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Diastereoselective Aldol and Reformatsky Reactions of α-Halo Carbonyl Compounds and Aldehydes Mediated by Titanium(II) Chloride

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Highly diastereoselective aldol reactions of α-bromo ketones with several aldehydes were successfully carried out by using a combination of titanium(II) chloride and copper or sodium iodide in dichloromethane–pivalonitrile at low temperature. Similarly, Reformatsky reactions of α-bromo thioester with aliphatic aldehydes proceeded to afford β-hydroxy thioesters in good yields under mild conditions.

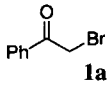
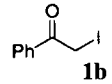
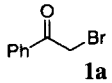
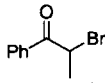
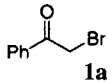
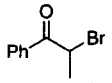
Aldol reaction is frequently employed as one of the most important synthetic tools for regioselective carbon–carbon bond formation, and many useful regio- and stereo-controlled syntheses via various metal enolates have been reported.[1] There are two general methods for the generation of active enolates from a donor carbonyl compound: that is, (1) abstraction of an acidic α-hydrogen of a donor carbonyl compound with basic metal compounds such as LDA to form the corresponding metal enolates, which in turn are converted to the appropriate metal compounds by successive transmetallation; and (2) the oxidative metallation of α-halo ketones with organometallic compounds or low-valent metals to directly generate the desired metal enolates, key intermediates of a typical Reformatsky reaction.[2] Organometallic reductants such as aluminum, lithium, boron, antimony, or manganese compounds have been employed in these reactions; however, the diastereoselectivities of the products on treatment with acceptor carbonyl compounds were rather low.[3] The Reformatsky-type reactions of α-halo carbonyl compounds were carried out by using such reductants as Sn(0),[4] Sn(II),[5] Co(0),[6] Cr(II),[7] Sm(II),[8] or In(0),[9] and high diastereoselectivities were attained under nearly neutral conditions. In the above cases, some limitations have remained in the preparation of reducing reagents or in the general applicability of reactants, carbonyl compounds. In 1998, Saigo et al. reported that the aldol and Reformatsky reactions of α-bromo carbonyl compounds gave the corresponding products with high diastereoselectivities when low-valent germanium reagent, prepared from germanium(II) iodide or germanium(IV) chloride and potassium metal, was used.[10] Also, Baba et al. recently reported that the highly diastereoselective aldol reactions of α-iodo ketones took place in aqueous media by using distannane compound.[11]

Highly diastereoselective aldol reactions of α-halo ketones and aldehydes were expected to proceed by using low-valent titanium species for the generation of titanium(IV) enolates, since they reacted with aldehydes to form the corresponding aldols with high diastereoselectivities.[1] It was already reported that the aldol reaction of α-chloro ketones and aldehydes was promoted by low-valent titanium species generated from a catalytic amount of titanium(IV) chloride and zinc; however, both yields and diastereoselectivities obtained there were rather low.[12] It was also presented that the α,β-unsaturated ketones were produced via aldol and successive dehydration reactions between 2-bromoacetophenone and various aldehydes by using titanium(IV) chloride and potassium iodide.[13] This reaction proceeded via titanium(IV) enolates under rather severe conditions, and the diastereoselectivities were not described. On the other hand, Oshima et al. reported recently that the titanium(IV) enolates were formed from either α-iodo aldehydes or α-iodo ketones by using titanium(IV) chloride and allylsilane, and the diastereoselective aldol reactions were successfully performed by treating with acceptor aldehydes.[14]

Preliminary results on the aldol and Reformatsky reactions of α-bromo ketones and α-bromo thioester with several aliphatic aldehydes by using a combination of titanium(II) chloride and copper have been reported.[15] Here, we would like to describe full details of the diastereoselective aldol and Reformatsky reactions of α-halo carbonyl compounds with various aldehydes.

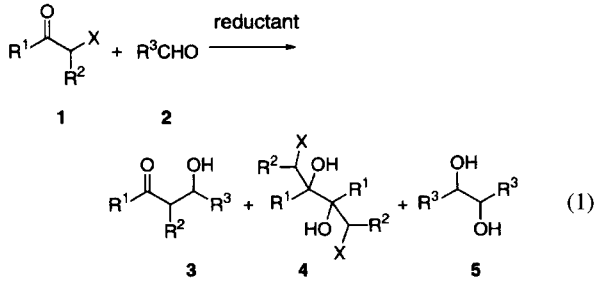
In the first place, an aldol reaction of 2-bromoacetophenone (**1a**) and benzaldehyde (**2a**) was tried by using $TiCl_2$ in dichloromethane at room temperature (Eq. 1). The desired aldol was obtained in 26% yield along with two kinds of pinacol coupling products (**4a**, 6%; **5a**, 8%) which originated from 2-bromoacetophenone and benzaldehyde under the above conditions (Table 1, entry 1). Two respective reductive generations of the titanium(IV) enolate from α-bromo ketone and of ketyl radical from aldehyde and α-bromo ketone took place with low-valent titanium species in parallel; therefore, the corresponding aldol and undesirable pinacols were competitively formed. When 2-iodoacetophenone (**1b**) was used, the desired aldol was produced in

Table 1. Aldol Reaction of α-Halo Ketones with Benzaldehyde (**2a**)[a]

