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Enolate formation from cyclopropyl ketones via iodide-induced ring opening and its use for stereoselective aldol reaction

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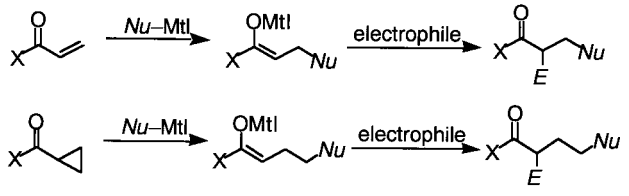
Abstract—Treatment of cyclopropyl ketones with $TiCl_4$-*n*-Bu_4NI mixed reagent provides (*Z*)-titanium enolates which afford *syn*-α-iodethyl-β-hydroxyketones stereoselectively upon subsequent reaction with various aldehydes. The aldol adducts are cyclized into *trans*-acyltetrahydrofurans in good yield by active alumina. In contrast, the use of Et_2AlI in place of $TiCl_4$-*n*-Bu_4NI provides the corresponding *anti* aldol adducts with high stereoselectivity. These methods can complementarily provide both *syn* and *anti* isomers of α-iodoethyl-β-hydroxyketones from cyclopropyl ketones and aldehydes.

Conjugate addition reaction of various nucleophiles to α,β-unsaturated compounds such as 1,2-enones has been recognized as an efficient route for enolate formation.[1] The sequential reaction of the resulting enolate with electrophiles provides an extremely effective methodology for construction of the carbon framework of organic molecules (Scheme 1).[2] Ring opening of cyclopropyl ketones is also an attractive method for synthetic chemists to prepare enolates and has been explored extensively.[3,4] Herein we wish to report that metal iodides can mediate enolate formation from cyclopropyl ketones, and the sequential trapping of the resulting metal enolates with aldehydes affords 3-hydroxy-2-(2′-iodoethy)ketones stereoselectively.

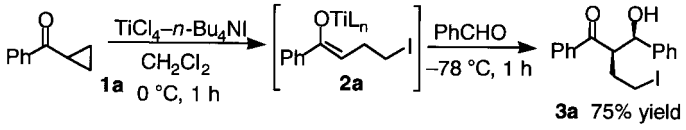


Scheme 1.

1. Enolate formation from cyclopropyl ketones via $TiCl_4$-*n*-Bu_4NI-induced ring opening

Treatment of tetrabutylammonium iodide with $TiCl_4$ in dichloromethane at 0°C provided a dark-red solution.[5] To the resulting solution was added cyclopropyl phenyl ketone (**1a**) at 0°C. After stirring for 1 h, an addition of benzaldehyde afforded *syn* aldol adduct **3a** in 75% yield (Scheme 2). Results of the aldol reaction of the enolate **2** with various aldehydes are summarized in Table 1. The titanium enolate **2** is reactive toward both aromatic and aliphatic aldehydes. For example, acetaldehyde afforded the *syn* adduct **3e** in 80% yield without contamination by the *anti*-isomer (entry 5). Ring opening of cyclopropyl methyl ketone (**1b**) also proceeds facilely with this reagent. Interestingly, exclusive formation of *syn*-β-hydroxy ketones **3** was observed in most cases except the reaction of **1b** with acetaldehyde (entry 8).

Starting from cyclopropyl phenyl ketone (**1a**), the initial products, *syn*-β-hydroxy ketones, were partially converted into *trans*-acyltetrahydrofuran derivatives **4** under the reaction conditions. For example, an addition of 2-methylpropanal to the titanium enolate **2** derived from **1a** and



Scheme 2.

Keywords: cyclopropyl ketones; aldol reaction; nucleophiles.

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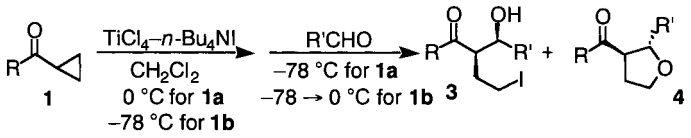
Table 1. $TiCl_4$-*n*-Bu_4NI-induced aldol reaction of cyclopropyl ketone



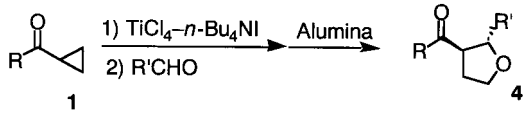
Entry	Cyclopropyl ketone	R′CHO	Yield (%)			
			3	(*syn*/*anti*)	**4**	
1	R=Ph: **1a**[a]	PhCHO	**3a**	75 (>99/1)	**4a**	14
2	R=Ph: **1a**[a]	*n*-$C_9H_{19}CHO$	**3b**	55 (>99/1)	**4b**	13
3	R=Ph: **1a**[a]	*i*-C_3H_7CHO	**3c**	64 (>99/1)	**4c**	23
4	R=Ph: **1a**[a]	*t*-C_4H_9CHO	**3d**	–	**4d**	88
5	R=Ph: **1a**[a]	CH_3CHO	**3e**	80 (>99/1)	–	–
6	R=CH_3: **1b**[b]	PhCHO	**3f**	72 (>99/1)	–	–
7	R=CH_3: **1b**[b]	*t*-C_4H_9CHO	**3g**	54 (>99/1)	–	–
8	R=CH_3: **1b**[b]	CH_3CHO	**3h**	85 (80/20)	–	–

[a] Cyclopropyl phenyl ketone (**1a**) was treated at 0°C and the aldehyde was added at −78°C.
[b] Cyclopropyl methyl ketone (**1b**) was treated at −78°C. The aldehyde was added at −78°C and the reaction mixture was warmed to 0°C.

$TiCl_4$-*n*-Bu_4NI provided *trans*-2-isopropyl-3-benzoyltetrahydrofuran in 23% yield along with the corresponding *syn* aldol adduct **3c** (Table 1, entry 3). The formation of **4** could not be prevented in the case of **3a**, **3b**, **3c** and **3d** because of the facile conversion into **4**.[6] In contrast, the corresponding tetrahydrofuran **4** could not be found in the crude product when cyclopropyl methyl ketone (**1b**) was employed instead of **1a**. The crude products (a mixture of **3** and **4**, or **3**) were treated with active alumina in ether to afford **4** as a single product with high stereoselectivity.[7] Results of the sequential treatment of **1a** and **1b** with $TiCl_4$-*n*-Bu_4NI and alumina to provide acyltetrahydrofurans are shown in Table 2.

The formation of *syn*-isomers can be explained as follows (Scheme 3). The attack of the iodide in the titanium reagent at the cyclopropane ring occurs perpendicularly to the carbonyl group in the favored conformation of **1** to furnish (*Z*)- enolates **2**. The successive aldol reaction takes place through the six-membered transition state **A** to provide the *syn*-aldol adducts.

