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Direct, practical, and powerful crossed aldol additions between ketones and ketones or aldehydes utilizing environmentally benign $TiCl_4-Bu_3N$ reagent

Yoo Tanabe,* Noriaki Matsumoto, Takahiro Higashi, Tomonori Misaki, Tomotaka Itoh, Misako Yamamoto, Kumi Mitarai and Yoshinori Nishii

Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen Sanda, Hyogo 669-1337, Japan

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Abstract—An efficient $TiCl_4-Bu_3N$—(cat. TMSCl)-promoted aldol addition between ketones and ketones or aldehydes was performed. This environmentally benign method is advantageous from a green chemical viewpoint with regard to yield, substrates variation, reagent availability, and simple procedures. This method was applied to a short step formal synthesis of (*R*)-muscone, a natural macrocyclic musk. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The crossed aldol addition of carbonyl compounds (or carbonyl equivalents) is one of the most important reactions in a large variety of organic syntheses due to its broad utility.[1] A number of methods have been explored, which are generally classified into two categories: (a) carbonyl substrates are converted to their metal enolates by treatment with strong basic reagents (e.g. LDA and MHMDS) followed by the addition of carbonyl acceptors, and (b) carbonyl substrates are converted to enol silyl ethers, which react with carbonyl acceptors promoted by Lewis acids or other catalysts.

Ti-mediated aldol additions, originally called the Mukaiyama and Narasaka aldol reaction, are regarded as the pioneering and most powerful protocols conducting cross-coupling between different ketones.[2] From the recent viewpoint of environmentally benign or green chemistry, however, the indirect use of enol silyl ethers has disadvantages because the preparation is slightly tedious and atom-economy is poor. In 1989, we reported a related direct Ti-Claisen condensation between carboxylic esters.[3] Later, Evans and co-workers disclosed direct $TiCl_4-Et_3N$ (or i-Pr_2NEt)-promoted stereoselective aldol additions utilizing oxazolidines with aldehydes, which allow for to its efficient asymmetric synthesis (the Evans' protocol).[4] These findings prompted us to explore a direct, practical, and powerful Ti-mediated aldol addition of ketones and esters. We report here the direct and practical methods using environmentally benign $TiCl_4-Bu_3N-$(cat. TMSCl) reagent for cross aldol additions between various ketones and ketones (or aldehydes),[5] and its application to the formal synthesis of (*R*)-muscone, a representative macrocyclic musk ingredient.[6]

The present protocol of Ti-mediated reactions, including a related aldol-type reaction of esters[7] and Ti-(or Zr-)Claisen condensation,[8] demonstrates that the reactivity of C–C bond formation rivals or surpasses numerous aldol additions so far reported (Scheme 1). The salient features are as follows.

1. High reaction velocities and yields.
2. Higher atom-economy and lower cost than the indirect methods using enol silyl ethers and ketene silyl acetals.
3. Use of readily available and very low toxic metal reagents (e.g. $TiCl_4$, $ZrCl_4$), and use of practical amines (Et_3N, Bu_3N) and solvents (toluene or CH_2Cl_2).
4. Toleration against basic labile functionalities.
5. Enhanced reactivity using catalytic TMSCl.
6. Achievement of the related powerful Ti-(or Zr-)Claisen condensation.

2. Results and discussion

Initially, we describe a direct crossed aldol reaction between two different ketones utilizing $TiCl_4-Bu_3N$ (Table 1). The salient features of this method are as follows. (a) When Et_3N, i-Pr_2NEt, TMEDA, pyridine, and DBU were used for two reactions (entries 2 and 6), the conversion yields were

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Keywords: aldol addition; titanium chloride; tributylamine; chlorotrimethylsilane; muscone.

* Corresponding author. Tel.: +81-975-85-8394; fax: +-81-975-85-9077; e-mail: tanabe@kwansei.ac.jp

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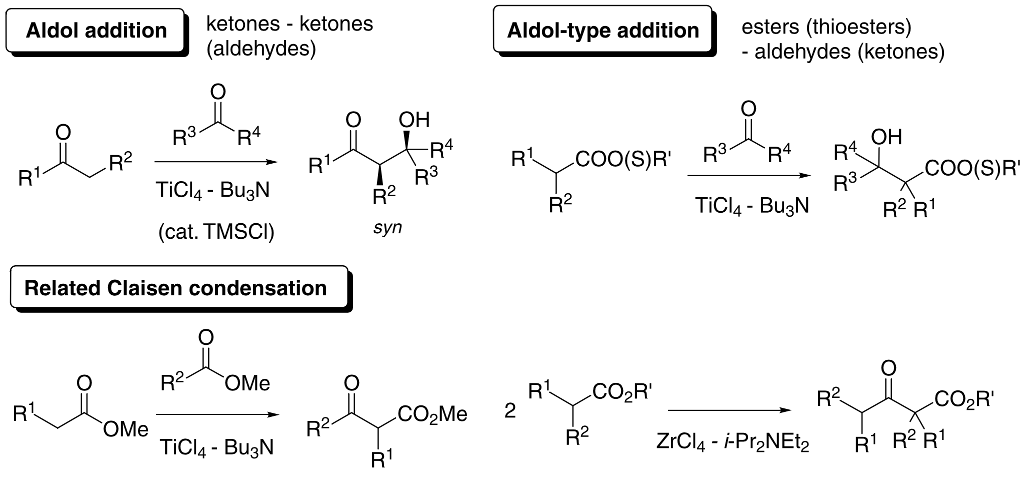
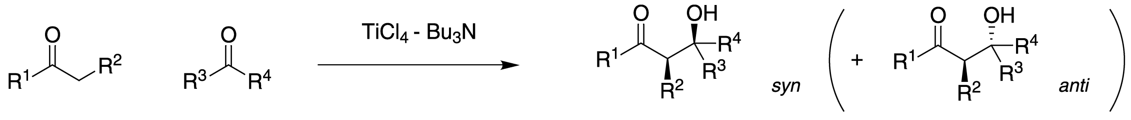
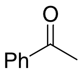
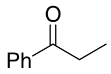
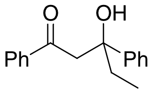
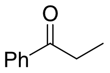
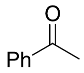
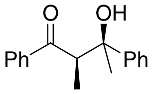
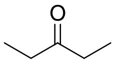
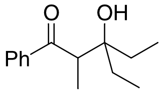
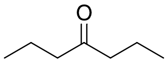
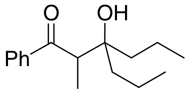
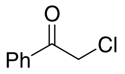
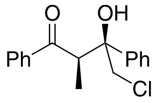
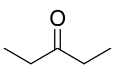
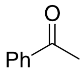
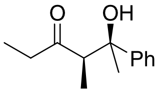
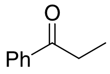
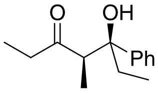
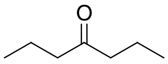
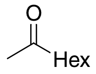
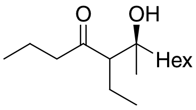
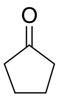
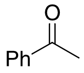
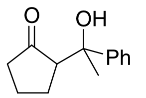


Scheme 1.

Table 1. Crossed Ti-aldol addition between two different ketones



Entry	Ketone	Ketone	Product	Yield (%)^{a,b}	*syn–anti*^{b,c}
1			 **1**	86	–
2			 **2**	95(60)	~100:0 (~0:100)
3			 **3**	86(60)	–
4			 **4**	81(60)	–
5			 **5**	91	~100:0
6			 **6**	84(45)	84:16^{d} (13:87)
7			 **7**	92	72:28^{d}
8^{e}			 **8**	60	60:40^{f}
9			 **9**	82	64:36

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[a] In CH_2Cl_2 at −78°C for 2–3 h unless otherwise noted. Molar ratio/ketone–$TiCl_4$–Bu_3N–ketone (acceptor)=1.0:1.2:1.4:1.2.

[b] Parentheses indicate the reported data using $Sn(OTf)_2$–*N*-ethylpiperidine.[9b]

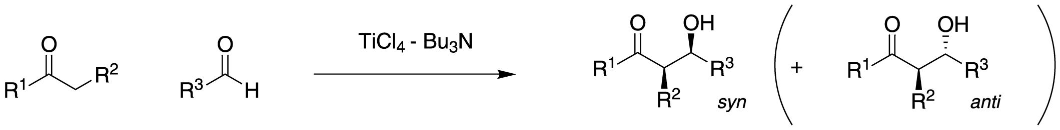
[c] Determined by ^1H NMR analyses of the crude products unless otherwise noted.

