol, *E*/*Z* = 97:3) was added to the mixture. After being stirred for 12 h, the reaction mixture was diluted with Et_2O (5 mL) and hexane (5 mL). The mixture was filtered through a Celite pad. The filtrate was concentrated to give the sufficiently pure crude product, which ^{1}H-NMR spectroscopic analysis indicated the *E*/*Z* ratio to be 97:3.

Table 3, entry 2 (from *Z* isomer): Similarly to the above procedure, (*Z*)-5-(4-chlorophenyl)-2-methylhex-4-en-3-one (6.8 mg, *E*/*Z* = 0:100) was treated with the mixture of $TiCl_4$ (3.00 M CH_2Cl_2; 0.01 mL), H_2O (0.5 μL), Bu_3N (8.5 μL) and TMEDA (4.5 μL) in CH_2Cl_2 (0.06 mL) at room temperature for 12 h. The ^{1}H-NMR spectroscopic analysis of the crude product indicated the *E*/*Z* ratio to be 97:3.

Transformation of α,β-Unsaturated *S*-Phenyl Thioester to (*E*)-*N*-Methyl-3-phenylbut-2-enamide. According to the reported procedure,[23] 40% $MeNH_2$ in H_2O (12 μL, 0.24 mmol) was added over 30 min to a stirred solution of *S*-phenyl (*E*)-3,4-dimethylpent-2-enethioate (50.9 mg, *E*/*Z* = 100:0) in MeOH (2.6 mL) at 0 °C. After 2 h, the reaction mixture was concentrated. The residue was gave purified by column chromatography on silica gel (hexane/AcOEt = 10:1) to give (*E*)-*N*-methyl-3-phenylbut-2-enamide (30.5 mg, 87%, *E*/*Z* = 100:0). TLC: R_f 0.14 (hexane/AcOEt = 10:1, stained white with anisaldehyde). mp 119-120 °C. IR (ATR): 3251, 3077, 2919, 1651, 1619, 1563, 1447, 1365, 1287, 1234, 875, 764, 689 cm^{-1}. ^{1}H NMR (600 MHz): δ = 2.55 (d, *J* = 1.1 Hz, 3H), 2.89 (d, *J* = 8.7 Hz, 3H), 5.70 (brs, 1H), 6.00 (q, *J* = 1.1 Hz, 1H), 7.30-7.37 (m, 3H), 7.40-7.43 (m, 2H). ^{13}C NMR (150 MHz): δ = 17.6, 26.1, 119.8, 126.1, 128.4, 142.7, 150.5, 167.6. LRMS (FAB+, $CHCl_3$+NBA): *m/z* 176 ($M+H^+$, 100), 145 (PhMeC=CHCO$^+$, 24). HRMS (FAB+, $CHCl_3$+NBA): Calcd for $C_{11}H_{14}NO$ ($M+H^+$) 176.1075, found 176.1077.

Transformation of α,β-Unsaturated *S*-Phenyl Thioester to (*E*)-3-Phenylbut-2-enal. DIBAL-H (1.0 M in hexane, 0.30 mL) was added to a stirred solution of *S*-phenyl (*E*)-3,4-dimethylpent-2-enethioate (50.4 mg, *E*/*Z* = 100:0) in methylcyclohexane (2.0 mL) at –78 °C. The reaction

mixture was stirred at –78 °C for 0.5 h and quenched with NaOH/H_2O/EtOH (0.3 g/1.25 mL/1.75 mL). The mixture was extracted with AcOEt (3×15mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 20:1) to give (*E*)-3-phenylbut-2-enal[30] (23.9 mg, 82%, *E*/*Z* = 93:7). TLC: R_f 0.47 (hexane/AcOEt = 10:1, stained black with anisaldehyde). ^{1}H NMR (400 MHz): δ = 2.58 (d, *J* = 1.4 Hz, 3H), 6.40 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.36-7.48 (m, 3H), 7.50-7.60 (m, 2H), 10.19 (d, *J* = 7.8 Hz, 1H).