Table 2. Alumina-induced cyclization of aldol adduct

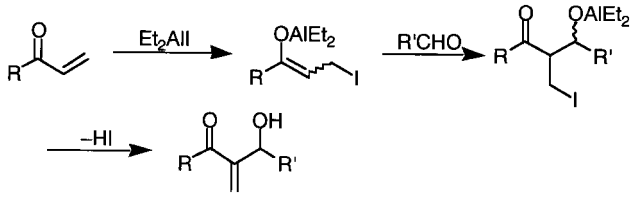


Entry	Cyclopropyl ketone	R′CHO	Yield (%)	
1	R=Ph: **1a**	PhCHO	**4a**	94
2	R=Ph: **1a**	*n*-$C_9H_{19}CHO$	**4b**	67
3	R=Ph: **1a**	*i*-C_3H_7CHO	**4c**	64
4	R=Ph: **1a**	CH_3CHO	**4e**	78
5	R=CH_3: **1b**	PhCHO	**4f**	72
6	R=CH_3: **1b**	*t*-BuCHO	**4g**	76
7	R=CH_3: **1b**	CH_3CHO	**4h**	60

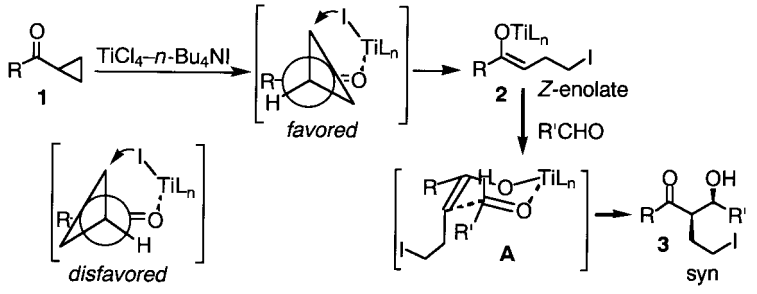
2. Enolate formation from cyclopropyl ketones via Et_2AlI-mediated ring opening

Conjugate addition of diethylaluminum iodide (Et_2AlI) to α,β-unsaturated carbonyl compounds and the sequential aldol condensation of the resulting aluminum enolates provides α-substituted-α,β-unsaturated carbonyl compounds directly.[8] The elimination of HI proceeds rapidly under the reaction conditions to generate the carbon–carbon double bond (Scheme 4).

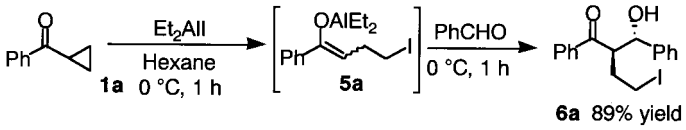
We found the $TiCl_4$-*n*-Bu_4NI-induced enolate formation as described in Section 1; then it was anticipated that Et_3AlI



Scheme 4.

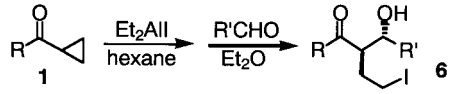


Scheme 3.



Scheme 5.

Table 3. Et_2AlI-induced aldol reaction of cyclopropyl ketone



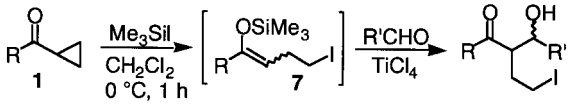
Entry	Cyclopropyl ketone **1**	Aldehyde		Yield (%) (*anti*/*syn*)
1	R=Ph: **1a**	PhCHO	**6a**	89 (>99/1)
2	R=Ph: **1a**	n-$C_9H_{19}CHO$	**6b**	68 (>99/1)
3	R=Ph: **1a**	i-C_3H_7CHO	**6c**	84 (>99/1)
4	R=Ph: **1a**	t-C_4H_9CHO	**6d**	73 (>99/1)
5	R=Ph: **1a**	CH_3CHO	**6e**	96 (71/29)
6	R=CH_3: **1b**	PhCHO	**6f**	89 (>99/1)
7	R=CH_3: **1b**	i-C_3H_7CHO	**6g**	94 (>99/1)
8	R=CH_3: **1b**	t-C_4H_9CHO	**6h**	54 (>99/1)
9	R=CH_3: **1b**	CH_3CHO	**6i**	93 (70/30)

would also work to open cyclopropyl ketones. Indeed, this proved to be the case, and the reaction of cyclopropyl ketones with Et_2AlI gave diethylaluminum 4-iodoenolates **5** which provided *anti* aldol adducts **6** with high stereoselectivity upon treatment with aldehydes. Et_2AlI was added to a solution of cyclopropyl phenyl ketone (**1a**) in hexane at 0°C. After stirring for 1 h at 0°C, ether and benzaldehyde were added to the resulting aluminum enolate **5a**. The reaction mixture was stirred for another 1 h at 0°C. After aqueous workup, purification of the crude product provided the *anti* aldol adduct **6a** in 89% yield without contamination by the *syn*-isomer (Scheme 5). It should be noted that no products arising from an elimination of HI from the aldol adduct could be detected.

The results of the aldol reaction with various aldehydes are shown in Table 3. Cyclopropyl phenyl ketone (**1a**) and methyl ketone **1b** are equally effective for the reaction. In each case, *anti*-3-hydroxy-2-(2′-iodoethyl)ketone **6** is obtained as a single stereoisomer except in the case where acetaldehyde is employed (entry 5 or 9).

At −78°C, an addition of benzaldehyde to the aluminum enolate **5a**, generated from **1a** and Et_2AlI, afforded a stereoisomeric mixture of *anti*-**6a** and *syn*-**3a** (38/62). Complete isomerization of *syn*-**3a** into *anti*-**6a** was observed upon treatment with Et_3Al (Scheme 6). On the basis of these facts, we assume that the exclusive formation of *anti* aldol adducts can be attributed to thermodynamic preference. Whereas the aldol reaction at −78°C proceeds under kinetic control without isomerization, the equilibrium is achieved rapidly at 0°C via the retro-aldol reaction to give a thermodynamically more stable *anti* adduct as a single product.[9] In the case of the reaction of acetaldehyde, no variation in the ratio of *anti*-**6e** and *syn*-**3e** was observed when the reaction mixture was stirred at 25°C for 3 h. Thus, the equilibrium was established at this ratio (*anti*/*syn*=70/30).