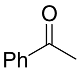
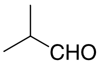
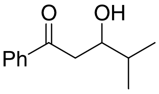
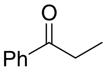
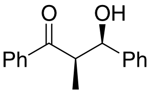
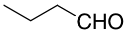
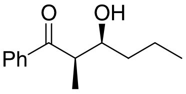
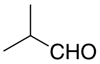
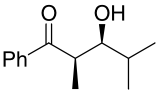
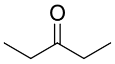
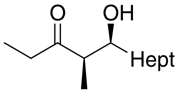
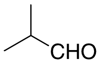
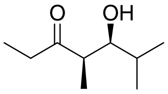
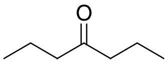
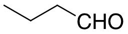
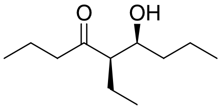
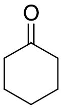
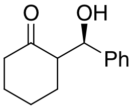
[d] Determined by isolated yields.

[e] Carried out at −78°C for 2 h and room temperature for 2 h.

[f] *syn* and *anti* not assigned.

Table 2. Crossed Ti-aldol addition between ketones and aldehydes



Entry	Ketone	Aldehyde	Product		Yield (%)[a,b]	*syn–anti*[b,c]
1				**10**	72	–
2		PhCHO		**11**	72 (71)	~100:0 (>95:5)
3				**12**	96 (74)	~100:0 (86:14)
4				**13**	95 (80)	96:4 (91:9)
5		Hept-CHO		**14**	92	92:8
6[d]				**15**	73 (73)	~100:0 (93:7)
7				**16**	83	~100:0
8		PhCHO		**17**	48 (41)	~100:0 (>95:5)

[a] In CH_2Cl_2 at −78°C for 2–3 h unless otherwise noted. Molar ratio/ketone–$TiCl_4$–Bu_3N–aldehyde (acceptor)=1.0:1.2:1.4:1.2.

[b] Parentheses indicate the reported data using $Sn(OTf)_2$–*N*-ethylpiperidine.[9b]

[c] Determined by ^1H NMR analyses.

[d] Reported data using $TiCl_4$-amine: *i*-Pr_2NEt (95%, 92:2) and Et_3N (73%, 87:13).[4c]

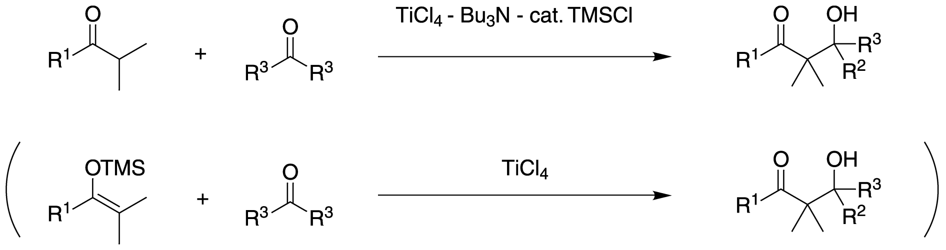
much lower (<20%) under identical conditions. (b) Among Lewis acid–amine reagents, $Sn(OTf)_2$–*N*-ethylpiperidine is the only agent known to conduct the cross-coupling between aromatic ketones, but it fails to do so between lower reactive aliphatic ketones,[9] whereas $TiCl_4$–Bu_3N promoted the desired reactions including aliphatic ketones (entries 8 and 9). (c) The yields were higher than those reported using $Sn(OTf)_2$. (d) In contrast to cases in which $Sn(OTf)_2$ was used, *syn*-selectivity was observed in each case. (e) Basic labile α-chloroacetophenone functioned as an acceptor (entry 5).

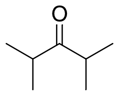
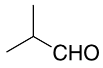
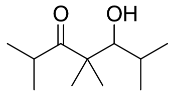
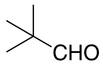
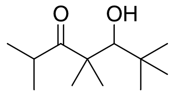
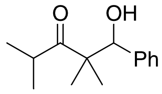
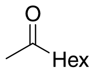
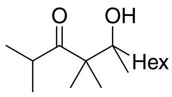
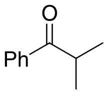
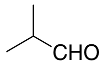
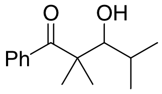
The reaction between ketones and aldehydes was then examined (Table 2). Two important features are as follows. (a) The yields were higher than those reported using $Sn(OTf)_2$.[9] (b) Consistent and higher *syn*-selectivities were observed, independent of the nature of the acceptors, due to the rigid Ti-chelated six-membered transition state.

For the reaction of sterically crowded unreactive substrates, catalytic TMSCl (0.05 equiv.) was an effective promoter. Table 3 lists the results using α,α-dimethylketones. The present method using TMSCl as a co-catalyst produced higher yields for every example examined, compared with same method without TMSCl (Method A) and with either the original Mukaiyama aldol reaction (Method B; $TiCl_4$ is added into the mixture of enol silyl ethers and aldehydes)[2a,b] or its related method (Method C; $TiCl_4$ and aldehydes are successively added into enol silyl ethers to generate $TiCl_3$-enolate)[10] using enol silyl ethers with aldehydes, both of which rank as the most powerful aldol addition systems. The role of the TMSCl co-catalyst in the present system is not clarified at present. We presume that TMSCl facilitates enolate generation and/or activates the carbonyl oxygen of acceptors. Related speculation was reported for the reaction of enol silyl ether with some electrophiles.[11]

The $TiCl_4$–Bu_3N–cat. TMSCl reagent was also applied to the preparation of important multi-functional α-chlorinated aldols (Table 4). The salient features are follows. (a) TMSCl

Table 3. Crossed Ti-aldol addition between sterically crowded ketones and aldehydes



Entry	Ketone	Aldehyde or ketone	Product	Time (h)	Yield (%)[a]	Yield (%)[a] (Method[b] A, B, C)
1[c]			 **18**	0.5	87[d]	(54, 71, 57)
2[e]			 **19**	16.5	51	(44, trace, trace)
3[c]		PhCHO	 **20**	2.0	98	(81, 46, 75)
4[e]			 **21**	2.5	45	(35, trace, trace)
5[c]			 **22**	0.5	73	(59, 58, 44)

[a] In CH_2Cl_2 at 0–5°C for 2–3 h unless otherwise noted.

[b] (A) $TiCl_4$–Bu_3N method without TMSCl. (B) The Mukaiyama Ti-aldol reaction. (C) Related method of the Mukaiyama Ti-aldol reaction.

[c] Molar ratio/ketone–$TiCl_4$–Bu_3N–aldehyde (acceptor)=1.0:1.2:1.4:1.2.

[d] In the place of Bu_3N; Et_3N (64%), *i*-Pr_2NEt (53%), and TMEDA (trace).

[e] Molar ratio/ketone–$TiCl_4$–Bu_3N–aldehyde or ketone (acceptor)=1.0:1.5:2.0:1.2.

had a significant effect on this reaction with aldehydes. (b) Use of equimolar TMSCl resulted in a somewhat reduced yield (entry 1). (c) ^{13}C NMR characterization supported the speculation that TMSCl contributed slightly to the smooth enolate formation of α-chloroacetophenone.[12] The obtained *syn*-α-chloroaldols are useful precursors for preparing the normally non-accessible and thermodynamically unfavorable *cis*-α,β-epoxyketones,[13] and are promising candidates for radical type manuplation through reductive dechlorination.[14]

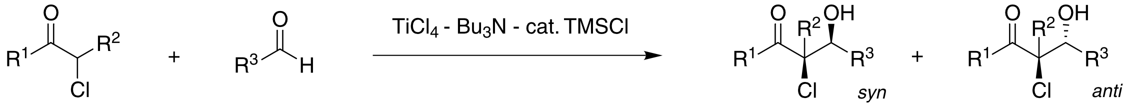
Next, we investigated the aldol addition of several α-oxygenated ketones (Table 5). Also in these cases, TMSCl significantly enhance the yields. A basic labile compound, phenacyl chloride, functioned as an acceptor while suppressing a subsequent Darzen's type reaction.[1b]

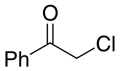
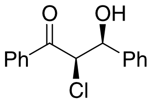
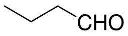
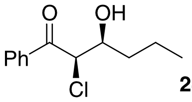
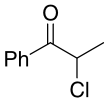
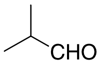
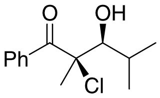
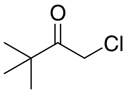
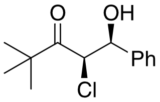
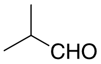
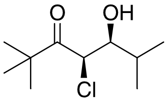
The present powerful Ti-aldol addition was successfully applied to a formal synthesis of (*R*)-muscone (**36**). Practical synthesis of natural macrocyclic musks, especially muscone and civetone, is one of the most important topics in perfume chemistry.[15] We recently reported a couple of total syntheses of civetone utilizing the related Ti-Claisen condensation.[8a,c] These works prompted us to investigate a short step synthesis of (*R*)-muscone (**36**) (Scheme 2).

