Asymmetric Direct Michael Addition of Acetophenone to α,β-Unsaturated Aldehydes

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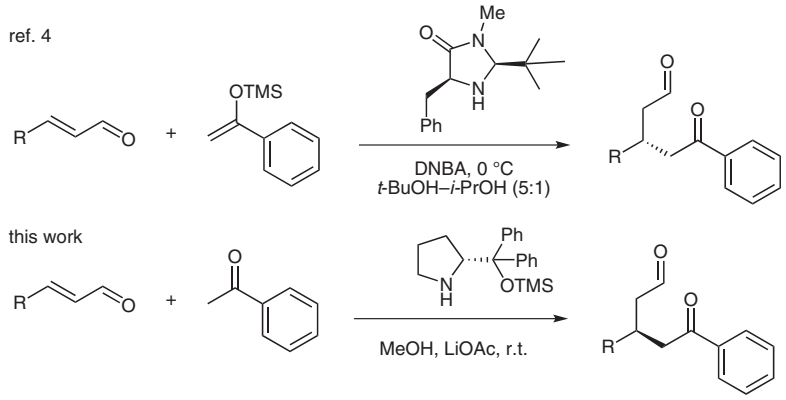
Abstract: The asymmetric direct Michael addition of α,β-unsaturated aldehydes with acetophenone catalyzed by a Jørgensen–Hayashi catalyst in methanol was developed and the corresponding Michael products of δ-keto aldehydes could be afforded in up to 82% yield and 98% ee.

Key words: asymmetric catalysis, Michael additions, ketones, aldehydes, enals

The Mukaiyama–Michael addition reaction has been shown to be a mild, versatile, and powerful method for carbon–carbon bond formation.[1] Considerable research efforts have focused on the development of a catalytic asymmetric version of this process.[2] Because of the preference of α,β-unsaturated aldehydes for 1,2-addition over 1,4-addition, the development of a catalytic asymmetric Michael addition to α,β-unsaturated aldehydes has proved to be more challenging.[3] In 2005, Wang reported a study of an organocatalytic asymmetric Mukaiyama–Michael addition of α,β-unsaturated aldehydes with nucleophilic silyl enol ethers employing MacMillan's chiral imidazolidinone catalyst (Scheme 1).[4] A catalytic asymmetric direct Michael reaction with atom economy would be more desirable in organic synthesis. We have recently reported catalytic asymmetric Michael addition reactions of α,β-unsaturated aldehydes with nitroalkanes and malonates with a Jørgensen–Hayashi catalyst.[5–8] Although the pK_a values of ketones are larger than those of nitroalkanes and malonates, we wondered whether asymmetric direct Michael reactions of α,β-unsaturated aldehydes with acetophenones could take place.

In this communication, we reveal that a Jørgensen–Hayashi catalyst provides the first enantioselective direct Michael reactions of α,β-unsaturated aldehydes with acetophenones and affords δ-keto aldehydes in high yields with excellent enantioselectivities (Scheme 1).

In the model reaction between cinnamaldehyde (**1a**) and acetophenone (**2a**) with catalyst **I** in a chloroalkane, the conversions were poor (Table 1, entries 1 and 2). To our delight, the reaction in methanol without any additive proceeded in 77% conversion with a chemoselectivity of 80:20 and with 96% enantioselectivity (entry 3). To increase the conversion, we introduced lithium acetate into the reaction system. We supposed that lithium acetate would increase the mole fraction of the lithium enolate of acetophenone generated in equilibrium, and could accelerate the nucleophilic reaction.[9] A survey of different reaction solvents revealed that methanol was the most suitable solvent for this procedure (entry 12). Performing the reactions in less polar or nonpolar solvents gave inferior results (entries 4–11). This might be because lithium acetate is too insoluble in other media to have an effect on the substrates. Furthermore, an alcoholic solvent may contribute to competitive hemiacetal formation with α,β-unsaturated aldehyde under equilibrium, which is beneficial to suppress 1,2-addition. Gratifyingly, up to 94% con-