Table 4. Me_3SiI-induced ring opening of cyclopropyl ketones and the sequential aldol reaction

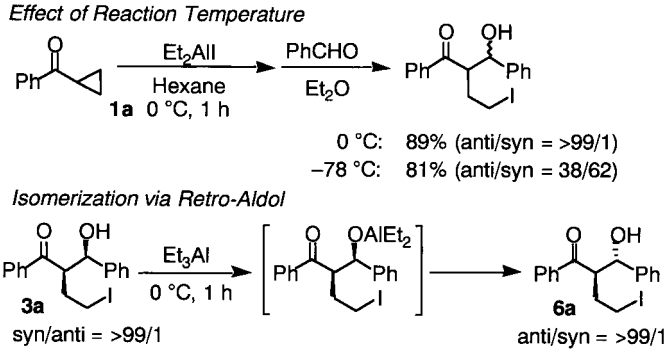


Entry	Cyclopropyl ketone **1**	Aldehyde	Yield (%) (*syn*/*anti*)
1	R=Ph: **1a**	PhCHO	69 (69/40)
2	R=Ph: **1a**	n-$C_9H_{19}CHO$	84 (60/40)
3	R=Ph: **1a**	n-$C_6H_{13}CHO$	86 (67/33)
4	R=Ph: **1a**	i-C_3H_7CHO	89 (86/14)
5	R=Ph: **1a**	t-C_4H_9CHO	65 (>99/1)
6	R=Ph: **1a**	CH_3CHO	79 (50/50)
7	R=CH_3: **1b**	PhCHO	78 (70/30)
8	R=CH_3: **1b**	i-C_3H_7CHO	65 (70/30)
9	R=CH_3: **1b**	n-$C_pH_{19}CHO$	88 (50/50)
10	R=CH_3: **1b**	t-C_4H_9CHO	49 (86/14)[a]
11	R=CH_3: **1b**	CH_3CHO	74 (50/50)

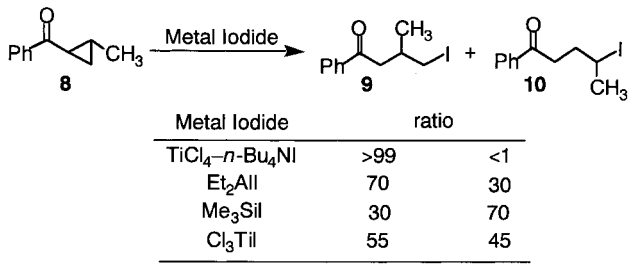
[a] 3-acetyl-2-*tert*-butyltetrahydrofuran (**4g**) was obtained in 18% yield.

3. Enolate formation from cyclopropyl ketones via Me_3SiI-mediated ring opening

Trimethylsilyl iodide[10] is known to open the cyclopropane ring of cyclopropyl ketones to provide silyl enolates.[11] Thus, we investigated the Mukaiyama aldol reaction of



Scheme 6.



Metal Iodide	ratio	
$TiCl_4$–*n*-Bu_4NI	>99	<1
Et_2AlI	70	30
Me_3SiI	30	70
Cl_3TiI	55	45

Scheme 7.

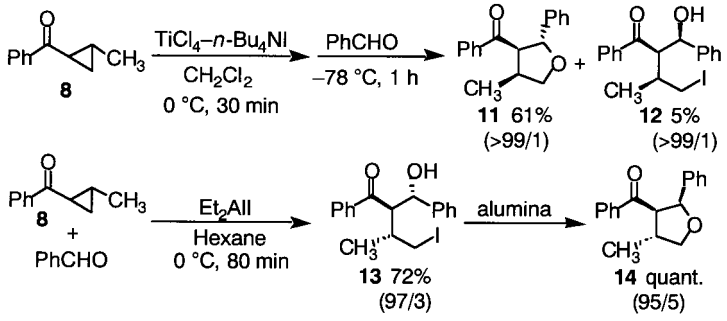
the resulting silyl 4-iodoenolates **7** with $TiCl_4$ in a one-pot procedure. Treatment of the silyl enolate **7**, prepared from cyclopropyl ketone **1** and Me_3SiI, with aldehydes in the presence of $TiCl_4$ afforded the corresponding aldol adducts as diastereoisomeric mixtures. The results are shown in Table 4. In most cases, no significant diastereoselectivity was observed. Therefore, the former two methods with $TiCl_4$-*n*-Bu_4NI and Et_2AlI are superior to the reaction with Me_3SiI from the viewpoint of diastereoselectivity.

4. Regioselective ring opening of substituted cyclopropyl ketone

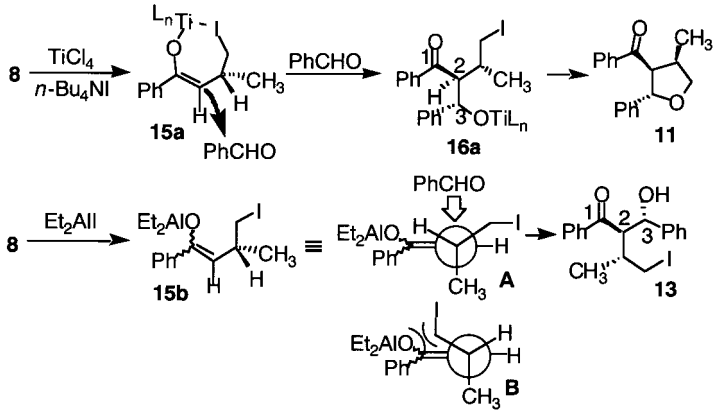
Regioselectivity in the ring opening of methyl-substituted cyclopropyl ketone **8** was examined with various metal iodides (Scheme 7).[12] It is notable that the $TiCl_4$-*n*-Bu_4NI mixed reagent attacked at the less hindered site of the cyclopropane ring exclusively. This fact can indicate that the $TiCl_4$-*n*-Bu_4NI mixed reagent possesses a nucleophilic character and low Lewis acidity because of its nature as an ate-complex. Et_2AlI also afforded the primary iodoketone **9** predominantly, whereas trimethylsilyl iodide exhibited the opposite regioselectivity to provide the secondary iodide **10** as a major product.

Treatment of **8** with $TiCl_4$-*n*-Bu_4NI followed by an addition of benzaldehyde afforded the trisubstituted tetrahydrofuran **11** in 61% yield as a single diastereomer (Scheme 8).[13] The *syn*-aldol adduct **12** was also obtained in 5% yield. On the other hand, the use of Et_2AlI instead of $TiCl_4$-*n*-Bu_4NI provided the *anti*-aldol adduct **13** in 72% yield with excellent stereoselectivity (one major isomer/three other isomers=97/3). The cyclization of the adduct **13** by active alumina furnished another stereoisomer of tetrahydrofuran derivative **14** quantitatively.

Stereochemical outcome of this reaction can be explained as follows (Scheme 9). Nucleophilic opening of the cyclopropane ring provides enolates **15a** and **15b**. In **15a**, coordination of the iodine atom to the titanium center restricts conformation of the enolate as shown in Scheme 9. The addition to benzaldehyde occurs from the opposite face to the methyl group to provide the aldol adduct **16a**. The relative stereochemistry between C2 and C3 is determined in the same fashion as shown in Scheme 3. In the case of the aluminum enolate **15b**, the addition proceeds through the favored conformation A. Isomerization of the stereochemistry at C2 via the retro-aldol reaction as discussed before affords the *anti*-aldol adduct **13** after hydrolysis.



Scheme 8.



Scheme 9.