Entry	α-Halo ketone	Reductant	Solvent	Temp	Yield (%)[b]		
					3 [*syn*/*anti*][c]	**4**	**5**
1	 **1a**	$TiCl_2$	CH_2Cl_2	rt.	26 [—]	6	8
2	 **1b**	$TiCl_2$	CH_2Cl_2	rt.	55 [—]	0	0
3	 **1a**	$TiCl_2$ + Zn	CH_2Cl_2	0 °C	22 [—]	16	23[d]
4	↑	$TiCl_2$ + Cu	CH_2Cl_2	−23 °C	79 [—]	0	5
5	↑	$TiCl_2$ + Cu[e]	CH_2Cl_2	−23 °C	41 [—]	0	11
6	 **1c**	$TiCl_2$ + Cu	CH_2Cl_2	−23 °C	20 [87/13]	0	6
7	↑	$TiCl_2$ + Cu	CH_2Cl_2–^{t}BuCN	−23 °C	96 [96/4]	0	3
8	↑	Cu	CH_2Cl_2–^{t}BuCN	rt.	0 [—]	0	0
9[f]	 **1a**	$TiCl_2$ + NaI	CH_2Cl_2–^{t}BuCN	rt.	79 [—]	0	1
10[f]	 **1c**	$TiCl_2$ + NaI	CH_2Cl_2–^{t}BuCN	rt.	94 [91/9]	0	2

a) Conditions: reductant/α-halo ketone/**2a** = 1/1/1. b) Isolated yields of diastereomixture based on **2a**. c) Determined by ^{1}H NMR. d) Cross pinacol coupling product from **1a** and **2a** was also obtained in 12% yield. e) $TiCl_2$/Cu = 1/0.2. f) $TiCl_2$/NaI/**1a(1c)**/**2a** = 2/2/2/1.

55% yield along with 1% of pinacol originating from benzaldehyde, where no pinacol which originated from 2-iodoacetophenone was detected (entry 2). The reaction was further tried by using 2-bromoacetophenone since α-iodo ketones were rather unstable and their syntheses and treatments had yet to be improved.



(1)

When a combination of $TiCl_2$ and Zn metal was used in the reaction of 2-bromoacetophenone and benzaldehyde, the desired aldol was obtained in 22% yield along with a mixture of pinacol coupling products formed by reductive coupling between two 2-bromoacetophenones, two benzaldehydes, or 2-bromoacetophenone and benzaldehyde. On the other hand, the aldol was obtained in 79% yield when a combination of $TiCl_2$ and Cu metal was used at −23 °C. The yield of pinacol formed from benzaldehyde there decreased down to 5% and no pinacol formed from 2-bromoacetophenone was detected (entries 3 and 4).[16] In this reaction, Cu powder did not react with $TiCl_2$ in dichloromethane while Cu disappeared immediately after adding the substrates, 2-bromoacetophenone and benzaldehyde. This suggested that Cu(0) helped the reduction of the 2-bromoacetophenone to generate enolate rather than that of benzaldehyde to form ketyl radical. In contrast, Zn powder reacted with $TiCl_2$ in the absence of the above substrates and thus formed lower (zero or one) valent titanium species reacted reductively with the substrates to form both enolates and ketyl radicals.

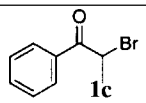
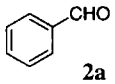
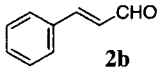
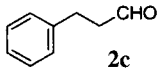
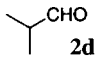
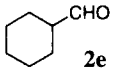
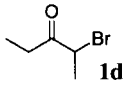
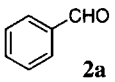
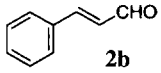
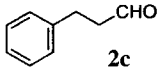
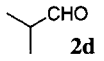
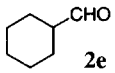
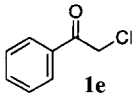
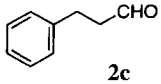
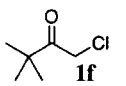
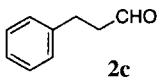
The yield of the desired aldol extremely decreased when the reaction of 2-bromopropiophenone (**1c**), a donor carbonyl compound, and benzaldehyde was tried by using $TiCl_2$ and Cu. It was reported from our laboratory that the addition of pivalonitrile was effective for low-valent titanium-promoted reductive coupling reaction of carbonyl compounds in dichloromethane.[17] The addition of pivalonitrile was also effective for the generation of enolates and the desired aldol was obtained in increased yield with higher diastereoselectivity (entries 6 and 7).[18]

Further, it was found that the aldol reaction of 2-bromoacetophenone or 2-bromopropiophenone with benzaldehyde proceeded smoothly at room temperature to produce the corresponding aldol in high yield when a combination of $TiCl_2$ and NaI was used under the above reaction conditions (Table 1, entries 9 and 10). Sodium iodide was expected to play a certain role in converting the bromide to

the corresponding iodide, and the reaction of 2-bromoacetophenone and NaI in dichloromethane–pivalonitrile at 0 °C in fact gave the 44/56 mixture of 2-bromo- and 2-iodo-acetophenone which was detected by HPLC. Additionally, it was expected to have worked also as a reductant. A combined use of iodide salts together with Lewis acid has sometimes been employed in reductive dehalogenation of α-halo carbonyl compounds.[19] In these reactions, it was assumed that metal enolates would be generated by respective attacks of iodide anion to halogen and Lewis acid to oxygen of α-halo carbonyl compounds.[5a,19] However, there are only a few cases in which the assumed intermediates, the metal enolates, were reported to have worked as donors in those aldol reactions. Fukuzawa et al. reported that a combination of $CeCl_3$ and NaI promoted the aldol reaction. On the other hand, the desired aldol was formed only in a poor yield along with a complex mixture by employing $AlCl_3$ or $TiCl_4$ instead of $CeCl_3$.[5a] As mentioned above, Lin et al. used $TiCl_4$/KI in the reaction of 2-bromoacetophenone and benzaldehyde, and the corresponding α,β-unsaturated ketone was obtained in moderate yield (65%) even at a high temperature (70 °C).[13] It was found now that the corresponding enolates were smoothly generated from α-iodo ketones by treating with titanium(II) chloride and thus the reaction was effectively improved compared to the cases of using $TiCl_4$.