Scheme 1 Mukaiyama–Michael addition versus direct Michael addition; DNBA = 2,4-dinitrobenzenesulfonic acid

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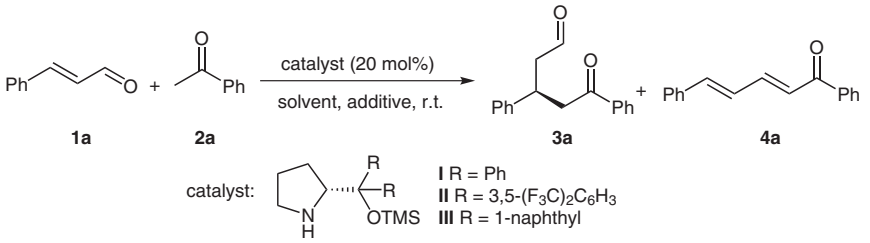
version with 85:15 chemoselectivity and 96% ee were obtained in the presence of lithium acetate in methanol (entry 12). These encouraging results indicated that the enantioselective direct Michael addition of acetophenone to α,β-unsaturated aldehyde was feasible.

Table 1 Optimization Studies[a]



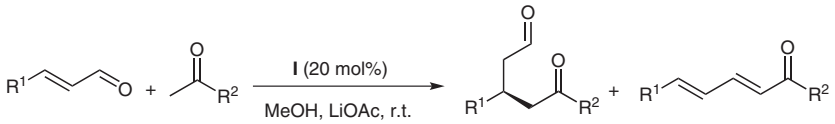
Entry	Additive base	Solvent	Cat.	Conversion[b,c] (%)	Ratio **3a/4a**[c,d]	ee[c,e] (%)
1	none	CH_2Cl_2	**I**	13	nd	nd
2	none	$CHCl_3$	**I**	9	nd	nd
3	none	MeOH	**I**	77	80:20	96
4	LiOAc	CH_2Cl_2	**I**	29	84:16	nd
5	LiOAc	$CHCl_3$	**I**	28	87:13	nd
6	LiOAc	THF	**I**	11	nd	nd
7	LiOAc	EtOAc	**I**	20	nd	nd
8	LiOAc	benzene	**I**	16	nd	nd
9	LiOAc	toluene	**I**	20	nd	nd
10	LiOAc	MeCN	**I**	28	13:87	nd
11	LiOAc	EtOH	**I**	62	84:16	96
12	LiOAc	MeOH	**I**	94	85:15	96
13	NaOAc	MeOH	**I**	92	89:11	93
14	KOAc	MeOH	**I**	93	88:12	94
15	$PhCO_2Li$	MeOH	**I**	96	90:10	93
16	4-$FC_6H_4CO_2Li$	MeOH	**I**	93	88:12	95
17	4-$MeOC_6H_4CO_2Li$	MeOH	**I**	95	87:13	94
18	LiOPh	MeOH	**I**	98	86:14	92
19	LiOH	MeOH	**I**	96	9:90	87
20	Et_3N	MeOH	**I**	94	80:20	95
21	DBU	MeOH	**I**	97	50:50	94
22	$PhCO_2H$	MeOH	**I**	55	86:14	nd
23	AcOH	MeOH	**I**	11	nd	nd
24	LiOAc	MeOH	**II**	n.r.	nd	nd
25	LiOAc	MeOH	**III**	n.r.	nd	nd

[a] Reaction conditions: cinnamaldehyde (**1a**; 0.1 mmol), acetophenone (**2a**; 0.3 mmol), catalyst (0.02 mmol), additive base (0.02 mmol), solvent (0.1 mL), r.t., 48 h.
[b] Conversion was determined by GC.
[c] Abbreviations: nd = not determined; n.r. = no reaction.
[d] The **3a/4a** ratio was determined by GC and NMR spectroscopy.
[e] The ee was determined by HPLC by using a Chiralpak® AD-H column.