5. Experimental

^{1}H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were taken on a Varian GEMINI 300 spectrometer in $CDCl_3$ as a solvent, and chemical shifts were given in δ value with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25 mm layer of Merck silica gel $60F_{254}$. Column chromatography was done with silica gel (Wakogel 200 mesh). The analyses were carried out at the Elemental Analysis Center of Kyoto University. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification; however, aldehydes were distilled and stocked under argon. Dichloromethane was dried with molecular sieves 4 Å. Hexane and ether were dried over slices of sodium metal.

5.1. General procedure for ring opening of cyclopropyl phenyl ketones with $TiCl_4$-*n*-Bu_4NI

The reaction of cyclopropyl phenyl ketone (**1a**) with benzaldehyde is representative (entry 1, Table 1). To a solution of $TiCl_4$ (2.0 mmol) in CH_2Cl_2 (5 mL) was added a solution of *n*-Bu_4NI (2.0 mmol) in CH_2Cl_2 (3 mL) at 0°C. After stirring for 10 min at 0°C, to the dark-red solution was added cyclopropyl phenyl ketone (**1a**, 0.15 g, 1.0 mmol). The reaction mixture was stirred for 1 h at 0°C and then cooled to −78°C. Benzaldehyde (0.13 g, 1.2 mmol) was added and the reaction mixture was stirred for another 1 h. Finally, the mixture was poured into saturated aqueous ammonium chloride. The mixture was extracted with ether (20 mL×3) and organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure and purification by silica gel chromatography afforded *syn*-3-hydroxy-2-(2′-iodoethyl)-1,3-diphenyl-1-propanone (**3a**, 0.29 g, 0.75 mmol) in 75% yield.

5.1.1. *syn*-3-Hydroxy-2-(2′-iodoethyl)-1,3-diphenyl-1-propanone (3a). IR (neat) 3440, 1675, 1597, 1449, 1262, 1133, 937, 759, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.23 (dddd, *J*=4.8, 7.5, 8.4, 14.4 Hz, 1H), 2.45 (dddd, *J*=5.4, 7.5, 8.4, 14.4 Hz, 1H), 2.80–3.15 (bs, 1H), 2.90 (ddd, *J*=7.5, 8.4, 9.9 Hz, 1H), 3.12 (ddd, *J*=5.4, 7.5, 9.9 Hz, 1H), 4.00 (ddd, *J*=4.8, 4.8, 8.4 Hz, 1H), 5.10 (d, *J*=4.8 Hz, 1H), 7.21–7.62 (m, 8H), 7.96 (d, *J*=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 4.51, 30.80, 53.39, 73.47, 125.97, 127.80, 128.50, 128.62, 128.85, 133.83, 136.75, 141.33, 204.67. The analytically pure sample could not be obtained because of its instability. Thus, the elemental analysis was done with the cyclized compound **4a**. To a mixture of active alumina (2 g) in ether (5 mL) was added a solution of the aldol adduct **3a** (0.29 g, 0.75 mmol) in ether (2 mL) at 0°C. After stirring for 1 h, alumina was filtered off and the filtrate was concentrated. The residual oil was purified by silica gel to afford *trans*-3-benzoyl-2-phenyltetrahydrofuran (**4a**, 0.19 g, 0.75 mmol) in quantitative yield: IR (neat) 3058, 3026, 2928, 2868, 1680, 1597, 1581, 1494, 1449, 1360, 1278, 1217, 1064, 754, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (dddd, *J*=5.4, 7.2, 7.8, 15.0 Hz, 1H), 2.47 (dddd, *J*=7.5, 8.1, 9.3, 15.0 Hz, 1H), 3.93 (ddd, *J*=7.2, 7.2, 9.3 Hz, 1H), 4.08 (ddd, *J*=7.2, 7.5, 7.8 Hz, 1H), 4.27 (ddd, *J*=5.4, 8.1, 8.1 Hz, 1H), 5.28 (d, *J*=8.1 Hz, 1H), 7.24–7.58 (m, 8H), 7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 32.09, 54.78, 68.49, 83.14, 125.96, 127.78, 128.56, 128.59, 128.70, 133.43, 136.58, 141.67, 200.04. Found: C, 81.09; H, 6.51%. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39%.

5.1.2. *syn*-3-Hydroxy-2-(2′-iodoethyl)-1-phenyldodecanone (3b). IR (neat 3436, 2920, 2850, 1673, 1665, 1448, 1216, 1001, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J*=6.6 Hz, 3H), 1.18–1.61 (m, 16H), 2.18–2.38 (m, 2H), 2.43–2.55 (m, 1H), 2.99 (ddd, *J*=6.6, 9.6, 9.6 Hz, 1H), 3.32 (ddd, *J*=4.5, 7.2, 9.6 Hz, 1H), 3.77 (dt, *J*=9.6, 3.6 Hz, 1H), 3.90 (dt, *J*=9.6, 3.6 Hz, 1H), 7.48–7.58 (m, 2H), 7.59–7.68 (m, 1H), 8.00–8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 5.22, 13.96, 22.52, 25.88, 29.13, 29.32, 29.37, 29.39, 30.55, 31.73, 34.86, 51.22, 71.88, 128.69, 128.94, 133.84, 137.03, 203.76. This compound was unstable to obtain the analytically pure sample. The elemental analysis was performed with *trans*-3-benzoyl-2-phenyltetrahydrofuran (**4a**) after cyclization: IR (neat) 2916, 2854, 1679, 1598, 1450, 1217, 777, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J*=6.9 Hz, 3H), 1.18–1.70 (m, 16H), 2.08–2.39 (m, 2H), 3.63 (ddd, *J*=7.5, 7.5, 9.6 Hz, 1H), 3.89 (ddd, *J*=7.5, 7.5, 7.5 Hz, 1H), 4.02 (ddd, *J*=5.1, 7.8, 7.8 Hz, 1H), 4.19 (ddd, *J*=5.1, 7.5, 7.5 Hz, 1H), 7.46–7.62 (m, 3H), 7.95–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.54, 26.16, 29.16, 29.36, 29.38, 29.47, 31.75, 31.80, 34.87, 51.41, 67.51, 81.99, 128.46, 128.80, 133.37, 136.88, 200.77. Found: C, 79.42; H, 10.00%. Calcd for $C_{20}H_{30}O_2$: C, 79.19; H, 9.87%.