The starting compound, 2,15-hexadecanedione (**33**), was easily prepared by double alkylation of 1,10-dibromodecane with 2 M amounts of methyl acetoacetate, followed by hydrolysis and decarboxylation in 46% overall yield. Radical coupling of 1,9-decadiene with 2 mol acetone is a practical alternative route to diketone **33**.[16]

The key intramolecular Ti-aldol addition of diketone **33** produced aldol adduct **34** in 52% yield under optimized conditions (Table 6, entry 3). The salient features are as follows. (a) Aldol adduct **34** was obtained for the first time, in contrast to the result when Tsuji's method was used for the aldol condensation utilizing *i*-$Bu_2Al(OPh)$–pyridine reagent to give isomeric enone mixtures of *E*-, *Z*- and β,γ-**35**:[17] the mixtures can be converted into racemic muscone but are not a substrate for the synthesis of (*R*)-muscone (**36**) (vide infra). (b) The reaction proceeded with a higher concentration (10–50 mM) compared with ring closing metathesis (ca. 4 mM), which is the key step of the recent total synthesis of **36**.[18] (c) Although the concentration was lower than the case of the related intramolecular Ti-Claisen (Dieckmann) condensation of dimethyl *Z*-octadecanedioate (100–300 mM), the slightly smaller amounts of the present reagent were used (Ti-Dieckmann reaction requires 2.8 equiv. of $TiCl_4$ and 3.0 equiv. of Bu_3N). Related 14- and 17-membered aldols (**39** and **40**) were prepared from diketones **37** and **38**, respectively (entries 6 and 7).

Table 4. Crossed Ti-aldol addition between α-chloroketones and aldehydes



Entry	Ketone	Aldehyde	*syn*-Product	Yield (%)[a,b]	*syn*–*anti*[c]
1		PhCHO	 **23**	81 (trace)[d]	89:11
2				63[d,e]	91:9
3				48[d,f]	88:12
4			 **24**	71 (47)	94:6
5			 **25**	63 (36)	92:8 (82:18)
6		PhCHO	 **26**	72 (44)	83:17 (70:30)
7			 **27**	58 (18)	80:20 (66:34)

[a] In CH_2Cl_2 at −78°C for 2–3 h. Molar ratio/α-chloroketone–$TiCl_4$–Bu_3N–aldehyde (acceptor)=1.0:1.2:1.4:1.2.

[b] Parentheses indicate the cases without TMSCl.

[c] Determined by ^1H NMR analyses of the crude products.

[d] Yields based on its TMS ethers.

[e] Use of 1.0 equiv. of TMSCl.

[f] Use of 0.05 equiv. of TMSOTf.

Stereoselective dehydration conditions of aldol **34** were screened (Table 7). Standard acid-catalyzed dehydrations using PTS, H_2SO_4, CF_3CO_2H, SO_2Cl_2–Et_3N, and $MeSO_2$-Cl–Et_3N–$Me_3N\cdot HCl$[19] afforded **35** in 57–97% with moderate and consistent stereoselectivity (*E*–*Z*=ca. 3:7) and produced considerable amounts of undesirable isomer β,γ-**35** (entries 1–5). Use of the Al(O*i*-Bu)$_3$ caused the retro-aldol reaction (entry 6). In clear contrast, dehydrations using Ti(O*i*-Pr)$_4$ and Ti(O*i*-Bu)$_4$ suppressed the formation of β,γ-**35** and exhibited high yields and *E*-selectivity (entries 7 and 8). Catalytic amounts (0.1 equiv) of NaSPh rapidly isomerized the *E*-rich enone 35 (*E*–*Z*=89:11) into *Z*-rich enone **35** (*E*–*Z*=27:73). These equilibrium ratios indicate that the thermodynamic stability of *E*-**35** and *Z*-**35** are ca. 3:7, respectively. Accordingly, the present Ti(OR)$_4$-mediated dehydration proceeded in a kinetically controlled manner.

Takasago group documented that the (*S*)- and (*R*)-Ru-BINAP asymmetric hydrogenation of both enones *E*-**35** and *Z*-**35**, respectively, afford *R*-muscone (**36**) with ca. 99% high enantioselectivity.[20] Consequently, jointed with this asymmetric hydrogenation, a formal chiral synthesis of **36** (estimated, 80% ee) was preformed.

Finally, we developed the present protocol for the aldol-type addition using simple phenyl esters[7] and its application to a short step synthesis of the lactone analog of dihydrojasmone.[21] As a notable recent application of the present reagent ($TiCl_4$–Bu_3N), the Merck process group demonstrated a multi-kilogram scale practical synthesis of the *anti*-MRSA carbapenem intermediate utilizing the $TiCl_4$–Bu_3N reagent as its key step (Scheme 3).[22]

In conclusion, we achieved an efficient, practical, and environmentally benign alternative to the $TiCl_4$-mediated Mukaiyama aldol reaction. Further application to the practical syntheses of perfumes and β-lactum antibiotics are under investigation in our laboratory.

3. Experimental

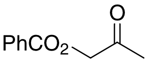
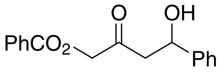
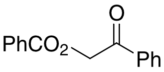
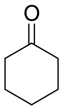
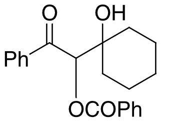
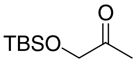
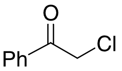
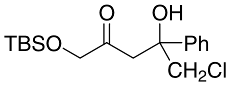
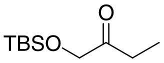
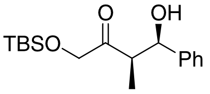
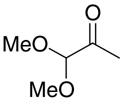
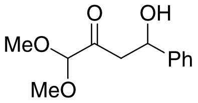
3.1. General

Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. ^1H NMR and ^{13}C NMR Spectra were recorded on either JEOL α, Varian 300 or JEOL EX-90 spectrometer using TMS as internal standard. IR Spectra were recorded on a JASCO FT/IR-8000 spectrophotometer.

3.2. Typical procedure of the crossed aldol addition between different ketones (Table 1, entry 2)

$TiCl_4$ (1 M CH_2Cl_2; 1.2 ml) and Bu_3N (185 mg, 1.4 mmol)

Table 5. Crossed Ti-aldol addition between α-oxygenated ketones and aldehydes

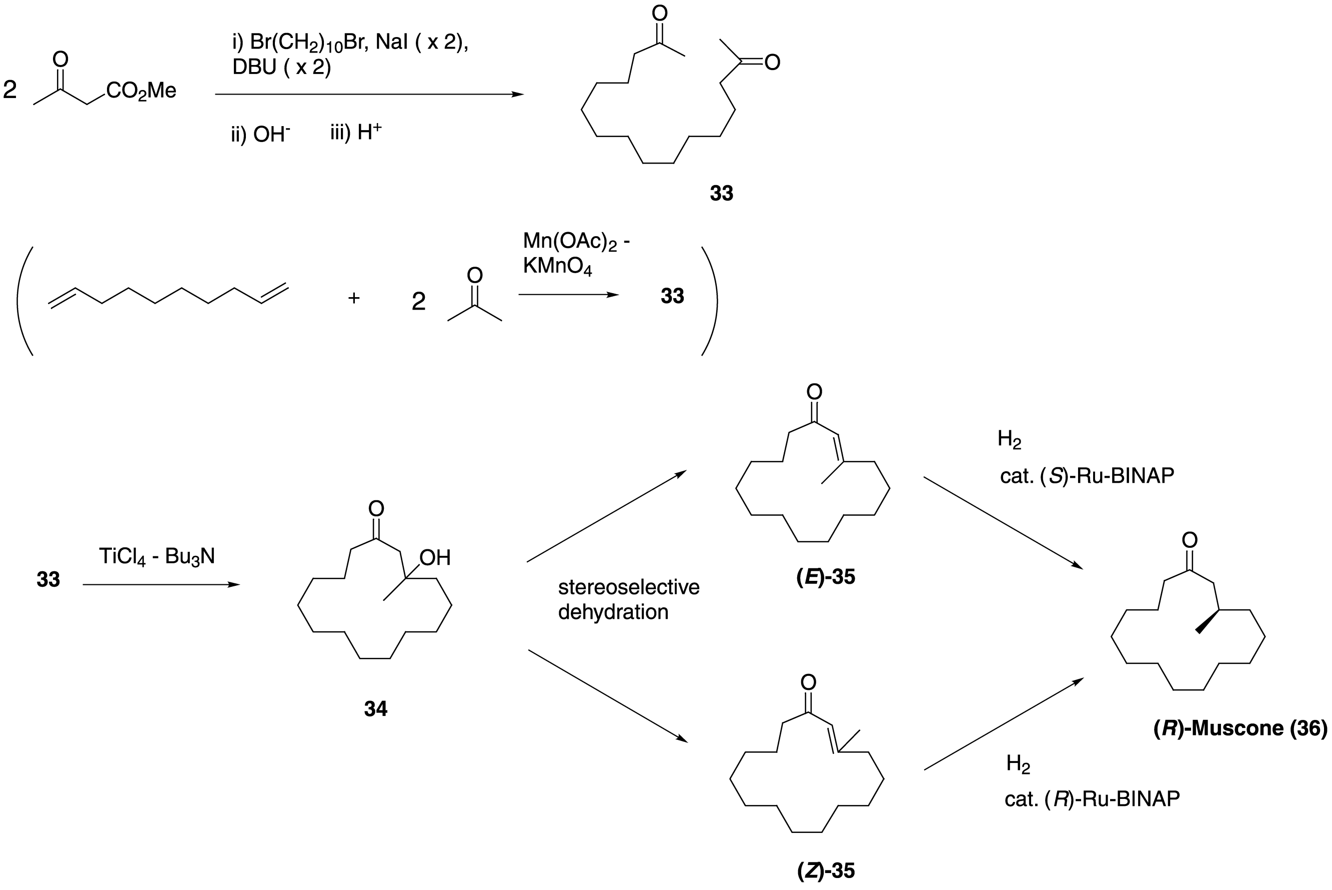
Entry	Ketone	Aldehyde or ketone	Product	Yield (%)[a,b]
1		PhCHO	 **28**	86 (68)
2			 **29**	78 (45)
3			 **30**	78 (23)
4		PhCHO	 **31**	89[c] (66)
5		PhCHO	 **32**	80 (58) 67[d]