Subsequently, further conditions were investigated. It is well known that an acidic environment facilitates the formation of an imine from the catalyst and the enal, while a base aids the activation of nucleophiles. Therefore, it is crucial to use the proper additive to promote the reaction efficiently and selectively. The experiments using different additives indicated that the chemoselectivity was dependent on the basicity of the additive base. The appropriate basicity was necessary to afford satisfying chemoselectivity. For example, similar results were obtained when other acetate additives and lithium benzoates were used as additive base (entries 13–17). The more basic lithium phenolate caused a decrease of chemoselectivity to 86:14 (entry 18). When lithium hydroxide was used, the major product became the 1,2-addition product (entry 19). An organic amine base was also tested. The using of triethylamine resulted in 94% conversion, 80:20 chemoselectivity, and 95% ee (entry 20). The more basic 1,8-diazabicyclo[5.4.0]undec-7-ene caused a decrease of chemoselectivity to 50:50 (entry 21). If the additive base was substituted by an acidic additive, the reaction did not proceed efficiently. With benzoic acid, only 55% conversion and a chemoselectivity of about 86:14 were obtained (entry 22). Moreover, the use of acetic acid resulted in very low conversion (entry 23). More experiments also indicated that other kinds of diarylprolinol catalysts **II** and **III** did not catalyze this reaction (entries 24 and 25). This might be attributed to the great steric bulk of these catalysts.

With the optimized reaction conditions in hand, the scope of the Michael reaction was investigated. The results are summarized in Table 2. It appears that for aromatic α,β-

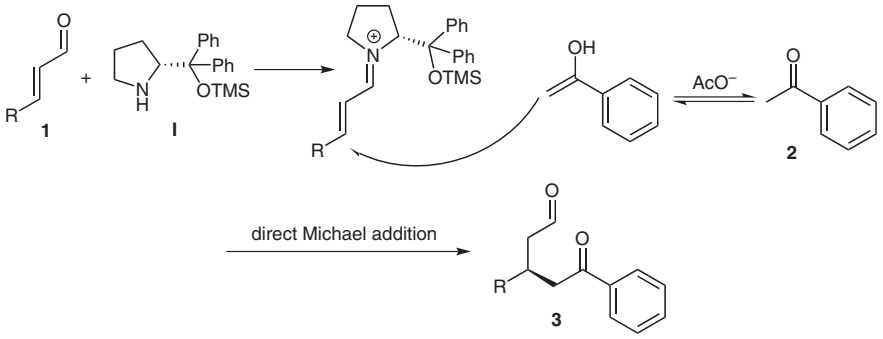
Table 2 Organocatalytic Asymmetric Direct Michael Additions of Acetophenones to α,β-Unsaturated Aldehydes[a]



1 2 3 4

Entry	R^1	R^2	Time (h)	Ratio **3/4**[b]	Yield[c] (%)	ee[d] (%)
1	Ph	Ph	48	85:15	74 (**3a**)	96
2	3-MeC_6H_4	Ph	48	90:10	75 (**3b**)	95
3	4-MeC_6H_4	Ph	48	91:9	82 (**3c**)	98
4	4-FC_6H_4	Ph	48	88:12	73 (**3d**)	94
5	4-BrC_6H_4	3-BrC_6H_4	24	90:10	76 (**3e**)	96
6	4-ClC_6H_4	2-FC_6H_4	24	87:13	73 (**3f**)	97
7	2-ClC_6H_4	3-BrC_6H_4	24	82:18	69 (**3g**)	97
8	4-$MeOC_6H_4$	Ph	36	90:10	78 (**3h**)	96
9	2-$MeOC_6H_4$	Ph	24	88:12	77 (**3i**)	98
10	2-$MeOC_6H_4$	2-HOC_6H_4	24	88:12	76 (**3j**)	94
11	2-$MeOC_6H_4$	3-BrC_6H_4	24	90:10	80 (**3k**)	95
12	2-$MeOC_6H_4$	4-$O_2NC_6H_4$	24	89:11	78 (**3l**)	96
13	4-ClC_6H_4	3-BrC_6H_4	24	85:15	79 (**3m**)	96
14	2-ClC_6H_4	2-ClC_6H_4	24	82:18	71 (**3n**)	98
15	2-ClC_6H_4	2-FC_6H_4	24	83:17	72 (**3o**)	97
16	4-BrC_6H_4	2-FC_6H_4	24	84:16	73 (**3p**)	96
17	Ph	2-furyl	48	85:15	74 (**3q**)	94
18	Et	Ph	48	nd[e]	mixture	nd[e]

