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Anti-selective and regioselective aldol addition of ketones with aldehydes using MgI_2 as promoter

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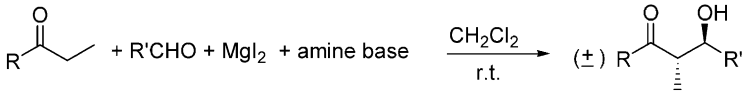
Abstract—The first example of a direct aldehyde–ketone coupling using the secondary amine piperidine as base in the presence of MgI_2 to generate high selectivity of anti-aldol products from unmodified ethyl ketones in high yield is reported. The coupling reactions were carried out in a one-pot reaction by mixing four reaction components at room temperature. In the case of unsymmetrical ketones, addition was made to the less hindered α-side.

1. Introduction

The stereoselective synthesis of anti-aldol products from unmodified ethyl ketones is of great interest to organic chemists,[1] especially in the area of natural product synthesis. Several methodologies have been reported that use boron reagents or metal complexes in the presence of a tertiary amine to convert unmodified ethyl ketones to enolates that then react with aldyhydes to form anti-aldol products. For example, the use of dicyclohexylboron chloride and triethylamine produce high selectivity for *E*-enolates and correspondingly high selectivity for the anti-aldol products;[2] this two step process requires hydrogen peroxide oxidation of the boron intermediate to obtain free aldol products. An alternative aldol coupling reaction eliminated this oxidation step by using ytterbium trifluoromethanesulfonate and a tertiary amine;[3] however, high anti-aldol products were produced only when sterically hindered aldehydes such as trimethylacetaldehyde were employed as the electrophilic acceptor. $TiCl_4$ has also been used as a reaction promoter with a tertiary amine;[4] however only when special unmodified ketones were used could high anti-aldol product ratios be realized. All of the previously mentioned approaches have their individual weaknesses, some of which include long reaction times, using air and moisture-sensitive reagents,[2] two step reactions that require enolate to be formed before aldehyde can be added,[2–4] and the random *anti*/*syn* selectivity of products.[3,4] Because of these weaknesses, the development of a general method for synthesizing anti-aldol products from unmodified ethyl ketones is needed.

Here we describe a direct method for the stereoselective coupling of aromatic and non-aromatic aldehydes with unmodified ethyl ketones to generate anti-aldol products. In the presence of stoichiometric quantities of MgI_2, the reaction of ethyl ketones with aldehydes at room temperature results in high yields of anti-3-hydroxy ketones (Scheme 1). In the case of unsymmetrical ketones, addition is made to the less hindered α-side.

We have recently reported that MgI_2 is a well-suited Lewis acid for the carbon–carbon bond forming reaction during the synthesis of β-iodo Baylis–Hillman adducts.[5] MgI_2 is thought to serve as a Lewis acid as well as an iodine source for Michael-type additions of α,β-acetylenic ketones or



Scheme 1.

Keywords: Piperidine; Anti-aldol reaction; Magnesium iodide; Ethyl ketone.
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esters. The initial ketone is proposed to be converted to an active β-iodo allenolate intermediate, which in turn reacts with an aldehyde to yield β-iodo Baylis–Hillman adducts. In an attempt to broaden the scope of this reaction, MgI_2 was combined with tertiary amines to determine if such a combination would promote formation of Mg-enolates directly from the original ketone. When 1.0 equiv of benzaldehyde, MgI_2, propiophenone, and diisopropylethylamine were added at room temperature in dichloromethane the aldol product 1,3-diphenyl-3-hydroxy-2-methylpropanone was generated within 30 min with a yield of 80%. This yield was optimized to 95% by using 1.3 equiv of diisopropylethylamine, 1.2 equiv of propiophenone, and 1.0 equiv of benzaldehyde.

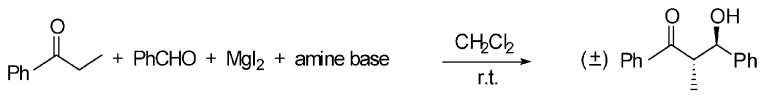
The diasteroselectivity of the initial reaction was modest (*anti*/*syn*=72/28) with negligible differences observed when the reaction temperature or solvent system was changed. Elevated reaction temperatures slightly improved the *anti*/*syn* ratio (70/30 at 0 °C and 74/26 at 40 °C) while the alternative solvents (benzene and toluene) had no effect on diasteroselectivity. Both diethyl ether and THF were unsuitable solvents, which required a reaction time of more than 10 h and gave rise to less then 10% yield within a 2 h reaction period. Other metal salts and organometallics including $MgBr_2$, $Mg(OTf)_2$, $MgCl_2$, $SnCl_4$, $Sn(OTf)_2$ was either much less active or inert. In fact, Choji Kashima[6] had already reported in 1998 using $MgBr_2$ in combination with *i*-Pr_2NEt mediates the aldol addition of *N*-acylpyrazoles to aldehydes and in some cases this system gives products with high anti-selectivity. This system was not suitable for the present reaction conditions. For example, when propiophenone was reacted with benzaldehyde in the presence of *i*-Pr_2NEt with $MgBr_2$ as the promoter, the *anti*/*syn* ratio of the product was 70/30. When piperidine was used as the amine base, less than 10% of the desired product was obtained after a 24 h period when propiophenone was reacted with benzaldehyde in the presence of $MgBr_2$ as the promoter. A survey of various tertiary amines was also met with limited success (Table 1); therefore we explored the possibility of using secondary amines as an amine base in the reaction. All of the secondary amines that were tested resulted in aldol products with increased anti-selectivity. The secondary amine piperidine proved to be the best suited for promoting the desired diastereoselectivity (Table 1).