Transformation of α,β-Unsaturated *S*-Phenyl Thioester to (*E*)-5-Phenylhex-4-en-3-one. According to the reported procedure with a modification,[25] EtZnI (0.50 M in THF/Et_2O/hexane; 1.2 mL, prepared from diethylzinc and iodine according to the reported procedure[31]) was added to a stirred solution of *S*-phenyl (*E*)-3,4-dimethylpent-2-enethioate (50.9 mg, *E*/*Z* = 100:0) and $PdCl_2(PPh_3)_2$ (14.0 mg, 10 mol %) in toluene (0.67 mL) at room temperature. After being stirred for 2 h, the reaction mixture was diluted with AcOEt and concentrated. The residue was gave purified by column chromatography on silica gel (hexane/AcOEt = 30:1) to give (*E*)-5-phenylhex-4-en-3-one[3f] (31.3 mg, 90%, *E*/*Z* = 100:0). TLC: R_f 0.52 (hexane/AcOEt = 10:1, stained black with anisaldehyde). ^{1}H NMR (400 MHz): δ = 1.13 (t, *J* = 7.3 Hz, 3H), 2.55 (d, *J* = 0.9 Hz, 3H), 2.57 (q, *J* = 7.3 Hz, 2H), 6.50 (q, *J* = 0.9 Hz, 1H), 7.33-7.42 (m, 3H), 7.45-7.52 (m, 2H).

Synthesis of *ar*-Atlantone. According to the typical procedure, the reaction of mesityl oxide (98.4 mg) and *p*-methylacetophenone (134.2 mg) at rt for 1 h gave *ar*-atlantone[27b] (167.2 mg, 78%, *E*/*Z* = 91:9). TLC: R_f 0.57 (hexane/AcOEt = 7:1, stained black with anisaldehyde). ^{1}H NMR ($CDCl_3$): δ = 1.92 (s, 3H), 2.22 (s, 3H), 2.37 (s, 3H), 2.56 (s, 3H), 6.19 (brs, 1H), 6.49 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H).

Synthesis of α-Atlantone. According to the typical procedure, the reaction of mesityl oxide (51.2 mg) and 1-(4-methyl-3-cyclohexen-1-yl)ethanone[32] (66.0 mg) at rt for 2 h gave α-atlantone[28c] (74.4 mg, 71%, *E*/*Z* = 90:10). TLC: R_f 0.56 (hexane/AcOEt = 10:1, stained black with anisaldehyde). ^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 3H), 1.65-2.20 (m, 7H), 1.85 (s, 3H), 2.13 (s, 6H), 5.41 (brs, 1H), 6.06 (brs, 1H), 6.08 (brs, 1H).

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra of the known compounds (the products in Table 1, the products in entries 1–4, 7–9, and 25 of Table 2, the products in Scheme 1, (*E*)-3-phenylbut-2-enal and (*E*)-5-phenylhex-4-en-3-one in Scheme 2, *ar*-atlantone and α-atlantone in Scheme 3). ^{1}H and ^{13}C NMR spectra of the new compounds (the products in entries 5, 6 and 10–24 of Table 2, and the thioester products in Scheme 2). This material is available free of charge *via* the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

This work was partially supported by JSPS KAKENHI Grant Number 23590009 and 26460010.

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(14) Lower temperatures than rt (even 0 °C) for the elimination step significantly decreased the reaction rate and did not improve the *E*/*Z* selectivity.

(15) NMP has been used as additive for $TiCl_4$-promoted asymmetric aldol reactions, see: (a) Crimmins, M. T.; She, J. *Synlett* **2004**, 1371. (b) Sreenithya, A.; Sunoj, R. B. *Org. Lett.* **2012**, *14*, 5752.

(16) When the reaction was initiated with Bu_3N (2.2 equiv.) at beginning, the yield of the desired enone was decreased to 52% yield.

(17) In this case, the desired enone, the aldol product (5-hydroxy-2-methyl-5-phenylhexan-3-one), and a self-aldol product (3-hydroxy-1,3-diphenylbutan-1-one) were obtained in 59%, 15%, and 21% yields, respectively, according to the ^{1}H NMR analysis of the crude product. When TMEDA (1.0 equiv.) was used (Table 1, entry 10), no self-aldol product but the aldol product was obtained in 3% yield along with the desired enone. These results indicate that the excess amount of TMEDA suppressed the elimination and promoted the retro-aldol reaction.

(18) Pyridine and DMAP have been used as effective additives for acetylation of aluminium hemiacetals (intermediates of DIBAL-H reduction of esters), see: (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.

(19) In Table 2, entry 7, β,γ-unsaturated ketone 3,4-dimethyl-1-phenylpent-3-en-1-one was obtained in 38% yield, which indicated that DMF did not deprotonate the carbonyl α-proton. In Table 2, entry 10, ring-opened product (*E*)-7-chloro-2-phenylhept-2-en-4-one was obtained in 57% yield.

(20) The configurations of the known enone products were assigned on comparison with the literature data and those of the unknown enones were determined by analogy.

(21) Water was added to reproduce the reaction conditions after the aldol reaction followed by the elimination of water.

(22) The reaction of phenyl acetate resulted in self-Claisen condensation. Tanabe *et al.* did not employ phenyl acetate and *S*-phenyl thioacetate for their $TiCl_4$-promoted aldol reaction, see ref. 11.

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