The yields and ratios of products as well as the yields of side products, i.e. pinacols originating from aldehydes, are summarized in Table 2. Both aromatic and aliphatic α-bromo ketones reacted smoothly with acceptor aliphatic aldehydes to give the corresponding aldol products in good yields with good *syn* diastereoselectivities when a combination of $TiCl_2$ and Cu was used (entries 3—5, 8—10). The reaction

Table 2. Aldol Reaction of α-Bromo Ketones with Aldehyde

Entry	α-Bromo ketone	Aldehyde	Yield (%)			
			$TiCl_2$ + Cu		$TiCl_2$ + NaI	
			3 [*syn*/*anti*][a]	**5**	**3** [*syn*/*anti*][a]	**5**
1	 **1c**	 **2a**	96 [96/4]	3	94 [91/9]	2
2		 **2b**	89 [91/9]	11	74 [90/10]	9
3		 **2c**	94 [91/9]	N.D.	74 [85/15]	N.D.
4		 **2d**	84 [84/16]	N.D.		
5		 **2e**	92 [85/15]	N.D.		
6	 **1d**	 **2a**	89 [89/11]	10	75 [78/22]	6
7		 **2b**	70 [85/15]	22	44 [85/15]	9
8		 **2c**	89 [83/17]	N.D.	70 [75/25]	N.D.
9		 **2d**	76 [73/27]	N.D.		
10		 **2e**	90 [75/25]	N.D.		
11	 **1e**	 **2c**	60 [—]	N.D.	49 [—]	N.D.
12	 **1f**	 **2c**	31 [—]	12		

a) Determined by ^{1}H NMR.

of α-bromo ketones and benzaldehyde or cinnamaldehyde, an acceptor, proceeded to give the corresponding aldols as major products with high diastereoselectivities along with a small amount of pinacol coupling products originating from the aldehydes (entries 1, 2, 6, and 7). The combination of $TiCl_2$/Cu or $TiCl_2$/NaI also promoted this aldol reaction when α-chloro ketones were used as donor carbonyl compounds (entries 11 and 12).

The reactions of 2-bromopropiophenone and several aldehydes also proceeded to give the corresponding aldols with high diastereoselectivities when $TiCl_2$ and NaI were used. However, the yields remained rather low by using 2-bromo-3-pentanone as a donor.

The reasons for these high diastereoselectivities mentioned above could be explained by considering the geometrical selectivity in a reduction step and the diastereofacial selectivity in a coupling step described in similar reactions using other reductants (Fig. 1).[20] Firstly, low-valent titanium species ($TiCl_2$ or its complex with Cu) reduced α-halo ketone to generate coordinated transition state consisting of low-valent titanium species, the carbonyl oxygen and halogen. In this step, *Z*-enolate would be generated preferentially because the structure **A** is more preferable compared to **B** due to the steric repulsion between methyl and R^1 groups. When an acceptor aldehyde approaches this *Z*-enolate, *syn* aldol was produced preferentially via a chair-form six-membered cyclic transition state in which the substituent (R^2) of the coming aldehyde takes the quasi equatorial position. Pivalonitrile would coordinate to the titanium atom in this six-membered cyclic transition state and the diastereofacial selectivity would further increase due to its steric effect.

Reformatsky reactions of ethyl iodoacetate and 3-phenylpropanal by using $TiCl_2$ and Cu did not proceed at all, instead 1,3-dioxolane was obtained in 59% yield by acetalization of the undesirable pinacol with the unreacted 3-phenylpropanal (Table 3, entry 1). On the other hand, the reaction of *S*-ethyl 2-bromopropanethioate and aliphatic aldehydes gave the corresponding β-hydroxy thioesters in moderate to good yields (entries 2—4). When a combination of $TiCl_2$ and NaI was employed, the reaction proceeded smoothly to afford β-hydroxy thioesters in higher yields and the amount of pinacol originating from benzaldehyde decreased.

Thus, the highly diastereoselective aldol reactions of α-bromo ketones with various aldehydes was effectively achieved by using a combination of $TiCl_2$/Cu or $TiCl_2$/NaI. Similarly, Reformatsky-type reactions of α-bromo thioester with aliphatic aldehydes took place by using the same reagents to afford β-hydroxy thioesters in good to high yields with moderate diastereoselectivities.