Using the secondary amine piperidine as a base for improved selectivity, we examined various symmetric and asymmetrical ketones that can undergo an aldol reaction. In the first reaction listed, propiophenone coupled with benzaldehyde in the presence of piperidine (1.2 equiv) and MgI_2 (1.1 equiv) in a 93/7 *anti*/*syn* ratio resulted in a 35% product yield within 30 min; a 95/5 *anti*/*syn* ratio with a 91% yield was realized when the reaction was allowed to go to completion over 2 h period using 1.5 equiv piperidine and 1.4 equiv MgI_2. Other aromatic aldehydes resulted in high diasteroselectivity (entries 2, 3 and 4, Table 2) within the 2 h reaction time, although product selectivity diminished when aliphatic aldehydes were employed (entries 5 and 6, Table 2). The anti-product was exclusively obtained when the bulkier aliphatic aldehyde trimethylacetaldehyde was used as an electrophilic acceptor (entry 7, Table 2). Cyclohexanone gave modest diasteroselectivity (entry 8 and 9, Table 2). The relatively low diasteroselectivity was also observed when 3-pentanone was reacted with benzaldehyde (entry 10, Table 2).

With regard to unsymmetrical ketones, both piperidine and the tertiary amines *N*,*N*-diisopropylethylamine and *N*-ethylpiperidine are well suited for producing aldol products with the same ratio of regioselectivity. However, in order to obtain reasonable yields, longer reaction times (2 h) and higher MgI_2 loading (1.4 equiv) are needed when piperidine is used as the base for the reaction. For example, the reaction of 3-methyl-2-butanone (1.4 equiv) with benzaldehyde (1.0 equiv) in the presence of MgI_2 (1.4 equiv) and piperidine (1.5 equiv) required 2 h for completion at room temperature with an 85% yield of expected products and regioselectivity 100:0. However, the same reaction took only 30 min to complete when *N*,*N*-diisopropylethylamine or *N*-ethylpiperidine was used in place of piperidine as the base for the reaction. Another advantage for using *N*,*N*-diisopropylethylamine or *N*-ethylpiperidine as the base for the reaction is that the amount of MgI_2 and starting ketone can be reduced to 1.2 equiv with no decrease in yield (entry 11–16, Table 3).

The *anti*/*syn* selectivities listed in Table 2 were measured by ^1H NMR spectroscopic analyses of the crude product mixture. In all cases, the carbinol proton signals for *anti* and *syn*-isomers were clearly distinguishable with the proton for

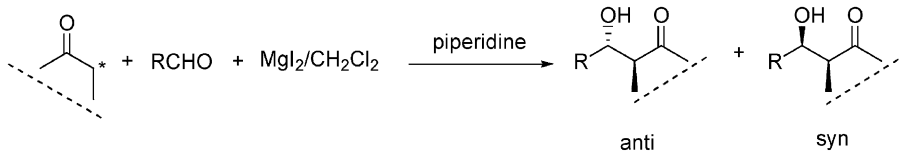
Table 1. Effect of amine bases for *anti*/*syn* selectivity

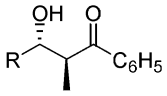
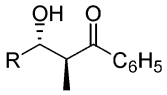
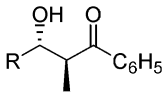
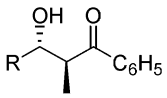
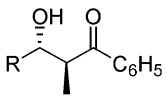
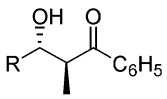
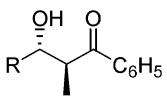
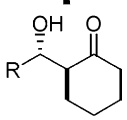
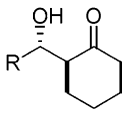
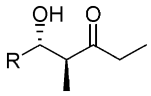


Entry	Amine base	Reaction time (min)	*anti*/*syn* selectivity[a]	Yield[b] (%)
1	Et_3N	30	72/28	90
2	*i*-Pr_2NEt	30	73/27	95
3	Bu_3N	30	76/24	92
4	*N*-ethylpiperidine	30	71/29	92
5	Pyrrolidine	240	82/18	50
6	2,2,6,6-Tetramethylpiperidine	30	80/20	90
7	Piperidine	120	95/5	91
8	DABCO	120	75/25	82
9	Pyridine	120	–	<10

[a] The isomeric ratio was determined by analysis of 300 MHz ^1H NMR spectra of crude products.
[b] Yields after purification by column chromatography.