5.1.3. *syn*-3-Hydroxy-2-(2′-iodoethyl)-4-methyl-1-phenylpentanone (3c). IR (neat) 2960, 1681, 1647, 1597, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, *J*=6.9 Hz, 3H), 1.02 (d, *J*=6.9 Hz, 3H), 1.73 (dsept, *J*=7.8, 6.9 Hz, 1H), 2.16 (dddd, *J*=3.6, 6.6, 9.9, 14.4 Hz, 1H), 2.49 (s, 1H), 2.51 (dddd, *J*=4.5, 5.7, 9.9, 14.4 Hz, 1H), 2.97 (ddd, *J*=5.7, 9.9, 9.9 Hz, 1H), 3.33 (ddd, *J*=4.5, 6.6, 9.9 Hz, 1H), 3.52 (dd, *J*=3.6, 7.8 Hz, 1H), 3.96 (ddd, *J*=3.6, 3.6, 9.9 Hz, 1H), 7.47–7.64 (m, 3H), 7.99–8.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 5.61, 18.55, 19.14, 29.73, 31.13, 48.61, 76.87, 128.61, 128.96, 133.82, 136.72, 203.73. This compound was transformed into *trans*-3-benzoyl-2-isopropyltetrahydrofuran (**4c**) for the elemental analysis: IR (nujol) 2854, 1679, 1466, 1451, 1376, 1211 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (d, *J*=6.9 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 1.79 (dqq, *J*=6.9, 6.9, 6.9 Hz, 1H), 2.06 (dddd, *J*=5.1, 6.9, 7.5, 12.3 Hz, 1H), 2.32 (dddd, *J*=7.2, 7.8, 9.9, 12.3 Hz, 1H), 3.73 (ddd, *J*=6.9, 6.9, 9.9 Hz, 1H), 3.88 (ddd, *J*=7.5, 7.8, 8.1 Hz, 1H) 4.00 (ddd, *J*=5.1, 7.2, 8.1 Hz, 1H), 4.10 (dd, *J*=6.9, 6.9 Hz, 1H), 7.46–7.62 (m, 3H), 7.96–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.30, 18.61, 32.05, 32.52, 48.50, 67.36, 86.49, 128.12, 128.52, 133.03, 136.44, 200.56. Found: C, 76.79; H, 8.26%. Calcd for $C_{14}H_{18}O_3$: C, 77.03; H, 8.31%.

5.1.4. *trans*-3-Benzoyl-2-*tert*-butyltetrahydrofuran (4d). IR (nujol) 1677, 1220, 1198, 1071, 661 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H), 1.99 (dddd, *J*=7.2, 7.2, 9.9, 12.0 Hz, 1H), 2.30 (dddd, *J*=5.4, 6.6, 7.2, 12.0 Hz, 1H), 3.81 (ddd, *J*=6.6, 7.2, 9.9 Hz, 1H), 3.88 (ddd, *J*=7.2, 7.2, 8.4 Hz, 1H), 3.98 (ddd, *J*=5.4, 7.2, 8.4 Hz, 1H), 4.20 (d, *J*=7.2 Hz, 1H), 7.43–7.60 (m, 3H), 7.95–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.89, 33.84, 33.89, 46.26, 68.05,

89.29, 128.41, 128.85, 133.33, 136.81, 201.30. Found: C, 77.27; H, 8.61%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

5.1.5. *syn*-3-Hydroxy-2-(2′-iodoethyl)-1-phenylbutanone (3e). IR (neat) 3414, 2964, 1672, 1596, 1579, 1427, 1215, 941, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, J=6.6 Hz, 3H), 2.20–2.51 (m, 3H), 2.98 (dt, J=6.6, 9.6 Hz, 1H), 3.28 (ddd, J=5.1, 6.6, 9.9 Hz, 1H), 3.69 (dt, J=9.3, 4.2 Hz, 1H), 4.11 (dq, J=9.3, 6.6 Hz, 1H), 7.44–7.65 (m, 3H), 7.98–8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 4.78, 21.10, 31.22, 52.61, 68.11, 128.71, 128.92, 133.86, 137.20 203.66. This compound was converted into *trans*-3-benzoyl-2-methyltetrahydrofuran (**4e**) upon treatment with alumina to obtain an analytically pure sample: IR (neat) 2970, 1678, 1598, 1580, 1449, 1372, 1220, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (d, J=6.0 Hz, 3H), 2.15 (m, 2H), 3.53–3.61 (m, 1H), 3.84–3.92 (m, 1H), 4.00–4.07 (m, 1H), 4.18–4.27 (m, 1H), 7.42–7.65 (m, 3H), 7.90–8.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.94, 31.55, 52.97, 67.53, 78.07, 128.48, 128.81, 133.42, 136.93, 200.51. Found: C, 75.96; H, 7.51%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

5.2. General procedure for ring opening of cyclopropyl methyl ketones with $TiCl_4$-*n*-Bu_4NI

The reaction of cyclopropyl methyl ketone (**1b**) with benzaldehyde is representative (entry 6, Table 1). To a solution of $TiCl_4$ (2.0 mmol) in CH_2Cl_2 (5 mL) was added a solution of *n*-Bu_4NI (2.0 mmol) in CH_2Cl_2 (3 mL) at 0°C. After stirring for 10 min, to the dark-red solution was added cyclopropyl methyl ketone (**1b**, 0.08 g, 1.0 mmol) at −78°C. The reaction mixture was stirred for 1 h. Benzaldehyde (0.13 g, 1.2 mmol) was added at −78°C and the reaction mixture was gradually warmed to 0°C with stirring for 1 h. Then, the mixture was poured into saturated aqueous ammonium chloride. The mixture was extracted with ether (20 mL×3) and organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration followed by purification by silica gel chromatography afforded *syn*-4-hydroxy-3-(2′-iodoethyl)-4-phenyl-2-butanone (**3f**) in 72% yield: IR (neat) 3392, 2958, 1697, 1493, 1177, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H), 2.08–2.27 (m, 2H), 2.50 (bs, 1H), 2.92–3.12 (m, 3H), 4.94 (d, J=5.4 Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 4.62, 30.54, 31.48, 59.80, 73.49, 125.98, 128.07, 128.68, 141.42, 211.37. Cyclization of this compound with alumina provided the analytically pure sample of *trans*-3-acetyl-2-phenyltetrahydrofuran (**4f**): IR (neat) 1710, 1364, 1060, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.23 (m, 2H), 3.15 (ddd, J=7.5, 8.4, 8.4 Hz, 1H), 4.00 (ddd, J=6.9, 7.8, 8.4 Hz, 1H), 4.16 (ddd, J=6.3, 7.2, 8.4 Hz, 1H), 4.99 (d, J=7.5 Hz, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 30.17 (2C), 60.12, 68.24, 82.49, 125.90, 127.86, 128.59, 141.59, 207.88. Found: C, 75.86; H, 7.60%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

5.2.1. *syn*-4-Hydroxy-3-(2′-iodoethyl)-5,5-dimethyl-2-hexanone (3g). IR (neat) 3236, 2934, 1711, 1355, 1170, 490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 9H), 2.00–2.31 (m, 3H), 2.24 (s, 3H), 2.92–3.13 (m, 2H), 3.29 (ddd, J=5.4, 6.9, 9.6 Hz, 1H), 3.54 (d, J=3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 5.59, 26.28, 30.17, 30.31, 30.39, 54.09, 77.08, 210.55. The elemental analysis was done with *trans*-3-acetyl-2-*tert*-butyltetrahydrofuran (**4g**) after cyclization of **3g** with alumina: IR (neat) 2954, 1713, 1364, 1081 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 9H), 1.91–2.12 (m, 2H), 2.21 (s, 3H), 2.96 (ddd, J=6.0, 6.0, 9.3 Hz, 1H), 3.78 (ddd, J=7.2, 7.5, 8.1 Hz, 1H), 3.86 (d, J=6.0 Hz, 1H), 3.89 (ddd, J=5.4, 6.9, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.68, 29.26, 30.58, 31.61, 52.41, 68.10, 88.51, 209.44. HRMS (*m*/*z*) Found: 170.1308. Calcd for $C_{10}H_{18}O_2$: 170.1307.