[a] In CH_2Cl_2 at −78°C for 2–3 h. Molar ratio/α-oxygenated ketone–$TiCl_4$–Bu_3N–ketone or aldehyde (acceptor)=1.0:1.2:1.4:1.2.

[b] Parentheses indicate the cases without TMSCl.

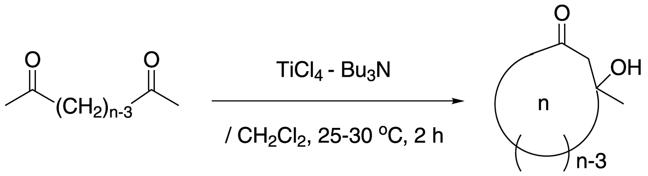
[c] *syn*–*anti*=92:8.

[d] Et_3N was used in the place of Bu_3N.



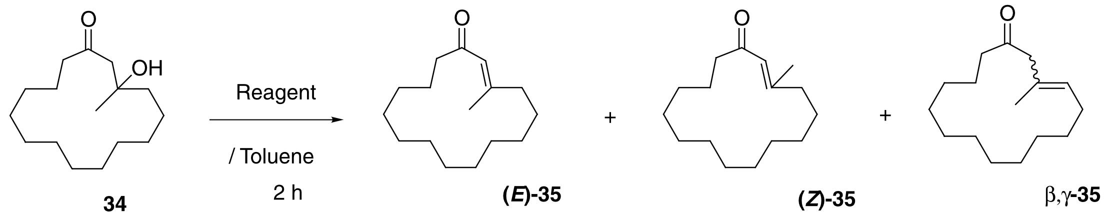
Scheme 2.

Table 6. Intramolecular Ti-aldol addition of dimethyl ketones



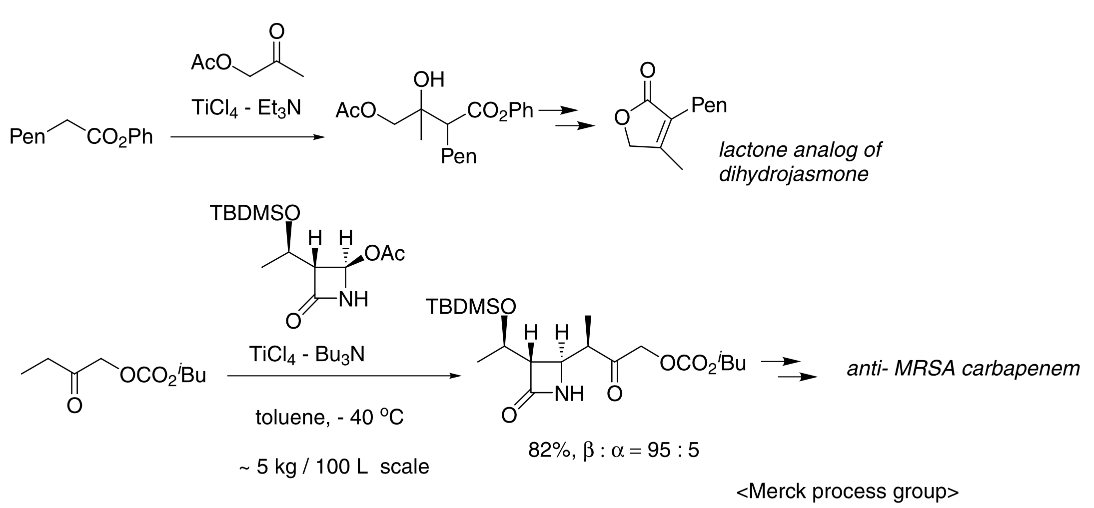
Entry	Diketone	Equiv.		Concentration (mM)	Product	Yield (%)
		$TiCl_4$	Bu_3N			
1	**33** (n=15)	1.5	3.0	10	**34** (n=15)	40
2		2.0	3.5	10		49
3		2.0	4.0	10		52
4		3.0	4.0	10		38
5		2.0	4.0	50		40
6	**37** (n=14)	2.0	4.0	10	**39** (n=14)	44
7	**38** (n=17)	2.0	4.0	10	**40** (n=17)	51

Table 7. Stereoselective dehydration of cyclic aldol **34**



Entry	Reagent	Equiv.	Temperature (°C)	Total yield (%)	Product ratio[a], (E)-(**35**)–(**Z**)-**35**–β,γ-**35**
1	PTS·H_2O	0.4	50	87	22:60:18
2	Conc. H_2SO_4	0.4	20–25	76	29:64:7
3	CF_3CO_2H	Excess	20–25	83	23:65:12
4	$SOCl_2$–Et_3N	10.0–10.0	20–25	57	18:43:39
5	MsCl–Et_3N–Me_3N·HCl	2.0–2.0–0.5	−40	97	25:57:18
6	Al(Oi-Bu)$_3$	2.0	20–25	Trace (retro aldol reaction)	
7	Ti(Oi-Pr)$_4$	2.0	20–25	85	89:11:0
8	Ti(Oi-Bu)$_4$	2.0	20–25	88	91:9:0

[a] Determined by ^{1}H NMR analyses of the crude products.



Scheme 3.

were successively added to a stirred solution of propiophenone (134 mg, 1.0 mmol) in CH_2Cl_2 (2.0 ml) at −78°C under an Ar atmosphere. After 30 min, acetophenone (144 mg, 1.2 mmol) was added to the mixture, which was stirred at −78°C for 2 h. The reaction mixture was quenched with water and was extracted twice with ether. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane–AcOEt=9:1) to give 3-hydroxy-2-methyl-1,3-diphenyl-1-butanone (**2**; 241 mg, 95%).

3.2.1. 3-Hydroxy-1,3-diphenyl-1-pentanone (1). Pale yellow crystals; mp 48.5–49.0°C. IR (KBr): 3478, 2969, 2919, 2363, 2342, 1637, 1402, 1387, 1217, 983 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.80 (3H, t, J=7.2 Hz), 1.82–1.97 (2H, m), 3.29 (1H, d, J=17.6 Hz), 3.83 (1H, d, J=17.6 Hz), 7.16–7.58 (8H, m), 7.87–7.90 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.75, 36.05, 47.32, 76.01, 124.96, 126.46, 128.01, 128.07, 128.63, 133.63, 137.00, 145.82, 201.69.

3.2.2. 3-Hydroxy-2-methyl-1,3-diphenyl-1-butanone (2). *syn*-Isomer; colorless oil. IR (neat): 3424, 1657, 1595, 1451, 1393, 1221, 970 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.01 (3H, d, J=7.2 Hz), 1.56 (3H, s), 3.86 (1H, q,

J=7.2 Hz), 4.73–4.85 (1H, br, –OH), 7.25–7.66 (8H, m), 8.02–8.04 (2H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=13.73, 29.92, 48.58, 75.26, 124.78, 126.48, 128.03, 128.27, 128.81, 133.78, 136.55, 145.88, 207.75.