[a] Reaction conditions: α,β-unsaturated aldehyde **1** (0.3 mmol), ketone **2** (0.9 mmol), **I** (0.06 mmol), LiOAc (0.06 mmol), MeOH (0.3 mL), r.t., indicated time.
[b] The **3/4** ratio was determined by GC and NMR spectroscopy.
[c] Isolated yield.
[d] The ee was determined by HPLC by using a Chiralpak® AD-H column and AY-H column.
[e] nd = not determined.



Scheme 2 Proposed working model of the Michael addition

unsaturated aldehydes, substituents on the benzene ring had a limited effect on the reaction results. Excellent enantioselectivities and high yields were obtained regardless of the type of substituent on the aryl moieties (entries 1–9). Furthermore, excellent enantioselectivities and high yields were also obtained independent of the electronic characteristics of the aromatic ketones. All of the aromatic ketones that have electron-withdrawing and heterocyclic substituents gave excellent enantioselectivities (entries 10–17). Notably, in all cases, the reactions were completed with excellent levels of enantioselectivities (94–98%), which indicated that this method has the potential to afford optically pure compounds. Apart from the additive base, the electronic properties of the cinnamaldehyde derivatives also affected the chemoselectivity of the reaction. The cinnamaldehyde derivatives containing electron-donating groups such as methyl and methoxy on the aromatic ring (entries 2, 3, and 8–12) afforded higher chemoselectivities than those with electron-withdrawing groups, such as chloro or bromo (entries 5–7 and 13–16). Unfortunately, for aliphatic α,β-unsaturated aldehydes, such as pentenal, a complex mixture was obtained, which was caused by Robinson annulation of aliphatic α,β-unsaturated aldehydes (entry 18).[10]

The absolute configuration of the Michael addition adduct was *S*, which was determined by comparison of the optical rotations to those reported in the literature.[4] A proposed working model of the Michael addition is showed in Scheme 2. The α,β-unsaturated aldehyde is activated by the Jørgensen–Hayashi catalyst to form an iminium cation. Enolization of acetophenone was likely promoted by cooperative action of the lithium cation and the acetate anion. Then the direct Michael addition was triggered by the active iminium cation, which was attacked by the enol to give the Michael product **3** in excellent enantioselectivity.

In summary, the first enantioselective direct Michael reaction of α,β-unsaturated aldehydes with acetophenone was developed, and was catalyzed by the Jørgensen–Hayashi catalyst **I**. This approach is a powerful tool for providing the synthetically important δ-keto aldehydes. However, the substrate scope of this reaction is still limited. For aliphatic α,β-unsaturated aldehydes, no desired products were obtained. Further research in this field is being carried out and the results will be presented in the future.

NMR spectra were recorded on a Varian DRX 400 spectrometer; $CDCl_3$ was used as the solvent with TMS as an internal reference. GC analysis was carried out on an Agilent 7890N instrument. Mass spectra (EI) were measured on a Waters Micromass GCT spectrometer. Optical rotations were determined on an Autopol III automatic polarimeter. HPLC was performed on an Agilent 1200 Series chromatograph with Chiral AD-H, AY-H (0.46 cm × 25 cm) columns, as noted. All reagents were obtained commercially and used without further purification, unless noted otherwise.