5.2.2. *syn*-4-Hydroxy-3-(2′-iodoethyl)-2-pentanone (3h). IR (neat) 3328, 2966, 1703, 1422, 1099, 459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, J=6.3 Hz, 3H), 1.25 (bs, 1H), 1.98–2.16 (m, 2H), 2.28 (s, 3H), 2.80 (ddd, J=4.2, 4.2, 8.7 Hz, 1H), 3.06 (ddd, J=6.9, 8.7, 9.9 Hz, 1H), 3.29 (ddd, J=5.4, 7.5, 9.9 Hz, 1H), 4.07 (dq, J=4.2, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 4.68, 20.61, 30.23, 31.64, 58.93, 67.43, 211.51. The elemental analysis was done with *trans*-3-acetyl-2-methyltetrahydrofuran (**4h**) after cyclization. IR (neat) 2922, 1711, 1448, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (d, J=6.3 Hz, 3H), 2.10–2.20 (m, 2H), 2.21 (s, 3H), 2.75 (ddd, J=7.5, 7.5, 9.0 Hz, 1H), 3.80 (ddd, J=5.7, 7.2, 8.4 Hz, 1H), 3.95 (ddd, J=5.7, 7.2, 8.4 Hz, 1H), 4.03 (dq, J=6.0, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.32, 29.58, 29.80, 58.78, 67.20, 77.02, 208.32. HRMS (*m*/*z*) Found: 128.0823. Calcd for $C_7H_{12}O_2$: 128.0837.

5.3. General procedure for ring opening of cyclopropyl ketones with Et_2AlI

The reaction of cyclopropyl phenyl ketone (**1a**) with benzaldehyde is representative (entry 1, Table 3). To a hexane solution of Et_2AlI (0.4 M, 4.0 mL, 1.6 mmol) was added cyclopropyl phenyl ketone (**1a**, 0.12 g, 0.8 mmol) at 0°C. The reaction mixture was stirred for 1 h and then benzaldehyde (0.10 g, 0.96 mmol) was added at 0°C. The reaction mixture was stirred for another 1 h, and then, the mixture was poured into saturated aqueous ammonium chloride. The mixture was extracted with ether (20 mL×3) and organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration and purification by silica gel chromatography afforded *anti*-3-hydroxy-2-(2′-iodoethyl)-1,3-diphenyl-1-propanone (**6a**, 0.27 g, 0.71 mmol) in 94% yield: IR (neat) 3426, 1672, 1597, 1581, 1493, 1207, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (dddd, J=6.9, 7.2, 7.8, 14.4 Hz, 1H), 2.28 (dddd, J=6.0, 6.9, 7.2, 14.4 Hz, 1H), 2.98 (ddd, J=7.2, 7.2, 10.2 Hz, 1H), 3.11 (d, J=5.7 Hz, 1H), 3.14 (ddd, J=6.9, 6.9, 10.2 Hz, 1H), 4.11 (ddd, J=6.0, 6.6, 7.8 Hz, 1H), 4.98 (dd, J=6.6, 5.7 Hz, 1H), 7.22–7.59 (m, 8H), 7.96 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 3.68, 33.45, 52.63, 75.26, 126.25, 128.10, 128.66, 128.66, 128.75, 133.76, 137.68, 142.11, 204.48. The aldol adduct **6a** was unstable to obtain the analytically pure sample. Then, the compound (0.27 g, 0.71 mmol) was converted into *anti*-3-hydroxy-2-ethyl-1,3-diphenyl-1-propanone **6a′** upon treatment with *n*-Bu_3SnH (0.29 g, 1.0 mmol) and Et_3B (0.1 mmol) in hexane at 25°C. After stirring for 30 min, the solvent was removed under reduced pressure and the residue was dissolved with ethyl acetate (20 mL). Potassium fluoride (1.0 g) and a saturated aqueous solution of KF (2 mL) were added and the mixture was vigorously stirred for 2 h. The mixture was filtered through a pad of Celite and the

filtrate was concentrated. The residue was purified by silica gel to provide **6a′** of which spectral data was identical with the authentic sample.[14]

5.3.1. *anti*-3-Hydroxy-2-(2′-iodoethyl)-1-phenyl-1-dodecanone (6b). IR (neat) 3420, 2922, 1679, 1449, 1211, 705, 446 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, J=6.6 Hz, 3H), 1.10–1.58 (m, 16H), 2.19–2.37 (m, 2H), 2.93 (bs, 1H), 3.15 (ddd, J=6.3, 7.2, 9.9 Hz, 1H), 3.27 (ddd, J=6.6, 7.5, 9.9 Hz, 1H), 3.58–3.85 (m, 2H), 7.47–7.63 (m, 3H), 8.00–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 4.50, 13.95, 22.49, 25.90, 29.10, 29.26, 29.33, 29.34. 31.71, 33.02, 35.66, 50.07, 72.09, 128.57, 128.91, 133.91, 137.31, 205.24. The elemental analysis was done with the reduced product **6b′**: IR (neat) 3428, 2918, 1666, 1597, 1459, 1208, 1002, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (dd, J=6.9, 6.9 Hz, 3H), 0.94 (t, J=7.5 Hz, 3H), 1.18–1.52 (m, 16H), 1.83 (ddq, J=2.1, 7.5, 7.5 Hz, 2H), 2.97 (d, J=8.1 Hz, 1H), 3.46 (ddd, J=4.5, 6.9, 6.9 Hz, 1H), 3.88 (m, 1H), 7.45–7.65 (m, 3H), 7.93–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.80, 13.93, 22.52, 23.33, 25.89, 29.15, 29.39 (2c), 29.42, 31.74, 35.70, 51.80, 72.50, 128.32, 128.77, 133.42, 137.98, 206.75. Found: C, 78.70; H, 10.63%. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59%.