Experimental

General. Melting points were recorded on a Yanaco MP-S3 micro melting point apparatus. Elemental analyses were performed by Mitsui Chemical Analysis & Consulting Service Inc, Kanagawa, Japan. FT-IR spectra were recorded on a Horiba FT-300 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270L, a JEOL JNM-LA400, and a JEOL JNM-LA500 spectrometers using tetramethylsilane (TMS) or chloroform-*d* ($CDCl_3$) as internal standard. The following abbreviations are used for ^{13}C NMR spectra: *s* = *syn* isomer, *a* = *anti* isomer. High-resolution mass spectra were recorded on a JEOL JMS-SX102A instrument with 4-nitrobenzyl alcohol as a matrix. Thin-layer chromatography used routinely for purification and separation of product mixtures was performed on Wakogel B5F. Analytical thin-layer chromatography was performed using E. Merck 0.25

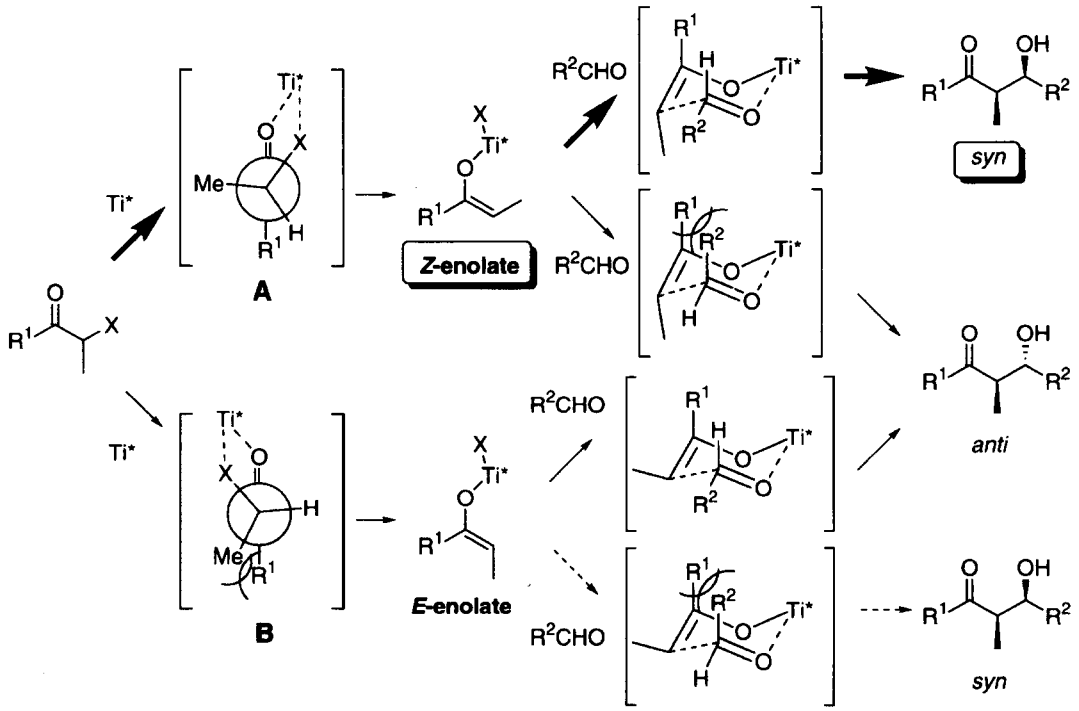
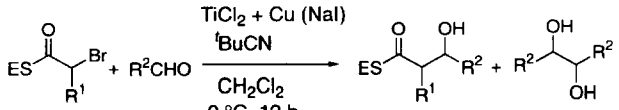
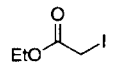
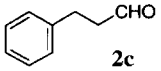
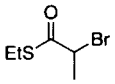
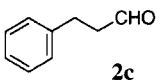
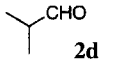
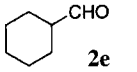
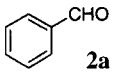


Fig. 1.

Table 3. Reformatsky-Type Reaction of α-Halo Esters with Aldehydes



Entry	α-Bromo ester	Aldehyde	Yield (%)			
			$TiCl_2$ + Cu		$TiCl_2$ + NaI	
			7 [*syn*/*anti*][a]	5	7 [*syn*/*anti*][a]	5
1	 **6a**	 **2c**	N.D.	59[b]	N.D.	N.D.
2	 **6b**	 **2c**	69 [74/26]	2	71 [79/21]	N.D.
3		 **2d**	74 [64/36]	N.D.		
4		 **2e**	81 [63/37]	N.D.		
5		 **2a**	21 [82/18]	76	43 [83/17]	47

a) Determined by ^{1}H NMR. b) Obtained as 1,3-dioxolane from a pinacol and another aldehyde.

mm silica gel 60 F_{254} plates, and visualization was accomplished with ethanolic phosphomolybdic acid. All reactions were carried out under argon atmosphere in dried glassware.

The ratio of 2-bromo- and 2-iodo-acetophenone was determined by HPLC analysis (detection: UV 254 nm) using 4.6×250 mm Shodex SIL-5B column equipped with Hitachi LC-6200 HPLC system (retention time: 43.4 min for iodide, 44.1 min for bromide).

Dichloromethane and pivalonitrile were distilled from diphosphorus pentaoxide, then calcium hydride, and dried over MS 4A. All aldehydes and α-halo ketones were purchased from Tokyo Kasei Kogyo, Kanto Chemical, Aldrich Chemical, or Merck, and used after purification by distillation or recrystallization. *S*-Ethyl 2-bromopropanethioate was prepared following the literature procedure.[21]

Titanium(II) chloride was prepared according to the literature procedure.[22] (Anal. Found: Ti, 39.89; Cl, 59.28%. Calcd for $TiCl_2$: Ti, 40.31; Cl, 59.69%) Zinc powder (Kanto Chemical) was activated by 1 M HCl (M = mol dm^{-3}), washed with distilled water and ether successively, and dried over in vacuo. Copper powder was purchased from Soekawa Chemical and used as received. Sodium iodide was dried in vacuo.