Table 2. Anti-selective aldol addition of ketones with aldehydes using piperidine as base



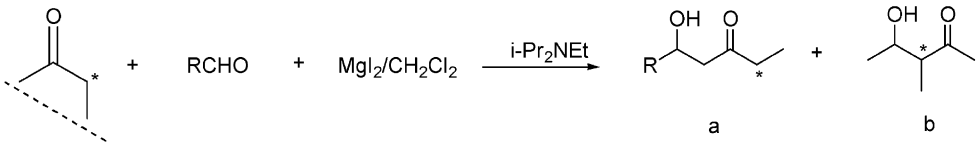
Entry	Ketone	R	Product		*anti*/*syn*[a]	Yield[b] (%)
1	Propiophenone	C_6H_5		**1**	95/5	91
2	Propiophenone	4-FC_6H_4		**2**	94/6	92
3	Propiophenone	4-BrC_6H_4		**3**	90/10	90
4	Propiophenone	4-MeC_6H_4		**4**	92/8	88
5	Propiophenone	$C_6H_5CH{=}CH$		**5**	88/12	92
6	Propiophenone	$CH_3CH{=}CH$		**6**	84/16	90
7	Propiophenone	$(CH_3)_3C$–		**7**	100/0	82
8	Cyclohexanone	C_6H_5		**8**	77/23	68
9	Cyclohexanone	4-ClC_6H_4		**9**	76/24	70
10	3-Pentanone	C_6H_5		**10**	76/24	70[c]

[a] Ratios were determined by ^{1}H NMR ($CDCl_3$, 300 MHz) on the crude products.
[b] Yields after purification by column chromatography.
[c] Two stereoisomers were inseparable.

the *anti*-isomer upfield relative to the proton for the *syn* isomer. In addition, they also appear in different vicinal coupling constants; for *anti*-isomers these numbers are approximately 8 Hz and *syn* isomers less than 5 Hz.

In order to better understand the mechanisms involved in this reaction, we designed an experiment to track the reaction intermediates. We added diisopropylethylamine (1.2 equiv) into a mixture of propiophenone (1.0 equiv) and MgI_2 (1.0 equiv) dissolved in $CDCl_3$, after stirring at room temperature for 1 h; the mixture was directly taken for ^{1}H NMR analysis. Unfortunately, the Mg-enolate was not observed due to the total formation of the propiophenone self-condensation aldol product. However, when diisopropylethylamine in the above reaction was replaced with piperidine (1.2 equiv) and stirred for 1 h at room temperature, we observed the Mg-enolate of propiophenone in its ^{1}H NMR spectrum, in which the *Z*-enolate vinyl proton showed as a quartet at δ 3.46 ppm and the *E*-enolate as a quartet at δ 4.13 ppm. The ratio of *Z*/*E* was 78/22, based on its ^{1}H NMR spectrum analysis. Also, from its ^{1}H NMR analysis, only 5 mol% of propiophenone was converted into Mg-enolate intermediate when stored at room temperature for 24 h. The reaction is therefore a 'balanced reaction' with aldehydes essential for the reaction to go to completion within 2 h. This raises an important question; can the reaction be carried out via the enamine pathway? We have experimental evidence that suggests that the reaction is more likely to follow the Mg-enolate pathway. (1) Propiophenone (1.0 equiv) and MgI_2 (1.0 equiv) were dissolved in anhydrous $CDCl_3$ and piperidine (1.2 equiv) was added via a syringe under a nitrogen atmosphere. After

Table 3. Regioselective aldol addition of unsymmetrical ketones with aldehydes using *N*,*N*-diisopropylethylamine as base



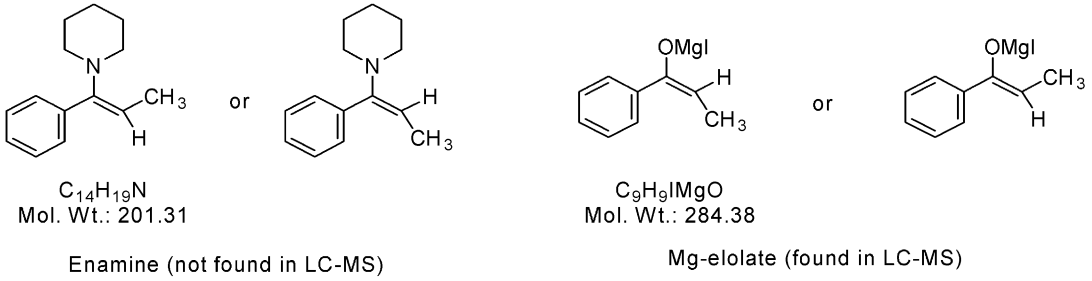
Entry	Ketone	R	Product	Ratio *a*/*b*[a]	Yield[b] (%)
11	2-Butanone	4-$PhCH_2OC_6H_4$	**11**	96/4	85
12	2-Butanone	2-Naphthyl	**12**	98/2	86
13	3-Methyl-2-butanone	C_6H_5	**13**	100/0	90
14	3-Methyl-2-butanone	2-Naphthyl	**14**	100/0	91
15	4-Phenyl-2-butanone	$C_6H_5CH{=}CH$	**15**	90/10	81[c]
16	4-Phenyl-2-butanone	4-$PhCH_2OC_6H_4$	**16**	98/2	85

[a] Ratios were determined by ^1H NMR ($CDCl_3$, 300 MHz) on the crude products.
[b] Yields after purification by column chromatography.
[c] Two regioisomers were inseparable.