5.3.2. *anti*-3-Hydroxy-2-(2′-iodoethyl)-4-methyl-1-phenyl-1-pentanone (6c). IR (neat) 3462, 2954, 1664, 1597, 1206, 1002, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J=6.6 Hz, 3H), 1.02 (d, J=6.6 Hz, 3H), 1.58–1.72 (m, 2H), 2.20–2.36 (m, 2H), 3.10–3.47 (m, 3H), 3.90–4.00 (m, 1H), 7.45–7.69 (m, 3H), 8.00–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 4.65, 18.59, 19.54, 32.43, 33.46. 46.78, 77.53, 128.60, 129.03, 134.08, 137.07, 205.98. The elemental analysis was performed for the reduced product **6c′**: IR (neat) 3440, 2952, 1677, 1597, 1460, 1001, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J=6.9 Hz, 3H), 0.96 (t, J=7.5 Hz, 3H), 0.99 (d, J=6.9 Hz, 3H), 1.69 (dqq, J=6.6, 6.6, 6.6 Hz, 1H), 1.77–1.90 (m, 2H), 3.20 (d, J=8.4 Hz, 1H), 3.50–3.63 (m, 2H), 7.45–7.64 (m, 3H), 7.93–8.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.90, 17.97, 19.70, 23.89, 32.12, 48.48, 77.93, 128.30, 128.82, 133.51, 137.78, 207.19. Found: C, 76.24; H, 9.24%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

5.3.3. *anti*-3-Hydroxy-2-(2′-iodoethyl)-4,4-dimethly-1-phenyl-1-pentanone (6d). IR (neat) 3448, 2952, 1658, 1596, 1205, 1002, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (s, 9H), 2.22 (dddd, J=6.0, 6.0, 7.5, 13.5 Hz, 1H), 2.37 (dddd, J=6.0, 6.0, 7.5, 13.5 Hz, 1H), 3.19–3.33 (m, 2H), 3.43 (d, J=8.7 Hz, 1H), 3.93 (dd, J=6.0, 7.5 Hz, 1H), 4.59 (d, J=8.7 Hz, 1H), 7.45–7.66 (m, 3H), 8.04 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 4.68, 26.79, 35.12, 36.06, 43.03, 81.09, 128.58, 129.06, 134.19, 136.47, 206.94. Treatment of **6d** with n-Bu_3SnH provided the analytically pure sample: IR (neat) 3450, 2958, 1656, 1450, 1206, 1002, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 9H), 0.10 (t, J=7.5 Hz, 3H), 1.91 (quin, J=7.5 Hz, 2H), 3.52–3.62 (m, 2H), 4.74 (d, J=9.0 Hz, 1H), 6.48–7.66 (m, 3H), 7.95–8.00; ^{13}C NMR ($CDCl_3$) δ 12.38, 26.33, 26.80, 36.15, 44.50, 82.45, 128.37, 129.01, 133.80, 137.38, 208.45. Found: C, 76.88; H, 9.59%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.59%.

5.3.4. *anti*-3-Hydroxy-2-(2′-iodoethyl)-1-phenyl-1-butanone (6e). IR (neat) 3352, 2924, 1675, 1448, 1215, 702 cm^{-1};^1H NMR ($CDCl_3$) δ 1.23 (d, J=6.6 Hz, 3H), 2.16–2.52 (m, 3H), 3.12 (dt, J=9.6, 7.2 Hz, 1H), 3.23–3.34 (m, 1H), 3.76 (dt, J=4.5, 7.5 Hz, 1H), 4.03–4.15 (m, 1H), 7.44–7.65 (m, 3H), 7.98–8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 64.22, 21.69, 32.97, 51.80, 68.13, 128.63, 128.96, 133.97, 137.40, 204.79. Spectral data for the reduced product **6e′** was as follows: IR (neat) 3358, 2964, 1678, 1597, 1459, 1212, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.5 Hz, 3H), 1.25 (d, J=6.6 Hz, 3H), 1.70–1.90 (m, 2H), 2.89 (d, J=7.2 Hz, 1H), 3.42 (ddd, J=5.7, 5.7, 6.9 Hz, 1H), 4.08–4.21 (m, 1H), 7.44–7.64 (m, 3H), 7.94–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.56, 21.54, 23.12, 53.66, 68.35, 128.35, 128.76, 133.41, 137.95, 206.24. Found: C, 74.71; H, 8.44%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

5.3.5. *anti*-4-Hydroxy-3-(2′-iodoethyl)-4-phenyl-2-butanone (6f). IR (neat) 3398, 1709, 1357, 1172, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (dddd, J=4.8, 6.9, 7.2, 14.4 Hz, 1H), 2.00 (dddd, J=6.0, 8.1, 8.1, 14.4 Hz, 1H), 2.15 (s, 3H), 2.87 (ddd, J=6.9, 8.1, 13.2 Hz, 1H), 2.97 (ddd, J=6.0, 7.2, 13.2 Hz, 1H), 3.05–3.02 (bs, 1H), 3.13 (ddd, J=4.8, 7.8, 8.1 Hz, 1H), 4.66 (d, J=7.8 Hz, 1H), 7.29–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 3.32, 32.23, 32.74, 58.81, 75.11, 126.20, 128.15, 128.62, 141.72, 212.79. Reduction of **6f** with n-Bu_3SnH afforded **6f′** which was identical with the authentic sample.[4c]

5.3.6. *anti*-4-Hydroxy-3-(2′-iodoethyl)-5-methyl-2-hexanone (6g). IR (neat) 3390, 2958, 1708, 1357, 1169, 981 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J=6.9 Hz, 3H), 0.97 (d, J=6.9 Hz, 3H), 1.67 (dd, J=6.6, 6.9 Hz, 1H), 2.00–2.18 (m, 2H), 2.27 (s, 3H), 2.48–2.60 (bs, 1H), 3.02 (ddd, J=5.4, 6.6, 6.9 Hz, 1H), 3.11–3.25 (m, 2H), 3.33 (dd, J=6.6, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 3.82, 17.30, 19.59, 31.61, 32.34, 32.52, 53.86, 77.09, 214.07. The titled compound was unstable to obtain the analytically pure sample. The elemental analysis was done with the reduced product (**6g′**) which was obtained by treatment with n-Bu_3SnH: IR (neat) 3366, 2910, 1702, 1459, 1364, 1052, 983 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88–1.00 (m, 9H), 0.60–1.80 (m, 3H), 2.22 (s, 3H), 2.49 (d, J=7.5 Hz, 1H), 2.67 (ddd, J=6.6, 6.9, 6.9 Hz, 1H), 3.40–3.52 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 11.65, 16.73, 19.77, 22.38, 31.19, 31.44, 55.84, 77.08, 215.08. HRMS (m/z) Found: 140.1195. Calcd for $C_9H_{18}O_2$-H_2O: 140.1201.

5.3.7. *anti*-4-Hydroxy-3-(2′-iodoethyl)-5,5-dimethyl-2-hexanone (6h). IR (neat) 3376, 2868, 1703, 1693, 1365, 1166, 458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 9H), 2.01 (dt, J=6.9, 6.9 Hz, 2H), 2.25 (s, 3H), 2.98 (dd, J=6.9, 6.9 Hz, 1H), 3.14–3.21 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 4.28, 26.62, 32.25, 34.45, 35.99, 49.87, 80.88, 215.66. The physical data for the reduced product **6h′** is as follows: IR (neat) 3434, 2956, 2870, 1692, 1480, 1365, 1166, 1002 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 9H), 0.10 (t, J=7.5 Hz, 3H), 1.64–1.88 (m, 2H), 2.27 (s, 3H), 2.69 (ddd, J=2.1, 7.2, 7.2 Hz, 1H), 3.32 (dd, J=2.1, 8.7 Hz, 1H), 4.09 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.23, 25.19, 26.60, 32.35, 35.92, 51.50, 81.73, 217.17. HRMS (m/z) Found: 157.1200. Calcd for $C_{10}H_{20}O_2$-CH_3: 157.1229.