General Procedure for Aldol Reaction of α-Bromo Ketones and Aldehydes with $TiCl_2$ and Cu. To a suspension of $TiCl_2$ (0.4 mmol) and Cu powder (0.5 mmol) in CH_2Cl_2 (0.8 mL) was added ^{t}BuCN (1.6 mmol) under argon atmosphere at room temperature. After the resulting black and brown suspension was cooled down to −78 °C, a solution of α-bromo ketone (0.3 mmol) in CH_2Cl_2 (0.5 mL) and a solution of aldehyde (0.3 mmol) in CH_2Cl_2 (0.5 mL) were successively added dropwise. The mixture was warmed up to −23 °C and stirred for 3 h. Phosphate buffer (pH 7) was added and the precipitate was removed by filtration, and then the filtrate was separated. The aqueous layer was extracted with ether (3 mL×3), and the combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by TLC to afford the β-hydroxy ketone.

General Procedure for Aldol Reaction of α-Bromo Ketones and Aldehydes with $TiCl_2$ and NaI. To a suspension of NaI (1.0 mmol) in CH_2Cl_2 (2.0 mL) and ^{t}BuCN (8.0 mmol) was added α-bromo ketone (1.0 mmol) and the mixture was stirred for 0.5 h under argon atmosphere at room temperature. After the resulting yellow suspension was cooled down to −78 °C, $TiCl_2$ (1.0 mmol) was added through the powder inlet attached to the reaction apparatus and the mixture was stirred for 0.5 h, and then a solution of aldehyde (0.5 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. The mixture was warmed up to room temperature and stirred for 2 h. The same work up as described above gave the β-hydroxy ketone.

3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (Table 2, entry 1):[23] (*Syn*/*anti* = 96/4) ^{1}H NMR δ = 1.07 (d, 0.12H, J = 7.2 Hz), 1.19 (d, 2.88H, J = 6.9 Hz), 3.10 (br, 0.04H), 3.65 (br, 0.96H), 3.70 (dq, 0.96H, J = 6.9, 3.1 Hz), 3.70 (dq, 0.04H, J = 7.2, 8.0 Hz), 4.98 (d, 0.04H, J = 8.0 Hz), 5.24 (d, 0.96H, J = 3.1 Hz), 7.23—7.61 (m, 8H), 7.92—7.96 (m, 2H); ^{13}C NMR δ = 11.2 (*s*), 15.6 (*a*), 47.0 (*s*), 47.9 (*a*), 73.1 (*s*), 76.7 (*a*), 126.0 (*s*), 126.7 (*a*), 127.2 (*s*), 127.8 (*a*), 128.2 (*s*), 128.38 (*s*), 128.40 (*a*), 128.44 (*a*), 128.6 (*a*), 128.7 (*s*), 133.2 (*a*), 133.5 (*s*), 135.6 (*s*), 136.7 (*a*), 141.8 (*s*), 142.2 (*a*), 204.8 (*a*), 205.6 (*s*).

(*E*)- 3- Hydroxy- 2- methyl- 1, 5- diphenyl- 4- penten- 1- one (Table 2, entry 2):[24] (*Syn*/*anti* = 91/9) ^{1}H NMR δ = 1.30 (d, 3H, J = 7.3 Hz), 3.12 (br, 0.09H), 3.45 (br, 0.91H), 3.60—3.69 (m, 1H), 4.60 (m, 0.09H), 4.77 (d, 0.91H, J = 5.6 Hz), 6.24 (dd, 0.91H, J = 5.6, 15.9 Hz), 6.27 (dd, 0.09H, J = 7.1, 15.8 Hz), 6.70 (d, 1H, J = 15.9 Hz), 7.19—7.58 (m, 8H), 7.95 (m, 2H); ^{13}C NMR δ = 11.8 (*s*), 15.2 (*a*), 45.4 (*s*), 46.2 (*a*), 72.2 (*s*), 75.1 (*a*), 126.37 (*s*), 126.44 (*a*), 127.5 (*s*), 127.7 (*a*), 128.35 (*a*), 128.39 (*s*, *a*), 128.43 (*s*), 128.6

(*a*), 128.7 (*s*), 129.2 (*s*), 129.6 (*a*), 130.9 (*s*), 131.9 (*a*), 133.2 (*a*), 133.4 (*s*), 135.8 (*s*), 136.4 (*a*), 136.5 (*a*), 136.6 (*s*), 204.6 (*a*), 205.1 (*s*).

3-Hydroxy-2-methyl-1,5-diphenyl-1-pentanone (Table 2, entry 3):[25] (*Syn*/*anti* = 91/9) ^{1}H NMR δ = 1.22 (d, 0.27H, J = 7.1 Hz), 1.26 (d, 2.73H, J = 7.1 Hz), 1.66—1.74 (m, 1H), 1.89—1.99 (m, 1H), 2.66—2.74 (m, 1H), 2.86—2.93 (m, 1H), 3.32 (br, 1H), 3.40—3.46 (m, 1H), 3.83—3.90 (m, 0.09H), 4.05—4.09 (m, 0.91H), 7.15—7.29 (m, 5H), 7.43—7.47 (m, 2H), 7.54—7.58 (m, 1H), 7.88—7.94 (m, 2H); ^{13}C NMR δ = 11.2 (*s*), 15.5 (*a*), 32.2 (*a*), 32.4 (*s*), 36.1 (*s*), 36.8 (*a*), 44.7 (*s*), 45.8 (*a*), 70.7 (*s*), 73.4 (*a*), 125.8 (*a*), 125.9 (*s*), 128.26 (*a*), 128.39 (*s*), 128.43 (*s*, *a*), 128.47 (*s*, *a*), 128.7 (*s*, *a*), 133.2 (*a*), 133.5 (*s*), 135.7 (*s*), 136.5 (*a*), 141.9 (*s*), 142.0 (*a*), 205.7 (*a*), 205.8 (*s*).