3.2.3. 3-Ethyl-3-hydroxy-2-methyl-1-phenyl-1-pentanone (3). Colorless oil. IR (neat): 3483, 2959, 2936, 2361, 2342, 1665, 1456, 1212, 974 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.83 (3H, t, J=7.2 Hz), 0.89 (3H, t, J=7.2 Hz), 1.25 (3H, d, J=7.2 Hz), 1.44–1.57 (3H, m), 1.64–1.71 (1H, m), 3.62 (1H, q, J=7.2 Hz), 7.48–7.52 (2H, m), 7.60–7.63 (1H, m), 7.48–7.98 (2H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=7.71, 8.00, 12.57, 26.54, 29.86, 43.58, 76.00, 128.27, 128.82, 133.64, 136.82, 208.17.

3.2.4. 3-Hydroxy-2-methyl-1-phenyl-3-propyl-1-hexanone (4). Yellow oil. IR (neat): 3490, 2963, 2874, 1665, 1451, 1346, 1215, 974, 710 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.78 (3H, t, J=7.2 Hz), 0.97 (3H, t, J=7.2 Hz), 1.21–1.63 (8H, m), 1.25 (3H, d, J=7.2 Hz), 3.58 (1H, q, J=7.2 Hz), 7.48–7.63 (3H, m), 7.94–7.96 (2H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=12.63, 14.56, 14.69, 16.67, 17.07, 37.29, 40.59, 44.36, 75.58, 128.25, 128.81, 133.60, 136.80, 208.11.

3.2.5. 4-Chloro-3-hydroxy-2-methyl-1,3-diphenyl-1-butanone (5). *syn*-Isomer; yellow oil. IR (neat) 3447, 3063, 2978, 1659, 1451, 1221, 760, 702 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$): δ=1.09 (3H, d, J=7.2 Hz), 3.73 (1H, d, J=11.1 Hz), 3.88 (1H, d, J=11.1 Hz), 4.24 (1H, q, J=7.2 Hz), 7.28–7.67 (8H, m), 8.02–9.06 (2H, m). ^{13}C NMR (75 MHz; CDCl$_3$): δ=14.01, 44.40, 52.25, 77.70, 125.42, 127.45, 128.18, 128.52, 128.90, 134.12, 135.91, 141.69, 207.09.

3.2.6. 5-Hydroxy-4-methyl-5-phenyl-3-hexanone (6). *syn*-Isomer; colorless crystals; mp 45.5–46.0°C. IR (neat): 3449, 2982, 2938, 1690, 1449, 1393, 1373, 976, 700 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.88 (3H, t, J=7.2 Hz), 1.09 (3H, d, J=7.2 Hz), 1.52 (3H, s), 2.48–2.67 (2H, m), 2.99 (1H, q, J=7.2 Hz), 7.22–7.43 (5H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=7.40, 12.69, 29.60, 37.45, 53.83, 74.89, 124.68, 126.53, 128.06, 145.65, 219.21. *anti*-Isomer; colorless oil. IR (neat): 3446, 2980, 2940, 1696, 1449, 1379, 1364, 763 cm^{-1}. ^{1}H NMR (400 MHz CDCl$_3$): δ=0.75 (3H, t, J=7.2 Hz), 1.27 (3H, d, J=7.2 Hz), 1.45 (3H, s), 1.89–1.95 (1H, m), 2.32–2.39 (1H, m), 3.15 (1H, q, J=7.2 Hz), 7.18–7.39 (5H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=6.98, 12.02, 27.00, 37.31, 53.29, 75.03, 124.53, 126.59, 128.15, 148.00, 218.76.

3.2.7. 5-Hydroxy-4-methyl-5-phenyl-3-heptanone (7). *syn*-Isomer; colorless oil. IR (neat): 3464, 2976, 2940, 2361, 2342, 1698, 1458, 1377, 1316, 968 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.64 (3H, t, J=7.2 Hz), 0.85 (3H, d, J=7.6 Hz), 1.10 (3H, t, J=7.2 Hz), 1.72–1.83 (2H, m), 2.52–2.69 (2H, m), 3.00 (1H, q, J=7.2 Hz), 7.21–7.53 (5H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=7.37, 7.82, 12.71, 34.19, 37.72, 53.59, 78.09, 125.39, 126.30, 127.94, 128.35, 128.89, 143.07, 219.82. *anti*-Isomer; colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.63 (3H, t, J=7.2 Hz), 0.73 (3H, t, J=7.2 Hz), 1.27 (3H, d, J=7.2 Hz), 1.59–1.68 (1H, m), 1.85–1.98 (2H, m), 2.31–2.41 (1H, m), 3.18 (1H, q, J=7.2 Hz), 7.17–7.35 (5H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=6.95, 7.24, 11.65, 31.54, 37.28, 52.86, 76.66, 125.38, 126.42, 127.99, 145.61, 218.88.

3.2.8. 5-Ethyl-6-hydroxy-6-methyl-4-dodecanone (8). *syn*- and *anti*-Mixture; pale yellow oil. IR (neat): 3505, 2961, 2934, 2874, 2361, 1701, 1458, 1375, 1142, 1040, 918 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.86–0.95 (9H, m), 1.13 (3H, s), 1.19–1.63 (14H, m), 2.40–2.60 (3H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=12.69, 12.89, 13.67, 14.06, 16.16, 16.21, 20.63, 21.11, 22.59, 23.64, 23.83, 26.37, 26.75, 29.80, 31.80, 39.45, 42.36, 44.69, 49.32, 49.48, 59.62, 60.06, 73.55, 74.24.

3.2.9. 2-(1-Hydroxy-1-phenylethyl)cyclopentanone (9). *syn*- and *anti*-Mixture; pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ=1.57–2.00 (5H, m), 1.58 (1.1H, s), 1.73 (1.9H, s), 2.20 (1H, m), 2.48 (1H, m), 7.20–7.49 (5H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=19.97, 23.48, 28. 92, 39.73, 58.28, 75.35, 125.12, 126.67, 128.06, 145.47, 221.72.

3.2.10. 3-Hydroxy-4-methyl-1-phenyl-1-pentanone (10). Yellow oil. IR (neat): 3547, 2955, 2892, 1667, 1480, 1449, 1169, 1007, 752 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ=1.00 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.8 Hz), 1.77–1.84 (1H, m), 2.54–2.77 (1H, br, –OH), 3.05 (1H, d, J=17.6 Hz), 3.18 (1H, d, J=17.6 Hz), 3.98–4.02 (1H, m), 7.46–7.61 (3H, m), 7.96–7.98 (2H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=17.88, 18.52, 33.08, 41.91, 72.35, 128.05, 128.46, 128.64, 133.46, 136.87, 201.35.

3.2.11. 3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (11). *syn*-Isomer; pale yellow crystals; mp 72.5–73.0°C. IR (KBr): 3526, 1672, 1597, 1580, 1449, 1325, 1221, 974 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ=1.21 (3H, d, J=7.6 Hz), 1.39–1.71 (1H, br, –OH), 3.67–3.73 (1H, m), 5.25 (1H, d, J=3.2 Hz), 7.24–7.61 (8H, m), 7.93–7.97 (2H, m). ^{13}C NMR (100 MHz, CDCl$_3$): δ=11.13, 46.99, 73.03, 126.00, 127.29, 128.23, 128.45, 128.64, 128.77, 133.58, 135.58, 141.75, 205.78.

3.2.12. 3-Hydroxy-2-methyl-1-phenyl-1-hexanone (12). *syn*-Isomer; yellow oil. IR (neat): 3447, 2961, 2936, 2361, 2342, 1672, 1456, 1213, 972 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$): δ=0.95 (3H, d, J=7.2 Hz), 1.26 (3H, d, J=7.2 Hz), 1.33–1.67 (4H, m), 3.47 (1H, dq, J=3.0, 7.2 Hz), 4.05 (*syn*; 1H, ddd, J=3.0, 4.2, 8.4 Hz), 7.46–7.52 (2H, m), 7.57–7.63 (1H, m), 7.94–7.98 (2H, m). ^{13}C NMR (75 MHz; CDCl$_3$): 11.03, 14.02, 19.24, 36.42, 44.47, 71.00, 128.41, 128.73, 133.40, 135.83, 205.93.