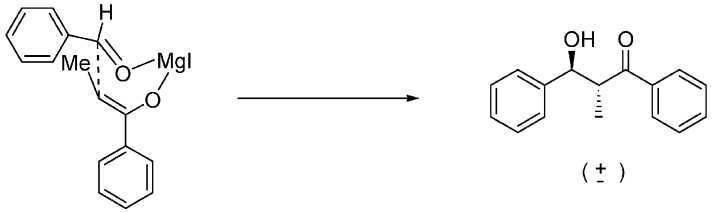
stirring 2 h at room temperature, the solution was filtered through a short silicon gel pad and the filtrate directly injected into an LC-MS. No enamine peak was observed from the LC-MS analysis (Scheme 3). (2). When piperidine was replaced with 2,2,6,6-Tetramethylpiperidine in the above reaction an Mg-enolate peak was observed with a molecular weight of 284 (Scheme 2).

Since the *Z*-enolate was formed predominantly, the well-known chair Zimmerman–Traxler transition state cannot be adopted; however, the Evans' 'boat–metal transition state'[7] can be employed to satisfactorily explain our results (Scheme 3).

In conclusion, we present here the first example of using a secondary amine as a base in combination with MgI_2 to perform direct aldehyde–ketone coupling to generate high anti-aldol products in high yield. Aldol coupling reactions were carried out in a one-pot reaction by mixing the four reaction components at room temperature under the protection of nitrogen gas. This is in contrast to the recently reported Lewis acid mediated aldol addition of



Scheme 2. LC-MS confirmed the intermediates in MgI_2 promoted anti-aldol reaction.



Scheme 3. Boat transition state for MgI_2 promoted anti-aldol reaction.

unsymmetrical ketones using $TiCl_4$[8] to generate high *syn* selective products. In fact, we observed that $TiCl_4$ as an aldol promoter was limited in its scope to stimulate aldol additions with aliphatic ketones. For example, when the aromatic ketone propiophenone was tested as a substrate to react with benzaldehyde, less than a 10% yield of the corresponding *syn* product was observed after 16 h at room temperature.[9] With this new MgI_2 promoting system, both aromatic and aliphatic ketones are suitable for direct coupling to generate anti-products without the formation of activated silyl enol ether.

2. Experimental

2.1. General

All reactions were conducted at room temperature in a flask (10.0 mL) with magnetic stirring. Dichloromethane was dried and freshly distilled from calcium hydride under the nitrogen atmosphere. Other commercial chemicals were used without further purification and their stoichiometrics were calculated based on the reported purities from the manufacturers. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded on a Varian 500 MHz NMR spectrometer. Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet) and m (multiplet). ^{13}C NMR spectra were recorded at 125 MHz using $CDCl_3$ as the solvent and the internal reference. Chemical shifts are given in ppm from tetramethylsilane. GC spectra were recorded at hp 6890 with hp 5973 Mass Selective Detective. Mass spectra were recorded with a JEOL JMS-D300 mass spectrometer using direct inlet electron impact ionization (70 eV). The Mass Spectroscopy Laboratory at the Crompton Corporation and University of Texas at Austin conducted high-resolution Mass spectral analysis.

2.1.1. General procedure A (Table 2). Anti-aldol addition with unmodified ketones using piperidine as base. Dichloromethane (5.0 mL), aldehyde (1.0 mmol, 1.0 equiv), ketone (1.4 mmol, 1.4 equiv), and magnesium iodide (1.4 mmol, 398.0 mg, 98% purity) were added to a dry 25 mL flask. The resulting mixture was protected by nitrogen gas and at room temperature piperidine (1.5 mmol, 0.147 mL) was added dropwise via a syringe. The resulting mixture was stirred for 2 h at room temperature and quenched by the addition of dilute 2 N HCl (4.0 mL). Dichloromethane was completely evaporated and 8.0 mL of ethyl acetate was added to the mixture. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate two more times (2×8.0 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. Purification was carried out by column chromatography [hexane (saturated with acetonitrile, up layer)/ethyl acetate=10:1] to give the pure anti-product.

Compound **1**. 218 mg, 91%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3488 (s), 3456 (s), 1676 (s), 1456 (s), 1215 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.98 (m, 2H), 7.57 (tt, J=7.5, 1.0 Hz, 1H), 7.34–7.49 (m, 6H), 7.29 (tt, J=7.5, 1.5 Hz, 1H), 4.99 (dd, J=8.0, 4.5 Hz, 1H), 3.83 (qn, J=7.5 Hz, 1H), 2.98 (d, J=4.5 Hz, OH), 1.07 (d, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.9, 142.2, 136.7, 133.3, 128.6×2, 128.4×2, 128.4×2, 127.9,126.7×2, 76.7, 47.9, 15.7; MS: (EI, 70 eV) 222 (M−H_2O, 100), 207 (40), 193 (6.6), 179 (16), 145 (10), 105 (69.8), 91 (14), 77 (52), 51 (19); HRMS: cald for $C_{16}H_{16}O_2$: 240.115; found: 240.112.