3-Hydroxy-2,4-dimethyl-1-phenyl-1-pentanone (Table 2, entry 4):[26] (*Syn*/*anti* = 84/16) ^{1}H NMR δ = 0.94 (d, 0.48H, J = 6.8 Hz), 0.96 (d, 2.52H, J = 6.8 Hz), 1.00 (d, 0.48H, J = 6.9 Hz), 1.03 (d, 0.48H, J = 6.6 Hz), 1.25 (d, 2.52H, J = 7.1 Hz), 1.27 (d, 0.48H, J = 7.6 Hz), 1.74—1.82 (m, 1H), 3.00—3.04 (m, 0.16H), 3.10—3.17 (m, 0.84H), 3.60—3.72 (m, 2H), 7.47—7.61 (m, 3H), 7.91—7.98 (m, 2H); ^{13}C NMR δ = 10.8 (*s*), 15.9 (*a*), 16.9 (*a*), 18.9 (*s*), 19.1 (*s*), 19.9 (*a*), 30.7 (*s*), 31.2 (*a*), 41.8 (*s*), 42.4 (*a*), 76.6 (*s*), 79.1 (*a*), 128.3 (*a*), 128.4 (*s*), 128.67 (*a*), 128.72 (*s*), 133.1 (*a*), 133.3 (*s*), 135.8 (*s*), 136.6 (*a*), 205.7 (*s*), 206.2 (*a*).

3-Cyclohexyl-3-hydroxy-2-methyl-1-phenyl-1-propanone (Table 2, entry 5):[23] (*Syn*/*anti* = 85/15) ^{1}H NMR δ = 0.93—1.33 (m, 5H), 1.23 (d, 2.55H, J = 7.1 Hz), 1.28 (d, 0.45H, J = 7.3 Hz), 1.44—1.51 (m, 1H), 1.65—1.79 (m, 4H), 1.99 (d, 0.15H, J = 12.6 Hz), 2.10 (d, 0.85H, J = 12.9 Hz), 3.18 (br, 1H), 3.56—3.58 (m, 0.15H), 3.65—3.74 (m, 1.85H), 7.46—7.50 (m, 2H), 7.56—7.60 (m, 1H), 7.93—7.95 (m, 2H); ^{13}C NMR δ = 10.5 (s), 16.0 (*a*), 25.8 (*s*), 26.0 (*s*), 26.2 (*a*), 26.3 (*s*), 26.4 (*a*), 27.5 (*a*), 29.17 (*s*), 29.21 (*a*), 29.3 (*s*), 30.1 (*a*), 40.1 (*s*), 41.2 (*a*), 41.3 (*s*), 41.6 (*a*), 75.4 (*s*), 78.7 (*a*), 128.2 (*a*), 128.3 (*s*), 128.6 (*a*), 128.7 (*s*), 133.2 (*s*), 133.3 (*a*), 135.8 (*s*), 136.5 (*a*), 205.7 (*s*), 206.3 (*a*).

1-Hydroxy-2-methyl-1-phenyl-3-pentanone (Table 2, entry 6):[23] (*Syn*/*anti* = 89/11) ^{1}H NMR δ = 0.91 (d, 0.33H, J = 7.2 Hz), 0.98 (t, 2.67H, J = 7.1 Hz), 1.03 (t, 0.33H, J = 7.2 Hz), 1.08 (d, 2.67H, J = 7.2 Hz), 2.23—2.34 (m, 1H), 2.37—2.55 (m, 1H), 2.79—2.87 (m, 0.89H), 2.90—2.95 (m, 0.11H), 3.12 (br, 0.11H), 3.25 (br, 0.89H), 4.72 (d, 0.11H, J = 8.2 Hz), 5.01 (d, 0.89H, J = 4.2 Hz), 7.21—7.35 (m, 5H); ^{13}C NMR δ = 7.3 (*a*), 7.4 (*s*), 10.6 (*s*), 14.3 (*a*), 35.4 (*s*), 36.4 (*a*), 52.3 (*s*), 52.6 (*a*), 73.3 (*s*), 76.6 (*a*), 125.9 (*s*), 126.5 (*a*), 127.3 (*s*), 127.8 (*a*), 128.2 (*s*), 128.4 (*a*), 141.8 (*s*), 142.2 (*a*), 216.0 (*a*), 216.1 (*s*).

(*E*)-5-Hydroxy-4-methyl-7-phenyl-6-hepten-3-one (Table 2, entry 7):[23] (*Syn*/*anti* = 85/15) ^{1}H NMR δ = 1.05 (t, 2.55H, J = 7.3 Hz), 1.06 (t, 0.45H, J = 7.2 Hz), 1.10 (d, 0.45H, J = 7.3 Hz), 1.17 (d, 2.55H, J = 7.1 Hz), 2.45—2.62 (m, 2H), 2.73—2.79 (m, 1H), 2.79 (br, 0.15H), 3.04 (br, 0.85H), 4.37 (t, 0.15H, J = 7.1 Hz), 4.60 (t, 0.85H, J = 4.4 Hz), 6.15 (dd, 0.85H, J = 6.1, 15.8 Hz), 6.17 (dd, 0.15H, J = 8.6, 15.9 Hz), 6.58 (d, 0.15H, J = 15.9 Hz), 6.62 (d, 0.85H, J = 15.8 Hz), 7.21—7.38 (m, 5H); ^{13}C NMR δ = 7.48 (*a*), 7.54 (*s*), 11.1 (*s*), 14.2 (*a*), 35.5 (*s*), 36.3 (*a*), 50.5 (*s*), 51.2 (*a*), 72.5 (*s*), 75.1 (*a*), 126.47 (*s*), 126.53 (*a*), 127.7 (*s*), 127.8 (*a*), 128.56 (*s*), 128.59 (*a*), 129.1 (*s*), 129.7 (*a*), 131.1 (*s*), 132.0 (*a*), 136.4 (*a*), 136.6 (*s*), 215.77 (*a*), 215.84 (*s*).