3.2.13. 3-Hydroxy-2,4-dimethyl-1-phenyl-1-pentanone (13). *syn*-Isomer; colorless oil. IR (neat): 3503, 2963, 1678, 1451, 1215, 972, 710 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$): δ=0.96 (3H, d, J=6.9 Hz), 1.04 (3H, d, J=6.6 Hz), 1.25 (3H, d, J=6.9 Hz), 1.78 (1H, dqq, J=8.1, 6.6, 6.9 Hz), 3.64 (*syn*; 1H, dd, J=2.7, 8.1 Hz), 3.68 (1H, dd, J=2.7, 6.9 Hz), 7.46–7.52 (2H, m), 7.57–7.63 (1H, m), 7.93–7.99 (2H, m). ^{13}C NMR (75 MHz; CDCl$_3$): 10.72, 19.07, 19.13, 30.69, 41.76, 76.60, 128.40, 128.76, 133.40, 135.84, 205.89.

3.2.14. 5-Hydroxy-4-methyl-3-dodecanone (14). *syn*-Isomer; colorless oil. IR (neat): 3455, 2930, 2857, 1703, 1460, 1377, 974 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$): δ=0.88 (3H, t, J=6.9 Hz), 1.06 (3H, t, J=7.2 Hz), 1.13 (3H, d, J=7.2 Hz), 1.24–1.36 (10H, m), 1.41–1.55 (2H, m), 2.50 (1H, dq, J=29.1, 7.2 Hz), 2.56 (1H, dq, J=29.1, 7.2 Hz), 2.58 (1H, dq, J=3.0, 7.2 Hz), 3.90 (1H, ddd, J=3.0, 4.5, 8.4 Hz). ^{13}C NMR (75 MHz; CDCl$_3$): δ=7.60, 9.95, 14.05, 22.61, 26.02, 29.22, 29.53, 31.78, 34.01, 35.08, 49.70, 71.13, 216.69.

3.2.15. 5-Hydroxy-4,6-dimethyl-3-heptanone (15). *syn*-Isomer; colorless oil. ^{1}H NMR (300 MHz; CDCl$_3$): δ=0.86 (3H, d, J=6.6 Hz), 1.02 (3H, d, J=6.6 Hz), 1.06 (3H, t, J=7.2 Hz), 1.12 (3H, d, J=7.2 Hz), 1.66 (1H, dqq, J=8.5, 6.6, 6.6 Hz), 2.43–2.66 (2H, m), 2.75 (1H, dq, J=3.0, 7.2 Hz), 3.52 (*syn*; 1H, dd, J=3.0, 8.5 Hz). ^{13}C NMR (75 MHz; CDCl$_3$): 7.64, 9.47, 18.94, 19.06, 30.52, 34.84, 47.06, 76.25, 216.92.

3.2.16. 5-Ethyl-6-hydroxy-4-nonanone (16). *syn*-Isomer; colorless oil. IR (neat) 3450, 2936, 2876, 1701, 1462, 1379, 1145, 1117, 1009 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$) δ=0.90 (3H, t, J=7.5 Hz), 0.93 (6H, t, J=7.5 Hz), 1.24–1.40 (2H, m), 1.42–1.54 (2H, m), 1.57–1.82 (4H, m), 2.42 (1H, ddd, J=7.2, 7.2, 17.7 Hz), 2.51 (1H, ddd, J=4.2, 4.2, 9.3 Hz), 2.52 (1H, ddd, J=7.2, 7.2, 17.7 Hz), 3.78 (1H, ddd, J=4.2, 4.2, 8.4 Hz). ^{13}H NMR (75 MHz; CDCl$_3$) δ=12.43, 13.70, 13.96, 16.63, 19.27, 19.58, 36.68, 46.57, 57.99, 71.22, 215.81.

3.2.17. 2-(1-Hydroxy-1-phenylethyl)cyclohexanone (17).[9b] Typical procedure of the crossed aldol addition of α,α-dimethylketones with aldehydes and 2-octanone promoted by TiCl$_4$–Bu$_3$N–cat. TMSCl (Table 3, entry 1): TiCl$_4$ (1 M CH$_2$Cl$_2$; 1.2 ml), TMSCl (6 μl, 0.05 mmol), and Bu$_3$N (185 mg, 1.4 mmol) were successively added to a stirred solution of diisopropyl ketone (114 mg, 1.0 mmol) in CH$_2$Cl$_2$ (2.0 ml) at 0–5°C under an Ar atmosphere. After 30 min, 2-methylpropanal (87 mg, 1.2 mmol) was added to the mixture, which was stirred at −78°C for 30 min. The reaction mixture was quenched with water and was extracted twice with ether. The organic phase was washed with water, brine, dried (Na$_2$SO$_4$) and concentrated. The obtained crude oil was purified by SiO$_2$-column chromatography (hexane–AcOEt=6:1) to give 5-hydroxy-2,4,4,6-tetramethyl-3-heptanone (**18**; 241 mg, 87%). colorless oil. IR (neat): 3526, 3506, 2971, 2361, 2340, 1698, 1472, 1385, 1015, 995 cm^{-1}. ^{1}H NMR (400 MHz; CDCl$_3$): δ=0.84 (3H, d, J=6.4 Hz), 0.99 (3H, d, J=6.4 Hz), 1.06 (3H, d, J=5.6 Hz), 1.08 (3H, d, J=5.6 Hz), 1.23 (6H, s), 1.79–1.87 (1H, m), 2.95–3.06 (1H, brs, −O*H*), 3.07–3.17 (1H, m), 3.49 (1H, d, J=3.2 Hz). ^{13}C NMR (100 MHz; CDCl$_3$): δ=17.18, 19.89, 20.19, 20.56, 22.55, 23.46, 29.67, 35.53, 51.63, 81.59, 222.74.

3.2.18. 5-Hydroxy-2,4,4,6,6-pentamethyl-3-octanone (19). Orange crystals; mp 36.5–37.5°C. ^{1}H NMR (400 MHz; CDCl$_3$): δ=0.97 (9H, s), 1.06 (3H, d, J=5.8 Hz), 1.08 (3H, d, J=5.8 Hz), 1.28 (3H, s), 1.30 (3H, s), 2.72–2.88 (1H, brs, −O*H*), 3.10–3.20 (1H, m), 3.58 (1H, s). ^{13}C NMR (100 MHz; CDCl$_3$): δ=20.25, 20.35, 22.96, 24.00, 28.55, 35.48, 36.92, 52.89, 83.50, 221.67.

3.2.19. 5-Hydroxy-2,4,4-trimethyl-5-phenyl-3-pentanone (20). Pale yellow crystals; mp 76.0–77.0°C. IR (KBr-disk): 3491, 2975, 2361, 2342, 1690, 1427, 1389, 1188, 1045, 1018 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$): δ=1.04 (3H, s), 1.06 (3H, d, J=6.9 Hz), 1.08 (3H, d, J=6.9 Hz), 1.15 (3H, s), 2.93–3.27 (1H, brs, −O*H*), 3.06–3.20 (1H, m), 4.95 (1H, s), 7.22–7.36 (5H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=17.40, 19.75, 19.84, 22.50, 34.96, 52.51, 78.05, 127.42, 127.56, 127.81, 140.08, 221.85.

3.2.20. 5-Hydroxy-2,4,4,5-tetramethyl-3-undecanone (21). Colorless oil. IR (neat) 3484, 2959, 2932, 1686, 1470, 1379, 1231 cm^{-1}. ^{1}H NMR (400 MHz; CDCl$_3$): δ=0.88 (3H, t, J=6.8 Hz), 1.05 (3H, d, J=2.8 Hz), 1.07 (3H, d, J=2.4 Hz), 1.09 (3H, s), 1.24 (3H, s), 1.25 (3H, s), 1.27–1.41 (10H, m), 3.13–3.20 (1H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=14.02, 19.48, 19.77, 20.62, 20.99, 21.40, 22.59, 23.31, 30.03, 31.89, 35.89, 37.21, 54.37, 76.11, 224.97.

3.2.21. 3-Hydroxy-2,2,4-trimethyl-1-phenyl-1-pentanone (22). Pale yellow oil. IR (neat): 3490, 2965, 1669, 1470, 1260, 963 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$): δ=0.92 (3H, d, J=7.0 Hz), 0.97 (3H, d, J=7.0 Hz), 1.34 (3H, s), 1.41 (3H, s), 1.82–1.97 (1H, m), 2.46–2.74 (1H, brs, −O*H*), 3.71 (1H, d, J=4.0 Hz), 7.37–7.49 (3H, m), 7.60–7.65 (2H, m). ^{13}C NMR (75 MHz; CDCl$_3$): δ=17.72, 22.34, 23.12, 24.16, 30.13, 51.59, 82.16, 127.59, 128.05, 130.81, 139.49, 211.89.