5-Oxo-3,5-diphenylpentanal (3a); General Procedure

A mixture of α,β-unsaturated aldehyde **1** (0.3 mmol), ketone **2** (0.9 mmol), catalyst **I** (0.06 mmol), and LiOAc (0.06 mmol) in MeOH (0.3 mL) was stirred at r.t. for the time indicated in Table 2. Then the solvent was removed under vacuum and the residue was purified by column chromatography (silica gel); this gave the corresponding product. The ee was determined by HPLC.

5-Oxo-3,5-diphenylpentanal (3a)

Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 74%; yellow oil; $[\alpha]_D^{23}$ –1.2 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1 H), 7.95–7.93 (m, 2 H), 7.59–7.56 (m, 1 H), 7.48–7.45 (m, 2 H), 7.35–7.22 (m, 5 H), 4.02–3.97 (m, 1 H), 3.37 (d, *J* = 7.2 Hz, 2 H), 2.97–2.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 198.1, 143.2, 136.7, 133.2, 128.8, 128.6, 128.0, 127.4, 127.0, 49.6, 45.0, 35.4.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{16}O_2$: 252.1150; found: 252.1149.

HPLC: 96% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 16.0 min (major), 22.4 min (minor).

5-Oxo-5-phenyl-3-*m*-tolylpentanal (3b)

Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 75%; yellow oil; $[\alpha]_D^{22}$ –1.8 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (t, *J* = 2.0 Hz, 1 H), 7.95–7.93 (m, 2 H), 7.60–7.56 (m, 1 H), 7.49–7.45 (m, 2 H), 7.24–7.20 (m, 1 H), 7.10–7.04 (m, 3 H), 4.00–3.93 (m, 1 H), 3.36 (d, *J* = 7.2 Hz, 2 H), 2.91–2.83 (m, 2 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.3, 198.2, 143.2, 138.5, 136.8, 133.2, 128.7, 128.6, 128.2, 128.1, 127.7, 124.3, 49.5, 45.0, 35.4, 21.5.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{18}O_2$: 266.1307; found: 266.1323.

HPLC: 95% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 13.2 min (major), 15.6 min (minor).

5-Oxo-5-phenyl-3-*p*-tolylpentanal (3c)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 82%; yellow oil; $[\alpha]_D^{23}$ –2.6 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73–9.72 (m, 1 H), 7.95–7.93 (m, 2 H), 7.59–7.56 (m, 1 H), 7.48–7.45 (m, 2 H), 7.20–7.13 (m, 4 H), 3.99–3.96 (m, 1 H), 3.35 (d, *J* = 7.2 Hz, 2 H), 2.91–2.82 (m, 2 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 198.2, 140.2, 136.8, 136.5, 133.2, 129.5, 128.6, 128.2, 127.4, 49.7, 45.1, 35.0, 21.1.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{18}O_2$: 266.1307; found: 266.1309.

HPLC: 98% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 15.3 min (major), 21.0 min (minor).

3-(4-Fluorophenyl)-5-oxo-5-phenylpentanal (3d)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 73%; yellow oil; $[\alpha]_D^{23}$ –2.3 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1 H), 8.04–8.03 (m, 1 H), 7.85–7.83 (m, 1 H), 7.71–7.69 (m, 1 H), 7.37–7.28 (m, 4 H), 7.24–7.21 (m, 2 H), 3.98–3.94 (m, 1 H), 3.33–3.30 (m, 2 H), 2.92–2.85 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 197.9, 162.9, 138.9, 136.7, 133.3, 128.9, 128.7, 128.0, 115.7, 115.5, 49.7, 44.9, 34.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{15}O_2F$: 270.1056; found: 270.1057.

HPLC: 94% ee (AS-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 17.0 min (major), 23.8 min (minor).