Compound **2**. 238 mg, 92%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3609 (m), 3489 (m), 1674 (s), 1604 (s), 1510 (s), 1448 (m), 1215 (s), 1157 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.96 (m, 2H), 7.57 (tt, J=7.5, 1.0 Hz, 1H), 7.47 (m, 2H), 7.38 (m, 2H), 7.04 (m, 2H) 4.98 (dd, J=8.0, 4.5 Hz, 1H), 3.78 (qn, J=7.5 Hz, 1H), 3.08 (d, J=4.5 Hz, OH), 1.07 (d, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 205.0, 163.5, 161.6, 138.2, 136.8, 133.6, 128.9×2, 128.6×2, 128.5, 115.6, 115.4, 76.2, 48.3, 15.9; MS: (EI, 70 eV) 240 (M−H_2O, 100), 225 (41), 211 (5), 197 (9), 163 (9), 133 (33), 105 (91), 77 (61); HRMS: cald for $C_{16}H_{15}O_2F$: 258.1056; found: 258.1051.

Compound **3**. 287 mg, 90%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3606 (m), 3485 (m), 1680 (s), 1598 (s), 1456 (s), 1206 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.94 (m, 2H), 7.57 (tt, J=7.5, 1.0 Hz, 1H), 7.47 (m, 4H), 7.28 (m, 2H), 4.95 (dd, J=8.0, 4.5 Hz, 1H), 3.77 (qn, J=7.5 Hz, 1H), 3.14 (d, J=5.0 Hz, OH), 1.08 (d, J=6.0 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.6, 141.2, 136.4, 133.4, 131.5×2, 128.7×2, 128.4×2, 128.3×2, 121.6, 76.1, 47.7, 15.6; MS: (EI, 70 eV) 302 (71) 301 (43), 300 (M−H_2O, 75), 284 (25), 221 (46), 178 (15), 144 (16) 115 (68), 105 (100), 77 (66); HRMS: cald for $C_{16}H_{15}O_2Br$: 318.0255; found: 318.0251. Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.95 (m, 2H), 7.61 (tt, J=7.0, 1.5 Hz, 1H), 7.52–7.46 (m, 4H), 7.31–7.28 (m, 2H), 5.21 (t, J=2.4 Hz, 1H), 3.76 (d, J=2.1 Hz, 1H, OH), 3.64 (dq, J=7.3, 3.0 Hz, 1H), 1.16 (d, J=7.3 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 205.4, 140.9, 135.3, 133.7, 131.2×2, 128.9×2, 128.5×2, 127.7×2, 121.1, 72.4, 46.7, 11.2.

Compound **4**. 224 mg, 88%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3614 (m), 3501 (m), 1678 (s), 1609 (s), 1514 (s), 1218 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.99 (m, 2H), 7.56(tt, J=7.5, 1.0 Hz, 1H), 7.46 (m, 2H), 7.29 (m, 2H), 7.16 (m, 2H), 4.95 (dd, J=8.0, 4.5 Hz, 1H), 3.81 (qn, J=7.5 Hz, 1H), 2.89 (d, J=4.5 Hz, OH), 2.34 (s, 3H) 1.04 (d, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.9, 139.2, 137.6, 136.8, 133.2, 129.1×2, 128.6×2, 128.4×2, 126.6×2, 76.6, 47.9, 21.1, 15.6; MS: (EI, 70 eV) 236 (M−H_2O, 54), 221 (100), 207 (6), 193 (8), 178 (7), 144 (13), 105(42) 91 (12), 77 (34); HRMS: cald for $C_{17}H_{18}O_2$: 254.1307; found: 254.1310.

Compound **5**. 244 mg, 92%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3608 (w), 3065 (w), 1676 (s), 1600 (m), 1451 (m), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.99 (m, 2H), 7.58(tt, J=7.5, 1.0 Hz, 1H), 7.47 (m, 2H), 7.37 (m, 2H), 7.30 (t, J=7.4 Hz, 2H), 7.24 (t, J=7.4 Hz, 1H), 6.68 (d, 16.0 Hz, 1H), 6.28 (dd, J=16.0, 7.5 Hz, 1H), 4.61 (q, J=6.5 Hz, 1H), 3.71 (qn, J=7.2 Hz, 1H), 3.04 (d, J=5.6 Hz, OH), 1.27 (d, J=7.2 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.7, 136.5, 136.5, 133.4, 132.1, 129.6×2,

128.7×2, 128.5×2, 128.4×2, 127.8, 126.5, 75.3, 46.3, 15.4; MS: (EI, 70 eV) 248 (M−H_2O, 52), 175 (9), 134 (87), 132 (28), 106 (11), 105 (100) 91 (18), 77 (71); HRMS: cald for $C_{18}H_{18}O_2$: 266.1307; found: 266.1311.

Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.98 (d, J=8.0 Hz, 2H), 7.61 (t, J=8 Hz, 1H), 7.50 (t, J=8.0 Hz, 2H), 7.39 (d, J=7.5 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.24 (t, J=7.5 Hz, 1H), 6.73 (d, J=16.0 Hz, 1H), 6.26 (dd, J=16.0, 6.0 Hz, 1H), 4.83–4.79 (m, 1H), 3.65 (dq, J=7.0, 3.5 Hz, 1H), 3.34 (d, J=2.5 Hz, OH), 1.32 (d, J=7.0 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 205.3, 136.7, 135.7, 133.6, 131.2, 129.1×2, 128.7×2, 128.5×2, 127.7×2, 126.5×2, 72.0, 45.4, 11.7.

Compound **6**. 183 mg, 90%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3610 (w), 3604 (w), 1671 (s), 1446 (m), 1211 (m), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.96 (m, 2H), 7.60–7.56 (m, 1H), 7.50–7.46 (m, 2H), 5.77 (dq, J=15.1, 6.0 Hz, 1H), 5.54 (ddq, J=15.1, 7.2, 1.1 Hz, 1H), 4.53 (m, 1H), 3.53 (q, J=7.2 Hz, 1H), 2.74 (d, J=6.0 Hz, OH), 1.71 (dd, J=7.2, 1.1 Hz, 3H), 1.18 (d, J=7.4 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 204.9, 136.7, 133.2, 131.5, 128.9×2, 128.7×2, 128.4, 75.3, 46,2, 17.7, 15.3; MS: (EI, 70 eV) 186 (M−H_2O, 78), 148 (8), 135 (15), 134 (100), 133 (61), 105 (91), 78 (5), 71 (26); HRMS: cald for $C_{13}H_{16}O_2$: 204.115; found: 204.110. Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.94 (d, J=7.5 Hz, 2H), 7.61–7.57 (m, 1H), 7.49 (t, J=7.5 Hz, 2H), 5.78 (ddq, J=15.0, 6.5, 1.5 Hz, 1H), 5.55 (ddq, J=15.0, 6.5, 1.5 Hz, 1H), 4.52 (t, J=5.0 Hz, 1H), 3.54 (dq, J=7.3, 3.5 Hz, 1H), 2.98 (s, 1H, OH), 1.71 (d, J=6.5 Hz, 3H), 1.27 (d, J=7.3 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 205.2, 136.1, 133.3, 130.8, 128.7×2, 128.4×2, 127.8, 72.5, 45.5, 17.7, 11.8.

Compound **7**. 180 mg, 82%, a colorless oil. IR: ($CHCl_3$) 3610 (w), 3500 (w), 1711 (s), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.96 (m, 2H), 7.59 (m, 1H), 7.50 (m, 2H), 4.73 (d, J=9.0 Hz, OH), 3.80 (dq, J=7.5, 2 Hz, 1H), 3.43 (dd, J=9.0, 2.0 Hz, 1H), 1.45 (d, J=7.0 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR: (125 MHz, $CDCl_3$) 208.2, 136.3, 133.6, 128.8×2, 128.1×2, 84.9, 37.5, 36.2, 26.80×3, 18.9; HRMS: cald for $C_{14}H_{20}O_2$: 220.1463; found: 220.1459.

Compound **8**. 139 mg, 68%, a white solid, mp: 40–42 °C. Data for *anti*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.36–7.27 (m, 5H), 4.78 (dd, J=9.2, 2.4 Hz, 1H), 3.98(d, J=2.4 Hz, OH), 2.64–2.58 (m, 1H), 2.50–2.45 (m, 1H), 2.40–2.31 (m, 1H), 2.10–2.03 (m, 1H), 1.81–1.74 (m, 1H), 1.71–1.46 (m, 3H), 1.34–1.22 (m, 1H); ^{13}C NMR: (125 MHz, $CDCl_3$) 215.5, 140.8, 128.2×2, 127.8, 126.9×2, 74.6, 57.3, 42.6, 30.7, 27.7, 24.6; HRMS: cald for $C_{13}H_{16}O_2$: 204.115; found: 204.119. Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.36–7.21 (m, 5H), 5.39 (m, 1H), 3.05 (d, J=2.1 Hz, 1H), 2.62–2.57 (m, 1H), 2.47–2.43 (m, 1H), 2.42–2.32 (m, 1H), 2.11–2.06 (m, 1H), 1.87–1.82 (m, 1H), 1.75–1.60 (m, 3H), 1.57–1.43 (m, 1H); ^{13}C NMR: (125 MHz, $CDCl_3$) 214.9, 141.3, 128.1×2, 126.8, 125.5×2, 70.5, 57.1, 42.6, 27.9, 25.9, 24.8.