3.2.22. 2-Chloro-3-trimetylsiloxy-1,3-diphenyl-1-propanone (TMS-ether of 23). Because α-chloroaldol (**23**) adduct was relatively unstable, the yield was based on its TMS-ether, which was obtained by nearly neutral trimethylsilylation using TMS-imidazole/catalytic TBAF.[23] TiCl$_4$ (1 M CH$_2$Cl$_2$; 1.2 ml) was added to a stirred solution of phenacyl chloride (**1a**; 155 mg, 1.0 mmol) in CH$_2$Cl$_2$ (2.0 ml) at −78°C under an Ar atmosphere. TMSCl (6 μl, 0.05 mmol) and Bu$_3$N (259 mg, 1.4 mmol) were successively added to the mixture, which was stirred for 30 min. Then, benzaldehyde (127 mg, 1.2 mmol) was added to the mixture followed by being stirred at −78°C for 2 h. The mixture was quenched with water (10 ml), extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na$_2$SO$_4$) and concentrated. To the obtained crude oil (282 mg) in DMF (2.0 ml) was added *N*-TMS-imidazole (281 mg, 2.0 mmol) and TBAF (1 M THF; 0.02 ml). The mixture was allowed to stand for 10 min at room temperature, then, was quenched with water (10 ml). The combined organic phase was extracted twice with ether, washed with water, brine, dried (Na$_2$SO$_4$) and concentrated. The obtained crude oil was purified by SiO$_2$-column chromatography (hexane–AcOEt=14:1) to give 2-chloro-1,3-diphenyl-3-trimethylsiloxy-1-propanone (268 mg, 81%).

syn-Isomer; pale yellow oil. IR (neat): 2361, 2341, 1690, 1252, 1100, 889, 843 cm^{-1}. ^{1}H NMR (400 MHz; CDCl$_3$): δ=0.21 (9H, s), 5.22 (1H, d, J=8.0 Hz), 5.26 (1H, d, J=8.0 Hz), 7.22–7.99 (10H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=0.04, 62.32, 75.54, 127.39, 128.25, 128.28, 128.54, 128.60, 133.56, 135.16, 140.09, 193.56. *anti*-Isomer; pale yellow oil. ^{1}H NMR (400 MHz; CDCl$_3$): δ=−0.15 (9H, s), 5.08 (1H, d, J=9.2 Hz), 5.16 (1H, d, J=9.2 Hz), 7.22–7.99 (10H, m).

3.2.23. 2-Chloro-3-hydroxy-1-phenyl-1-hexanone (24). *syn*-Isomer; pale yellow oil. IR (neat): 3507, 2961, 2934, 2363, 1686, 1597, 1451, 1302, 1213, 1078, 910 cm^{-1}. ^{1}H NMR (90 MHz; CDCl$_3$): δ=0.78–1.14 (3H, t, *J*=7.0 Hz), 1.36–1.88 (4H, m), 2.59–2.98 (1H, br, –O*H*), 4.11–4.38 (1H, m), 5.08 (1H, d, *J*=4.3 Hz), 7.38–7.77 (3H, m), 7.91–8.18 (2H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=13.90, 18.86, 35.75, 60.70, 70.73, 128.93, 129.06, 134.26, 135.13, 194.68.

3.2.24. 2-Chloro-2,4-dimethyl-3-hydroxy-1-phenyl-1-pentanone (25). Colorless oil. IR (neat) 3486, 2965, 1678, 1447, 1254, 1020, 976 cm^{-1}. ^{1} H NMR (400 MHz; CDCl$_3$): δ=1.00 (3H, d, *J*=6.8 Hz), 1.02 (3H, d, *J*=7.2 Hz), 1.89 (3H, s), 2.02–2.10 (1H, m) 4.08 (1H, d, *J*=5.2 Hz), 7.38–7.48 (2H, m), 7.48–7.52 (1H, m), 7.98–8.01 (2H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=18.19, 22.22, 24.26, 30.48, 75.01, 79.60, 127.92, 129.40, 132.11, 135.73, 199.13.

3.2.25. 4-Chloro-5-hydroxy-1,1-dimethyl-5-phenyl-3-pentanone (26). Colorless crystals; mp 52.8–54.4°C. IR (KBr): 3320, 2975, 2934, 2361, 1711, 1476, 1456, 1370, 1323, 1211, 1067, 986 cm^{-1}. ^{1}H NMR (400 MHz; CDCl$_3$): δ=0.88 (9H, s), 4.68 (1H, d, *J*=7.6 Hz), 5.10 (1H, d, *J*=5.2 Hz), 7.29–7.42 (5H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=25.48, 55.00, 59.47, 74.14, 127.38, 128.43, 134.84, 138.12, 208.90.

3.2.26. 4-Chloro-2,2,6-trimethyl-5-hydroy-3-heptanone (27). Colorless oil. IR (neat): 3505, 2969, 2936, 2361, 1703, 1476, 1370, 1084, 1007 cm^{-1}. ^{1}H NMR (400 MHz; CDCl$_3$): δ=0.96 (3H, d, *J*=6.4 Hz), 1.03 (3H, d, *J*=6.4 Hz), 1.25 (9H, s), 1.80–1.88 (1H, m), 3.36–3.42 (1H, br, –O*H*), 3.54–3.60 (1H, m), 4.75 (1H, d, *J*=3.9 Hz). ^{13}C NMR (100 MHz; CDCl$_3$): δ=17.89, 19.21, 26.52, 30.59, 55.39, 75.90, 211.26.

3.2.27. 4-Hydroxy-2-oxo-4-phenybutyl benzoate (28). Colorless crystals; mp 115–118°C. IR (KBr): 3482, 3061, 2924, 2897, 1718, 1277, 752, 696 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$): δ=2.84 (1H, dd, *J*=3.3, 16.8 Hz), 2.99 (1H, dd, *J*=9.3, 16.8 Hz), 4.92 (2H, s), 5.24 (1H, ddd, *J*=3.3, 3.3, 9.3 Hz), 7.26–7.40 (5H, m), 7.44–7.50 (2H, m), 7.52–7.63 (1H, m), 8.07–8.11 (2H, m). ^{13}C NMR (75 MHz; CDCl$_3$): δ=47.93, 68.88, 69.89, 125.59, 127.91, 128.52, 128.66, 129.01, 129.92, 133.54, 142.54, 165.91, 203.84.

3.2.28. 1-(1-Hydroxycyclohexyl)-2-oxo-2-phenylethyl benzoate (29). Colorless crystals; mp 130–132°C. IR (KBr): 3459, 2930, 2853, 1703, 1684, 1285, 716, 687 cm^{-1}. ^{1}H NMR (300 MHz; CDCl$_3$): δ=1.18–1.28 (1H, m), 1.50–1.67 (8H, m), 1.85–1.90 (1H, m), 6.03 (1H, s), 7.43–7.52 (4H, m), 7.56–7.62 (2H, m), 8.07–8.12 (4H, m). ^{13}C NMR (75 MHz; CDCl$_3$): δ=21.16, 21.25, 25.42, 34.26, 34.68, 72.86, 78.40, 128.47, 128.72, 128.81, 129.13, 129.89, 133.45, 133.60, 137.20, 166.09, 197.72.

3.2.29. 1-(*t*-Butyldimethylsiloxy)-5-chloro-4-hydroxy-4-phenyl-2-pentanone (30). Yellow oil. IR (neat) 3482, 2955, 2932, 1717, 1256, 1109, 839 cm^{-1}. ^{1} H NMR (400 MHz; CDCl$_3$): δ=0.04 (3H, s), 0.05 (3H, s), 0.90 (9H, s), 3.19 (1H, d, *J*=16.8 Hz), 3.38 (1H, d, *J*=16.8 Hz), 3.68 (1H, d, *J*=20.2 Hz), 3.72 (1H, d, *J*=20.2 Hz), 4.07 (2H, s), 7.28–7.30 (1H, m), 7.33–7.37 (2H, m), 7.44–7.46 (2H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=−5.65, −5.59, 18.34, 25.86, 44.63, 53.56, 70.34, 75.69, 125.84, 128.55, 129.18, 143.48, 242.71.

3.2.30. 1-*t*-(Butyldimethylsiloxy)-4-hydroxy-3-methyl-4-phenyl-2-butanone (31). *syn*-Isomer; colorless crystals; mp 31.0–31.5°C. IR (KBr): 3432, 2930, 2857, 2361, 1725, 1456, 1256, 1163, 1005, 837 cm^{-1}. ^{1}H NMR (90 MHz; CDCl$_3$): δ=0.09 (6H, s), 0.90 (9H, s), 1.09 (3H, d, *J*=9.0 Hz), 3.02–3.28 (1H, m), 4.15 (2H, s), 5.07 (1H, d, *J*=5.0 Hz), 7.21–7.38 (5H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=−5.73, −5.65, 10.65, 18.17, 25.64, 48.18, 68.67, 73.29, 125.95, 127.34, 128.18, 141.78, 213.78.