5-Hydroxy-4-methyl-7-phenyl-3-heptanone (Table 2, entry 8):[23] (*Syn*/*anti* = 83/17) ^{1}H NMR δ = 1.03 (t, 3H, J = 7.3 Hz), 1.11 (d, 0.51H, J = 7.3 Hz), 1.14 (d, 2.49H, J = 7.1 Hz), 1.55—1.87 (m, 2H), 2.38—2.68 (m, 4H), 2.80—2.87 (m, 1H), 3.01 (br, 1H), 3.64—3.78 (m, 0.17H), 3.92 (m, 0.83H), 7.16—7.20 (m, 3H), 7.26—7.29 (m, 2H); ^{13}C NMR δ = 7.4 (*a*), 7.5 (*s*), 10.1 (*s*), 14.2 (*a*), 31.9 (*a*), 32.2 (*s*), 35.0 (*s*), 35.7 (*s*), 36.0 (*a*), 36.6 (*a*), 50.0 (*s*), 51.0 (*a*), 70.3 (*s*), 73.0 (*a*), 125.76 (*a*), 125.79 (*s*), 128.2 (*a*), 128.31 (*s*), 128.37 (*s*), 128.40 (*a*), 141.8 (*s*), 141.9 (*a*), 216.6 (*s*), 216.8 (*a*).

5-Hydroxy-4,6-dimethyl-3-heptanone (Table 2, entry 9):[3f,27] (*Syn*/*anti* = 73/27) ^{1}H NMR δ = 0.86 (d, 2.19H, J = 6.8 Hz), 0.91 (d, 0.81H, J = 6.6 Hz), 0.95 (d, 0.81H, J = 6.8 Hz), 1.02 (d, 2.19H, J = 6.6 Hz), 1.05 (t, 0.81H, J = 7.3 Hz), 1.06 (t, 2.19H, J = 7.3 Hz), 1.11 (d, 0.81H, J = 7.1 Hz), 1.12 (d, 2.19H, J = 7.1 Hz), 1.62—1.76 (m, 1H), 2.45—2.63 (m, 2H), 2.72—2.81 (m, 1H), 2.86 (br, 1H), 3.45 (d, 0.26H, J = 5.2 Hz), 3.52 (d, 0.76H, J = 7.9 Hz); ^{13}C NMR δ = 7.4 (*a*), 7.6 (*s*), 14.5 (*s*), 15.9 (*a*), 18.9 (*s*), 19.0 (*s*), 19.9 (*a*), 30.5 (*s*, *a*), 34.8 (*s*), 36.1 (*a*), 47.1 (*s*), 48.0 (*a*), 76.3 (*s*), 78.4 (*a*), 216.8 (*s*), 217.1 (*a*).

1-Cyclohexyl-1-hydroxy-2-methyl-3-pentanone (Table 2, entry 10):[27] (*Syn*/*anti* = 75/25) ^{1}H NMR δ = 0.92—1.00 (m, 2H), 1.05 (t, 0.75H, J = 7.3 Hz), 1.06 (t, 2.25H, J = 7.3 Hz), 1.11 (d, 2.25H, J = 7.0 Hz), 1.12 (d, 0.75H, J = 7.0 Hz), 1.14—1.39 (m, 4H), 1.56—1.78 (m, 4H), 2.43—2.62 (m, 2H), 2.70—2.83 (m, 1.25H), 2.84 (br, 0.75H), 3.43 (dd, 0.25H, J = 6.8, 5.1 Hz), 3.59 (d, 0.75H, J = 8.2 Hz); ^{13}C NMR δ = 7.4 (*a*), 7.6 (*s*), 9.3 (*s*), 14.5 (*a*), 25.8 (*a*), 25.97 (*s*), 26.03 (*a*), 26.27 (*s*), 26.33 (*s*, *a*), 26.6 (*a*), 28.9 (*s*), 29.3 (*s*), 30.2 (*a*), 34.7 (*s*), 36.0 (*a*), 40.0 (*s*), 40.7 (*a*), 46.7 (*s*), 47.3 (*a*), 75.1 (*s*), 78.1 (*a*), 216.7 (*s*), 217.2 (*a*).

3-Hydroxy-1,5-diphenyl-1-pentanone (Table 2, entry 11):[28] ^{1}H NMR δ = 1.67—1.93 (m, 2H), 2.65—2.86 (m, 2H), 2.93—3.11 (m, 2H), 3.31 (br, 1H), 4.11—4.20 (m, 1H), 7.02—7.22 (m, 5H), 7.35—7.40 (m, 2H), 7.46—7.51 (m, 1H), 7.83—7.86 (m, 2H); ^{13}C NMR δ = 31.8, 38.1, 45.0, 67.0, 125.8, 128.0, 128.36, 128.44, 128.6, 133.5, 136.6, 141.9, 200.8.