Compound **9**. 167 mg, 70%, a colorless oil. Data for *anti*-isomer: IR: ($CHCl_3$) 3591 (w), 3077 (w), 1771 (s), 1452 (s), 1209 (m), 902 (m); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.34–7.30 (m, 2H), 7.28–7.24 (m, 2H), 4.76 (dd, J=8.5, 2.5 Hz, 1H), 3.98 (d, J=3.0 Hz, OH), 2.60–2.52 (m, 1H), 2.51–2.45 (m, 1H), 2.40–2.31 (m, 1H), 2.13–2.02 (m, 1H), 1.82–1.77 (m, 1H), 1.72–1.62 (m, 1H), 1.61–1.51 (m, 2H), 1.33–1.22 (m, 1H); ^{13}C NMR: (125 MHz, $CDCl_3$) 215.3, 139.4, 133.5, 128.5×2, 128.3×2, 74.1, 57.3, 42.6, 30.74, 27.7, 24.7; MS: (EI, 70 eV) 220 (M−H_2O, 36), 140 (52), 132 (100), 104 (44), 89 (31); HRMS: cald for $C_{13}H_{15}O_2Cl$: 238.0761; found: 238.0766. Data for *syn*-isomer: ^{1}H NMR: (500 MHz, $CDCl_3$) 7.32–7.29 (m, 2H), 7.27–7.22 (m, 2H), 5.35 (m, 1H), 3.04 (d, J=3.0 Hz, OH), 2.60–2.52 (m, 1H), 2.49–2.41 (m, 1H), 2.41–2.32 (m, 1H), 2.13–2.06 (m, 1H), 1.89–1.82 (m, 1H), 1.73–1.64 (m, 3H), 1.57–1.47 (m, 1H); ^{13}C NMR: (125 MHz, $CDCl_3$) 214.6, 139.9, 132.6, 128.3×2, 127.1×2, 70.11, 57.0, 42.6, 27.9, 25.9, 24.8.

Compound **10**. 134 mg, 70%, a colorless oil, inseparable; ^{1}H NMR: (500 MHz, $CDCl_3$) 7.40–7.20 (m, 5H), 5.03 (d, J=4.0 Hz, 0.24H, *syn*-isomer), 4.74 (d, J=8.1 Hz, 0.76H, *anti*-isomer), 2.83 (dq, J=7.2, 4.0 Hz, 1H), 2.20–2.55 (m, 2H), 1.07 (d, J=7.2 Hz, 3H), 0.99 (t, J=7.0 Hz, 3H).

2.1.2. General procedure B (Table 3). Regio selective aldol addition with unmodified ketones using *N*,*N*-diisopropylethylamine as base. Dichloromethane (5.0 mL), aldehyde (1.0 mmol, 1.0 equiv), ketone (1.2 mmol, 1.2 equiv), and magnesium iodide (1.2 mmol, 340.0 mg, 98% purity) were added to a dry 25 mL flask. The resulting mixture was protected by nitrogen gas and at room temperature *N*,*N*-diisopropylethylamine (1.3 mmol, 0.226 mL) was added dropwise via a syringe. The resulting mixture was stirred for 30 min at room temperature and quenched by addition of dilute 2 N HCl (4.0 mL). Dichloromethane was completely evaporated and 8.0 mL of ethyl acetate was added to the mixture. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate two more times (2×8.0 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. Purification was carried out by column chromatography (hexane/ethyl acetate=10:1) to give the pure product.

Compound **11**. 241 mg, 85%, a colorless oil. Major isomer: mp: 80–82 °C. IR: ($CHCl_3$) 3609 (s), 3514 (w), 3019 (m), 1678 (s), 1214 (s), 969 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.45–7.40 (m, 2H), 7.40–7.35 (m, 2H), 7.34–7.30 (m, 1H), 7.29 (m, 2H), 6.97–6.92 (m, 2H), 5.13–5.08 (dt, J=9.5, 3 Hz, 1H), 5.05 (s, 2H), 3.27 (d, J=3.0 Hz, OH), 2.88–2.72 (m, 2H), 2.44 (q, J=7.5 Hz, 2H), 1.06 (t, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 212.1, 158.5, 137.1, 135.5, 128.8×2, 128.2, 127.6×2, 127.1×2, 115.1×2, 70.2, 69.8, 50.8, 37.1, 7.7; MS: (EI, 70 eV) 266 (M−H_2O, 16), 212 (8), 153 (0.6), 105 (0.3), 91 (100), 65 (13); HRMS: cald for $C_{18}H_{20}O_3$: 284.3550; found: 284.3556.

Compound **12**. 196 mg, 86%, a colorless oil; Major isomer: mp: 58–60 °C. IR: ($CHCl_3$) 3607 (w), 3551 (w), 3001 (w), 1675 (s), 1521 (m), 969 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.85–7.80 (m, 4H), 7.49–7.44 (m, 3H), 5.33 (dt, J=8.5, 2.5 Hz, 1H), 3.49 (d, J=3.0 Hz, OH), 2.97–2.84 (m, 2H), 2.47 (q, J=7.5 Hz, 2H), 1.07 (t, J=7.5 Hz, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) 211.8, 140.2, 133.2, 132.9, 128.3, 127.9, 127.6, 126.1, 125.8, 124.3, 123.7, 70.1, 50.6, 36.8, 7.4; MS:

(EI, 70 eV) 210 (M−H_2O, 38), 181 (100), 152 (46), 127 (8), 126 (6); HRMS: cald for $C_{15}H_{16}O_2$: 228.1412; found: 228.1416.