5.3.8. *anti*-4-Hydroxy-3-(2′-iodoethyl)-2-pentanone (6i).

IR (neat) 3354, 2966, 1703, 1356, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, J=6.3 Hz, 3H), 1.95–2.21 (m, 2H), 2.25 (s, 3H), 2.38 (s, 1H), 2.79 (dt, J=8.4, 5.4 Hz, 1H), 3.07 (dt, J=9.9, 7.5 Hz, 1H), 3.19 (dt, J=9.9, 6.3 Hz, 1H), 3.91 (dq, J=8.4, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 3.56, 21.46, 31.96, 32.14, 58.86, 67.89, 212.76. **6i′**: IR (neat) 3400, 2958, 1703, 1460, 1377, 936 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.5 Hz, 3H), 1.22 (d, J=6.6 Hz, 3H), 1.60–1.75 (m, 2H), 2.21 (s, 3H), 2.40–2.55 (m, 2H), 3.88–4.08 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 11.40, 21.42, 22.01, 31.16, 60.71, 68.05, 214.28. HRMS (*m*/*z*) Found: 130.1014. Calcd for $C_7H_{14}O_2$: 130.0994.

5.4. General procedure for ring opening of cyclopropyl ketones with Me_3SiI

The reaction of cyclopropyl phenyl ketone (**1a**) with benzaldehyde is representative (entry 1, Table 4). To a solution of Me_3SiI (0.17 mL, 1.2 mmol) in CH_2Cl_2 (5 mL) was added cyclopropyl phenyl ketone (**1a**, 0.15 g, 1.0 mmol) at 0°C and the mixture was stirred for 1 h. The mixture was cooled to −78°C and benzaldehyde (0.13 g, 1.5 mmol) and $TiCl_4$ (1.0 mL, 1.0 M CH_2Cl_2 solution, 1.0 mmol) were successively added. The reaction mixture was stirred for another 2 h, and then the mixture was poured into saturated aqueous ammonium chloride. The mixture was extracted with ether (20 mL×3) and organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration and purification by silica gel afforded 3-hydroxy-2-(2′-iodoethyl)-1,3-diphenyl-1-propanone (0.27 g, 0.69 mmol, **3a/6a**=60/40) in 69% yield.

5.5. Procedure for ring opening of 2-methylcyclopropyl phenyl ketones with $TiCl_4$-*n*-Bu_4NI

A solution of *n*-Bu_4NI (0.44 g, 1.2 mmol) in CH_2Cl_2 (3 mL) was added to a solution of $TiCl_4$ (1.2 mmol) in CH_2Cl_2 (7 mL) at 0°C. After stirring for 10 min, 2-methylcyclopropyl phenyl ketone (**8**, 0.16 g, 1.0 mmol) was added. The reaction mixture was stirred for 30 min at 0°C and then cooled to −78°C. Benzaldehyde (0.13 g, 1.2 mmol) was added and the reaction mixture was stirred for another 1 h. Finally, the mixture was poured into saturated aqueous ammonium chloride. The mixture was extracted with ether (20 mL×3) and organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure and purification by silica gel chromatography afforded (2*R**,3*R**,4*R**)-3-benzoyl-4-methyl-2-phenyltetrahydrofuran (**11**, 0.16 g, 0.61 mmol) in 61% yield: IR (neat) 2926, 1666, 1598, 1450, 1403, 1223, 753, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, J=7.2 Hz, 3H), 3.00 (dddq, J=5.1, 6.3, 8.4, 7.2 Hz, 1H), 3.76 (dd, J=5.1, 8.4 Hz, 1H), 3.99 (dd, J=8.4, 8.4 Hz, 1H), 4.41 (dd, J=6.3, 8.4 Hz, 1H), 5.56 (d, J=8.4 Hz, 1H), 7.20–7.59 (m, 8H), 7.92–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.45, 38.41, 58.99, 75.82, 81.18, 125.85, 127.53, 128.21, 128.41, 128.82, 133.44, 137.43, 142.28, 198.90. Found: C, 81.35; H, 7.06%. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81%.

5.6. Procedure for ring opening of 2-methylcyclopropyl ketones with Et_2AlI

To a solution of 2-methylcyclopropyl phenyl ketone (**8**, 0.15 g, 0.91 mmol) and benzaldehyde (0.12 g, 1.1 mmol) in hexane/ether (5 mL/5 mL) was added a hexane solution of Et_2AlI (1.8 mL, 1.0 M, 1.8 mmol) at 0°C. The reaction mixture was stirred for 80 min. The mixture was poured into saturated aqueous ammonium chloride. The mixture was extracted with ether (20 mL×3) and organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration and purification by silica gel chromatography afforded (1*R**,2*R**,3*R**)-3-hydroxy-2-(3′-iodoprop-2′-yl)-1,3-diphenyl-1-propanone (**13**, 0.26 g, 0.65 mmol, 97/3 isomeric mixture) in 72% yield: IR (neat) 3464, 2954, 1658, 1450, 1199, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, J=6.3 Hz, 3H), 2.00 (dddq, J=3.3, 3.9, 9.0, 6.3 Hz, 1H), 3.41 (dd, J=3.3, 10.2 Hz, 1H), 3.70 (dd, J=3.9, 10.2 Hz, 1H), 3.89 (dd, J=3.6, 9.0 Hz, 1H), 4.24 (s, 1H), 5.11 (d, J=3.6 Hz, 1H), 7.00–8.00 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 17.62, 19.38, 33.28, 55.99, 72.59, 125.28, 127.30, 128.17, 128.27, 128.47, 133.57, 138.21, 142.18, 206.40. Cyclization of **13** with active alumina gave **14**, which was supplied for an elemental analysis.

5.6.1. (2*S,3*R**,4*S**)-3-Benzoyl-4-methyl-2-phenyltetrahydrofuran (14).** IR (neat) 2870, 1736, 1680, 1598, 1450, 1241, 1158, 755, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, J=6.9 Hz, 3H), 2.84 (dddq, J=6.9, 7.2, 8.1, 6.9 Hz, 1H), 3.64 (dd, J=8.1, 8.4 Hz, 1H), 3.84 (dd, J=6.9, 8.4 Hz, 1H), 4.27 (dd, J=7.2, 8.4 Hz, 1H), 5.25 (d, J=8.4 Hz, 1H), 6.94–6.99 (m, 2H), 7.01–7.06 (m, 3H), 7.32–7.37 (m, 2H), 7.44–7.50 (m, 1H), 7.66–7.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.73, 35.58, 59.53, 75.23, 82.98, 126.78, 127.63, 127.73, 128.12, 128.40, 132.84, 137.97, 139.13, 198.05. Found: C, 81.22; H, 6.75%. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81%.

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