5-Hydroxy-2,2-dimethyl-7-phenyl-3-heptanone (Table 2, entry 12):[28] ^{1}H NMR δ = 1.13 (s, 9H), 1.63—1.75 (m, 1H), 1.78—1.90 (m, 1H), 2.52—2.89 (m, 4H), 3.36 (br, 1H), 4.01 (m, 1H), 7.14—7.30 (m, 5H); ^{13}C NMR δ = 26.2, 31.8, 38.0, 43.0, 44.3, 67.0, 125.8, 128.35, 128.44, 141.9, 217.8.

***S*-Ethyl 3-hydroxy-2-methyl-3-phenylpropanethioate** (Table 3, entry 5):[29] (*Syn*/*anti* = 82/18) ^{1}H NMR δ = 1.02 (d, 0.54H, J = 7.1 Hz), 1.16 (d, 2.46H, J = 7.1 Hz), 1.22 (t, 2.46H, J = 7.6 Hz), 1.26 (t, 0.54H, J = 7.3 Hz), 2.82—3.01 (m, 4H), 4.82 (d, 0.18H, J = 4.9 Hz), 5.11 (d, 0.82H, J = 2.5 Hz), 7.25—7.38 (m, 5H); ^{13}C NMR δ = 11.3 (*s*, *a*), 14.5 (*s*), 15.5 (*a*), 23.25 (*s*), 23.34 (*a*), 54.9 (*s*), 55.4 (*a*), 73.7 (*s*), 77.2 (*a*), 126.0 (*s*), 126.6 (*a*), 127.5 (*s*), 128.1 (*a*), 128.2 (*s*), 128.5 (*a*), 141.1 (*a*), 147.9 (*s*), 204.1 (*a*), 204.2 (*s*).

***S*-Ethyl 3-hydroxy-2-methyl-5-phenylpentanethioate** (Table 3, entry 2):[30] (*Syn*/*anti* = 74/26) ^{1}H NMR δ = 1.22 (d, 0.78H, J = 7.0 Hz), 1.23 (d, 2.22H, J = 7.0 Hz), 1.24 (t, 2.22H, J = 6.4 Hz), 1.25 (t, 0.78H, J = 6.4 Hz), 1.66—1.83 (m, 2H), 2.57 (br, 1H), 2.62—3.00 (m, 5H), 3.69—3.71 (m, 0.26H), 3.92—3.93 (m, 0.74H), 7.16—7.20 (m, 3H), 7.24—7.29 (m, 2H); ^{13}C NMR δ = 11.6, 14.5, 15.2, 23.16, 23.22, 28.1, 31.9, 32.2, 35.8, 36.7, 45.2, 53.0, 53.6, 71.3, 73.2, 125.82, 125.84, 128.35, 128.39, 128.42, 128.5, 141.7, 141.8, 204.18, 204.23; IR (neat) 3490, 2930, 1670, 1450, 960 cm^{-1}; FAB HRMS Calcd for $C_{14}H_{21}O_2S$: $[M+H]^+$, 253.1252. Found: *m*/*z* 253.1260.

***S*-Ethyl 3-hydroxy-2,4-dimethylpentanethioate** (Table 3, entry 3):[29] (*Syn*/*anti* = 64/36) ^{1}H NMR δ = 0.88 (d, 1.92H, J = 6.8 Hz), 0.93 (d, 1.08H, J = 6.6 Hz), 0.97 (d, 1.08H, J = 6.6 Hz), 1.01 (d, 1.92H, J = 6.6 Hz), 1.21 (d, 1.92H, J = 7.1 Hz), 1.24 (d, 1.08H, J = 7.3 Hz), 1.26 (t, 3H, J = 7.4 Hz), 1.66—1.77 (m, 1H), 2.46 (br, 1H), 2.80—2.92 (m, 3H), 3.40 (t, 0.36H, J = 7.4 Hz), 3.58 (t, 0.64H, J = 4.9 Hz); ^{13}C NMR δ = 11.2 (*s*), 14.57 (*a*), 14.59 (*s*), 15.8 (*a*),

16.6 (*a*), 18.4 (*s*), 19.1 (*s*), 19.8 (*a*), 23.17 (*a*), 23.22 (*s*), 30.6 (*s*), 31.2 (*a*), 50.5 (*s*), 50.9 (*a*), 77.0 (*a*), 78.9 (*s*), 204.6 (*s*), 204.7 (*a*).

S- Ethyl 3- cyclohexyl- 3- hydroxy- 2- methylpropanethioate (Table 3, entry 4):[29] (*Syn*/*anti* = 63/37) ^{1}H NMR δ = 0.97—1.10 (m, 2H), 1.19 (d, 3H, J = 6.8 Hz), 1.26 (t, 3H, J = 7.3 Hz), 1.12—1.42 (m, 4H), 1.54—2.07 (m, 5H), 2.49 (br, 1H), 2.80—2.92 (m, 3H), 3.43 (d, 0.37H, J = 5.9 Hz), 3.63 (d, 0.63H, J = 3.2, 7.6 Hz); ^{13}C NMR δ = 10.9 (*s*), 14.5 (*a*), 14.6 (*s*), 15.9 (*a*), 23.1 (*s*), 23.2 (*a*), 25.8 (*s*), 25.9 (*a*), 26.0 (*s*), 26.2 (*a*), 26.26 (*s*), 26.30 (*a*), 27.2 (*a*), 28.8 (*s*), 29.1 (*s*), 30.0 (*a*), 40.1 (*s*), 41.2 (*a*), 49.9 (*s*), 50.2 (*a*), 75.9 (*s*), 78.3 (*a*), 204.6 (*s*), 204.7 (*a*).

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