3.2.31. 4-Hydroxy-1,1-dimethoxy-4-phenyl-2-butanone (32). Yellow oil. IR (neat): 3482, 2938, 2836, 1732, 1454, 1198, 1071, 986 cm^{-1}. ^{1}H NMR (90 MHz; CDCl$_3$): δ=2.90–3.20 (2H, m), 3.41 (6H, s), 4.47 (1H, s), 5.05–5.30 (1H, m), 7.27–7.38 (5H, m). ^{13}C NMR (100 MHz; CDCl$_3$): δ=46.47, 54.85, 69.62, 103.99, 125.70, 127.70, 128.52, 142.85, 205.45.

3.2.32. 2,15-Hexadecanedione (33). Methyl acetoacetate (0.92 g, 8.0 mmol) and DBU (1.22 g, 8.0 mmol) were successively added to a stirred solution of NaI (0.66 g, 4.0 mmol) in DMF (2.0 ml) at room temperature. After 15 min, 1,10-dibromodecane (0.60 g, 2.0 mmol) was added to the mixture during 30 min, followed by stirring for 2 h. Water was added to the mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na$_2$SO$_4$) and concentrated to give crude oil, which was purified by SiO$_2$-column chromatography (hexane–AcOEt=5:1) to give the intermediate (457 mg). This crude product and 10% NaOH aqueous solution was stirred for room temperature for 2 h and 60°C for 3 h. To this mixture, 20% HCl aqueous solution was added (pH ~1). The mixture was extracted with AcOEt and the organic phase was washed with water, brine, dried (Na$_2$SO$_4$) and concentrated. The obtained crude crystals were recrystallized from EtOH to give the desired product. colorless crystals; mp 81.2–82.5°C. ^{1}H NMR (300 MHz; CDCl$_3$): δ=1.20–1.32 (16H, m), 1.50–1.63 (4H, m), 2.13 (6H, s), 2.41 (4H, t, *J*=7.4 Hz). ^{13}C NMR (75 MHz; CDCl$_3$): δ=23.87, 29.16, 29.36, 29.42, 29.52, 29.80, 43.80, 209.29.

3.2.33. 2,14-Pentadecanedione (37). Colorless crystals; mp 77.5–78.5°C. ^{1}H NMR (300 MHz; CDCl$_3$): δ=1.20–1.33 (14H, m), 1.49–1.62 (4H, m), 2.13 (6H, s), 2.41 (4H, t, *J*=7.4 Hz). ^{13}C NMR (75 MHz; CDCl$_3$): δ=23.84, 29.14, 29.34, 29.38, 29.47, 29.79, 43.78, 209.28.

3.2.34. 2,17-Octadecanedione (38). Colorless crystals; mp 92.0–93.5°C. ^{1}H NMR (300 MHz; CDCl$_3$): δ=1.21–1.33 (20H, m), 1.50–1.62 (4H, m), 2.13 (6H, s), 2.41 (4H, t, *J*=7.4 Hz). ^{13}C NMR (75 MHz; CDCl$_3$): δ=23.87, 29.17, 29.37, 29.44, 29.56, 29.59, 29.80, 43.80, 209.29.

3.2.35. 3-Hydroxy-3-methylcyclopentadecanone (34). Two lots of solutions (A) and (B) were prepared; TiCl$_4$ (110 μl, 1.00 mmol) diluted with CH$_2$Cl$_2$ (2.4 ml) under an argon atmosphere and (B) mixed solution of 2,15-hexadecanedione (**33**; 127 mg, 0.50 mmol) and Bu_3N (370 mg, 2.00 mmol) in CH_2Cl_2 (1.7 ml). Solutions of (A) and (B) were simultaneously and proportionally added to a stirred CH_2Cl_2 solvent (45.0 ml) at 25–30°C during 2 h under an argon atmosphere, using a microfeeder apparatus equipped with dual syringes (note: this procedure is critical). After completion of the feed, the mixture was further stirred for 0.5 h at the same temperature. Then, water was added to the stirring mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane–AcOEt=8:1) to give the desired product (68 mg; 52%; purity 97% base on ^{1}H NMR measurement). Colorless oil. IR (neat): 3484, 2930, 2855, 1703, 1460, 1408, 1372 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ=1.09–1.57 (20H, m), 1.17 (3H, s), 1.61–1.72 (1H, m), 1.72–1.84 (1H, m), 2.33–2.40 (1H, m), 2.43 (1H, d, J=16.8 Hz), 2.51 (0.5H, dd, J=16.4, 5.6 Hz), 2.53 (0.5H, dd, J=16.4, 5.6 Hz), 2.81 (1H, d, J=16.8 Hz), 3.80–4.09 (1H, brs, –O*H*); ^{13}C NMR (100 MHz; $CDCl_3$): δ=22.51, 23.68, 25.65, 26.11, 26.37, 26.50, 26.61, 26.67, 27.52, 27.70, 27.91, 41.17, 43.49, 50.70, 72.29, 213.94.

3.2.36. 3-Hydroxy-3-methylcyclobutadecanone (39). Colorless crystals; mp 34.5–35.4°C. ^{1}H NMR (300 MHz; $CDCl_3$): δ=1.01–1.50 (18H, m), 1.16 (3H, s), 1.70–1.80 (1H, m), 1.83–1.97 (1H, m), 2.30–2.39 (1H, m), 2.57–2.67 (1H, m), 2.62 (2H, dd, J=142.7, 17.7 Hz), 3.62–3.89 (1H, brs); ^{13}C NMR (75 MHz; $CDCl_3$): δ=22.63, 22.80, 23.59, 24.05, 24.86, 25.33, 25.71, 26.11, 26.57, 27.73, 40.38, 42.29, 49.34, 72.41, 213.31.

3.2.37. 3-Hydroxy-3-methylcycloheptadecanone (40). Colorless oil; ^{1}H NMR (300 MHz; $CDCl_3$): δ=1.11–1.39 (22H, m), 1.17 (3H, s), 1.43–1.79 (4H, m), 2.30–2.40 (1H, m), 2.45–2.53 (1H, m), 2.46 (1H, d, J=16.6 Hz), 2.78 (1H, d, J=17.2 Hz), 3.09–3.38 (1H, brs); ^{13}C NMR (75 MHz; $CDCl_3$): δ=23.32, 24.22, 26.86, 26.90, 26.96, 27.01, 27.22, 27.27, 27.54, 27.62, 27.67, 28.12, 28.72, 41.14, 44.17, 50.79, 72.15, 213.89.

3.2.38. (*E*)- and (*Z*)-3-Methyl-2-cyclopentadecenone (*E*-35 and *Z*-35). Ti(O*i*-Bu)$_4$ (103 μl, 0.30 mmol) was added to a stirred solution of 3-hydroxy-3-methylcyclopentadecanone (**34**; 37 mg, 0.15 mmol) at room temperature, followed by stirring for 24 h. The mixture was added to cold water and Et_2O, followed by Celite filtration. The separated organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane–Et_2O=8:1) to give the desired product (30 mg, 88%; *E*-**35**–*Z*-**35**=91:9). Colorless oil; IR (neat): 2930, 2859, 1686, 1615, 1458, 1387, 1364, 1225 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ=1.16–1.40 (15H, m), 1.44–1.70 (5H, m), 1.87 (*E*, 3H, d, J=1.5 Hz), 2.14 (*Z*, 3H, d, J=1.2 Hz), 2.16–2.21 (*Z*, 2H, m), 2.34–2.43 (2H, m), 2.73–2.76 (*E*, 2H, m), 6.08–6.12 (*E*, 1H, m), 6.13–6.18 (*Z*, 1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ=23.85, 23.94, 25.16, 25.16, 25.47, 25.48, 25.64, 26.19, 26.38, 26.38, 26.55, 26.63, 26.67, 26.70, 26.75, 26.80, 26.86, 26.95, 26.99, 27.05, 27.13, 31.76, 40.03, 43.60, 44.46, 123.72, 125.02, 158.63, 158.94, 202.06, 202.38.

3.3. Isomerization of *E*-rich 3-methyl-2-cyclopentadecenone (35) using NaSPh

NaSPh (3 mg, 0.03 mmol) was added to the *E*-rich substrate (**35**; *E*–*Z*=ca. 9:1; 59 mg, 0.19 mmol) in hexane (0.5 ml) at room temperature and the mixture was stirred for 1 h. Water was added to the mixture and the similar work up to the preparation of **35** gave the isomeric product (**35**; 56 mg, 95%, *E*–*Z*=73:27 based on ^{1}H NMR measurement).

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