5-(3-Bromophenyl)-3-(4-bromophenyl)-5-oxopentanal (3e)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 76%; yellow oil; $[\alpha]_D^{24}$ –4.2 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73–9.72 (m, 1 H), 8.04–8.02 (m, 1 H), 7.85–7.83 (m, 1 H), 7.72–7.69 (m, 1 H), 7.46–7.44 (m, 2 H), 7.35–7.33 (m, 1 H), 7.18–7.16 (m, 2 H), 3.97–3.93 (m, 1 H), 3.33–3.30 (m, 2 H), 2.92–2.90 (m, 1 H), 2.87–2.85 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 196.4, 142.0, 138.3, 136.2, 131.9, 131.1, 130.3, 129.2, 126.5, 123.0, 120.8, 49.4, 44.6, 34.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{14}O_2Br_2$: 407.9361; found: 407.9363.

HPLC: 96% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 20.9 min (major), 24.7 min (minor).

3-(4-Chlorophenyl)-5-(2-fluorophenyl)-5-oxopentanal (3f)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 73%; yellow oil; $[\alpha]_D^{24}$ –3.6 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71–9.70 (m, 1 H), 7.81–7.77 (m, 1 H), 7.56–7.51 (m, 1 H), 7.30–7.28 (m, 2 H), 7.24–7.21 (m, 3 H), 7.16–7.12 (m, 1 H), 4.00–3.95 (m, 1 H), 3.37–3.35 (m, 2 H), 2.93–2.78 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6, 196.0, 163.1, 160.6, 141.7, 134.9, 134.8, 132.5, 130.6, 128.9, 124.6, 116.8, 116.6, 49.6, 34.5, 29.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{14}O_2ClF$: 304.0666; found: 304.0670.

HPLC: 97% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 14.4 min (major), 19.4 min (minor).

5-(3-Bromophenyl)-3-(2-chlorophenyl)-5-oxopentanal (3g)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 69%; yellow oil; $[\alpha]_D^{23}$ –1.9 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1 H), 8.08–8.07 (m, 1 H), 7.89–7.87 (m, 1 H), 7.71–7.69 (m, 1 H), 7.41–7.30 (m, 3 H), 7.26–7.17 (m, 2 H), 4.47–4.43 (m, 1 H), 3.43–3.37 (m, 2 H), 2.98–2.92 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 196.5, 140.0, 138.3, 136.1, 133.5, 131.1, 130.3, 130.2, 128.3, 128.2, 127.3, 126.6, 123.0.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{14}O_2ClBr$: 363.9866; found: 363.9869.

HPLC: 97% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 24.1 min (major), 29.4 min (minor).

3-(4-Methoxyphenyl)-5-oxo-5-phenylpentanal (3h)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 78%; yellow oil; $[\alpha]_D^{22}$ –3.2 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1 H), 7.94–7.92 (m, 2 H), 7.59–7.55 (m, 1 H), 7.48–7.45 (m, 2 H), 7.22–7.20 (m, 2 H), 6.87–6.85 (m, 2 H), 3.98–3.94 (m, 1 H), 3.79 (s, 3 H), 3.33 (d, *J* = 6.8 Hz, 2 H), 2.90–2.88 (m, 1 H), 2.83–2.81 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 198.3, 158.4, 136.8, 135.1, 133.2, 128.6, 128.3, 128.0, 114.2, 55.2, 49.7, 45.2, 34.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{18}O_3$: 282.1256; found: 282.1257.

HPLC: 96% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 24.3 min (major), 35.2 min (minor).