Compound **13**. 173 mg, 90%, a colorless oil. IR: ($CHCl_3$) 3605 (w), 3514 (w), 2956 (m), 1699 (s), 1514 (m), 1066 (m), 973 (m); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.37–7.31 (m, 4H), 7.29–7.24 (m, 1H), 5.13 (dt, J=9.0, 3.5 Hz, 1H), 3.54 (d, J=3.5 Hz, OH), 2.92–2.78 (m, 2H), 2.62–2.52 (m, 1H), 1.08 (dd, J=7.0, 1.5 Hz, 6H); ^{13}C NMR: (125 MHz, $CDCl_3$) 215.1, 142.9, 128.4×2, 127.5, 125.5×2, 69.8, 48.7, 41.4, 17.7×2; MS: (EI, 70 eV) 174 (M−H_2O, 1), 159 (2), 135 (3), 119 (100), 105 (6), 91 (4); HRMS: cald for $C_{12}H_{16}O_2$: 192.1150; found: 192.1154.

Compound **14**. 220 mg, 91%, a white solid; mp: 54–56 °C. IR: ($CHCl_3$) 3609 (w) 3600 (s), 3000 (m), 1699 (s), 1467 (m), 1386 (m), 1221 (s), 1035 (s), 858 (m); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.84–7.79 (m, 4H), 7.48–7.42 (m, 3H), 5.29 (dt, J=8.5, 3.5 Hz, 1H), 3.65 (d, J=3.0 Hz, OH), 2.97–2.85 (m, 2H), 2.62–2.52 (m, 1H), 1.08 (dd, J=7.0, 1.5 Hz, 6H); ^{13}C NMR: (125 MHz, $CDCl_3$) 215.1, 140.3, 133.2, 132.8, 128.2, 127.9, 127.5,126.1, 125.7, 124.2, 123.7, 70.0, 48.6, 41.4, 17.8×2; MS: (EI, 70 eV) 224 (M−H_2O, 23), 181 (100), 152 (41), 127 (7), 115 (1); HRMS: cald for $C_{16}H_{18}O_2$: 242.1307; found: 242.1302.

Compound **15**. 227 mg, 81%, a colorless oil, inseparable; ^{1}H NMR: (300 MHz, $CDCl_3$) 7.40–7.15 (m, 10H), 6.40 (dd, J=16.0, 1.1 Hz, 1H), 6.17 (dd, J=16.0, 6.1 Hz, 1H), 4.75 (m, 0.9H), 4.41 (m, 0.1H), 3.07 (d, J=3.7 Hz, OH), 3.0–2.85 (m, 2H), 2.84–2.75 (m, 2H), 2.74–2.67 (m, 2H).

Compound **16**. 300 mg, 83%, a white solid; mp: 87–89 °C. IR: ($CHCl_3$) 3608 (w), 3512 (w), 2945 (w), 1680 (S), 1600 (m), 1289 (m), 1211 (m), 970 (s); ^{1}H NMR: (500 MHz, $CDCl_3$) 7.42–7.35 (m, 4H), 7.34–7.14 (m, 8H), 6.96–6.92 (m, 2H), 5.08 (dt, J=9.0, 3.0 Hz, 1H), 5.05 (s, 2H), 3.15 (d, J=3.0 Hz, OH), 2.90 (t, J=7.5 Hz, H), 2.88–2.70 (m, 4H); ^{13}C NMR: (125 MHz, $CDCl_3$) 210.3, 158.3, 140.6, 136.9, 135.2, 128.5×2, 128.5×2, 128.2×2 127.9, 127.4×2, 126.9×2, 126.2, 114.8×2, 70.0, 69.5, 51.2, 45.1, 29.4; MS: (EI, 70 eV) 342 (M−H_2O, 10), 212 (18), 181 (1), 152 (1), 91 (100), 65 (25); HRMS: cald for $C_{24}H_{24}O_3$: 360.1725; found: 360.1728.

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9. Procedure for reacting propiophenone with benzaldehyde (see Ref. 8): benzaldehyde (0.1 mL, 1.0 mmol) and propiophenone (0.13 mL, 1.0 mmol) were dissolved in 2.0 mL of anhydrous toluene. Under a nitrogen atmosphere and at room temperature, 0.1 mL (0.1 mmol, 1.0 M solution in toluene, Aldrich) of $TiCl_4$ was added dropwise via a syringe to the solution. The solution was stirred for an additional 16 h at room temperature. The ^{1}H NMR of the crude mixture showed that less than 10% of benzaldehyde was converted to an aldol product. This conclusion was based on the comparison of peak integrations of the carbinol proton of aldol the product (5.23 ppm) with the benzaldehyde proton (10.01 ppm).