3-(2-Methoxyphenyl)-5-oxo-5-phenylpentanal (3i)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 77%; yellow oil; $[\alpha]_D^{22}$ –3.2 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (t, *J* = 2.0 Hz, 1 H), 7.98–7.96 (m, 2 H), 7.59–7.56 (m, 1 H), 7.49–7.45 (m, 2 H), 7.23–7.21 (m, 2 H), 6.95–6.88 (m, 2 H), 4.30–4.27 (m, 1 H), 3.85 (s, 3 H), 3.47–3.34 (m, 2 H), 2.92–2.86 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.1, 198.8, 157.0, 136.9, 133.1, 130.8, 128.6, 128.5, 128.4, 128.1, 120.8, 110.8, 55.3, 48.0, 43.2, 30.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{18}O_3$: 282.1256; found: 282.1263.

HPLC: 98% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 18.0 min (major), 21.6 min (minor).

5-(2-Hydroxyphenyl)-3-(2-methoxyphenyl)-5-oxopentanal (3j)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 76%; yellow oil; $[\alpha]_D^{23}$ –4.9 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.25 (s, 1 H) 9.74–9.73 (m, 1 H), 7.84–7.82 (m, 1 H), 7.50–7.46 (m, 1 H), 7.24–7.21 (m, 2 H), 6.99–6.89 (m, 4 H), 4.27–4.24 (m, 1 H), 3.84 (s, 3 H), 3.43–3.39 (m, 2 H), 2.95–2.92 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.2, 193.9, 163.5, 162.5, 157.1, 147.9, 136.3, 130.5, 129.9, 128.0, 125.6, 120.8, 119.5, 118.8, 110.9, 55.3, 43.1, 37.4, 34.9.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{18}O_4$: 298.1205; found: 298.1207.

HPLC: 94% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 13.3 min (minor), 14.8 min (major).

5-(3-Bromophenyl)-3-(2-methoxyphenyl)-5-oxopentanal (3k)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 80%; yellow oil; $[\alpha]_D^{23}$ –4.7 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (t, *J* = 2.0 Hz, 1 H), 8.09–8.07 (m, 1 H), 7.90–7.88 (m, 1 H), 7.70–7.68 (m, 1 H), 7.37–7.33 (m, 1 H), 7.26–7.20 (m, 2 H), 6.95–6.88 (m, 2 H), 4.28–4.21 (m, 1 H),

3.86 (s, 3 H), 3.44–3.38 (m, 1 H), 3.32–3.26 (m, 1 H), 2.93–2.89 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8, 197.5, 156.9, 138.6, 135.9, 131.2, 130.4, 130.2, 128.4, 128.2, 126.6, 122.9, 120.8, 110.9, 53.5, 47.9, 43.4, 30.8.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{17}O_3Br$: 360.0361; found: 360.0365.

HPLC: 95% ee (AY-H column, 254 nm, *n*-hexane–EtOH, 1:1, 0.8 mL/min): 14.3 min (major), 23.1 min (minor).

3-(2-Methoxyphenyl)-5-(4-nitrophenyl)-5-oxopentanal (3l)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 78%; yellow oil; $[\alpha]_D^{23}$ –4.8 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1 H), 8.31–8.29 (m, 2 H), 8.11–8.09 (m, 2 H), 7.23–7.19 (m, 2 H), 6.95–6.87 (m, 2 H), 4.25–4.24 (m, 1 H), 3.83 (s, 3 H), 3.45–3.41 (m, 2 H), 2.98–2.92 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 197.4, 156.9, 150.3, 141.3, 130.1, 129.5, 128.4, 128.3, 123.8, 120.9, 110.9, 55.2, 47.9, 43.7, 30.9.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{17}NO_5$: 327.1107; found: 327.1110.

HPLC: 96% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 13.7 min (major), 18.0 min (minor).

5-(3-Bromophenyl)-3-(4-chlorophenyl)-5-oxopentanal (3m)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 79%; yellow oil; $[\alpha]_D^{24}$ –3.1 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73–9.72 (m, 1 H), 8.04–8.03 (m, 1 H), 7.85–7.83 (m, 1 H), 7.71–7.69 (m, 1 H), 7.37–7.33 (m, 1 H), 7.31–7.28 (m, 2 H), 7.24–7.21 (m, 2 H), 4.00–3.93 (m, 1 H), 3.33–3.30 (m, 2 H), 2.97–2.80 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 196.4, 141.5, 138.3, 136.2, 132.7, 131.1, 130.3, 129.0, 128.8, 126.5, 123.0, 49.5, 44.7, 34.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{14}O_2ClBr$: 363.9866; found: 363.9868.

HPLC: 96% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 19.3 min (major), 22.5 min (minor).

3,5-Bis(2-chlorophenyl)-5-oxopentanal (3n)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 71%; yellow oil; $[\alpha]_D^{23}$ –3.3 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1 H), 7.40–7.28 (m, 5 H), 7.25–7.18 (m, 3 H), 4.45–4.41 (m, 1 H), 3.44–3.41 (m, 2 H), 2.96–2.91 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6, 139.7, 138.9, 133.6, 131.9, 130.8, 130.5, 130.1, 128.9, 128.4, 128.2, 127.2, 127.0, 48.1, 47.2, 32.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{14}O_2Cl_2$: 320.0371; found: 320.0411.

HPLC: 98% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 14.6 min (minor), 17.1 min (major).

3-(2-Chlorophenyl)-5-(2-fluorophenyl)-5-oxopentanal (3o)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 72%; yellow oil; $[\alpha]_D^{23}$ –1.5 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (t, *J* = 2.0 Hz, 1 H), 7.85–7.81 (m, 1 H), 7.56–7.51 (m, 1 H), 7.41–7.38 (m, 1 H), 7.31–7.28 (m, 1 H), 7.25–7.23 (m, 2 H), 7.18–7.12 (m, 2 H), 4.51–4.48 (m, 1 H), 3.47–3.43 (m, 2 H), 2.93–2.88 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 196.0, 163.2, 160.6, 140.2, 134.8, 133.6, 130.6, 130.1, 128.2, 127.2, 125.4, 124.6, 116.8, 48.4, 47.9, 31.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{14}O_2ClF$: 304.0666; found: 304.0671.

HPLC: 97% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 12.6 min (minor), 14.3 min (major).

3-(4-Bromophenyl)-5-(2-fluorophenyl)-5-oxopentanal (3p)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 73%; yellow oil; $[\alpha]_D^{24}$ –4.3 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 7.81–7.77 (m, 1 H), 7.54–7.51 (m, 1 H), 7.44–7.40 (m, 2 H), 7.24–7.11 (m, 4 H), 3.98–3.95 (m, 1 H), 3.37–3.34 (m, 2 H), 2.88–2.79 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.5, 195.9, 142.3, 134.9, 134.8, 131.8, 130.6, 129.2, 124.6, 124.5, 120.6, 116.8, 116.5, 49.5, 49.4, 34.5.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{14}O_2FBr$: 348.0161; found: 348.0159.

HPLC: 96% ee (AD-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 16.5 min (major), 19.0 min (minor).

5-(2-Furyl)-5-oxo-3-phenylpentanal (3q)
Purified by column chromatography (silica gel, PE–EtOAc, 10:1); yield: 74%; yellow oil; $[\alpha]_D^{24}$ –5.6 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70–7.69 (m, 1 H), 7.56–7.55 (m, 1 H), 7.33–7.27 (m, 4 H), 7.23–7.16 (m, 2 H), 6.52–6.51 (m, 1 H), 3.98–3.93 (m, 1 H), 3.27–3.15 (m, 2 H), 2.95–2.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 187.2, 152.6, 146.5, 142.8, 128.8, 127.3, 127.0, 117.4, 112.3,49.3, 44.6, 35.4.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{15}H_{14}O_3$: 242.0943; found: 242.0948.

HPLC: 94% ee (AS-H column, 254 nm, *n*-hexane–*i*-PrOH, 9:1, 0.8 mL/min): 19.4 min (major), 26.9 min (minor).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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