Simple Synthesis of Tetrahydrofurans via Reaction of Enolates of γ-Chloroketones with Aldehydes

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Dedicated to Professor Wojciech Stec on the occasion of his 65th birthday

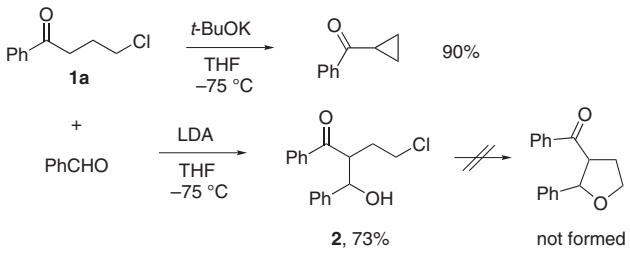
Abstract: Enolates of γ-chloropropyl ketones react with aldehydes in protic media to form aldol type adducts that cyclize to substituted tetrahydrofurans, whereas in aprotic media they react mainly along an intramolecular substitution pathway giving cyclopropyl ketones. A substantial increase in the nucleophilicity of the enolates and the electrophilicity of aldehydes favors the formation of tetrahydrofurans.

Key words: aldol reactions, enolates, halocarbanions, ketones, tetrahydrofurans

Carbanions possessing leaving groups are versatile intermediates in organic synthesis. Particularly well known and widely used are reactions of α-halocarbanions such as the Darzens synthesis of oxiranes,[1] synthesis of cyclopropanes via reaction with the Michael acceptors[2] and vicarious nucleophilic substitution of hydrogen VNS.[3] Intermolecular reactions of γ-halocarbanions are much less known, because fast intramolecular substitution leading to cyclopropanes is the dominant process.[4] Recently we have found that γ-halocarbanions generated by deprotonation of 4-chlorobutyronitrile, *tert*-butyl 4-chlorobutyrate and 3-chloropropyl phenyl sulfone with potassium *tert*-butoxide in tetrahydrofuran can be trapped by aldehydes, and subsequent intramolecular substitution in the intermediate aldol type O-anions give substituted tetrahydrofurans.[5] Modification of the electronic properties of the phenyl ring in 3-chloropropyl phenyl sulfone opened possibility for synthesis of substituted cyclopentanes and pyrrolidines via reaction of the γ-halocarbanions with Michael acceptors[6] and imines,[7] respectively.

Attempts to extend this concept to the reaction of carbanion of 4-chlorobutyrophenone (**1a**) with aldehydes failed. Under the standard conditions (*t*-BuOK, THF) the major process was the formation of cyclopropyl phenyl ketone. Its adduct to benzaldehyde was formed only in a small amount. Apparently, intramolecular substitution in the γ-chloroenolate proceeded faster than addition of the enolate to benzaldehyde. One can also suppose that in this particular case equilibrium of the addition was less favorable.

Our observation is in agreement with published results that lithium enolate of **1a** in the reaction with benzaldehyde does not form 3-benzoyl tetrahydrofuran but only cyclopropyl phenyl ketone, product of the intramolecular substitution.[8a] On the other hand the tin enolate of this ketone, when properly activated, adds to benzaldehyde, and subsequent intramolecular substitution gives tetrahydrofuran. Although treatment of **1a** in the presence of benzaldehyde even at low temperature resulted in an exclusive intramolecular substitution of the produced potassium enolate, under similar conditions the lithium enolate adds to benzaldehyde giving the aldol-type adduct **2**, as a mixture of diastereoisomers (ca. 1.3:1) that can be isolated in good yield (Scheme 1). Unfortunately attempts to convert this adduct via intramolecular substitution into the tetrahydrofuran carried out at higher temperature, via complexation of Li^+ or exchange for Bu_4N^+ failed; the only isolated product was the cyclopropane.



Scheme 1

These results can be rationalized assuming that the addition equilibrium is unfavorable, and consequently fast 1,3-substitution in the γ-chloroenolate shifts the system towards the cyclopropane. This supposition is supported by our observation that the enolate of **1a** reacts with highly electrophilic methyl phenyl glyoxalate giving the expected substituted tetrahydrofuran (Scheme 2) and that recently reported reaction of γ-chloroketones with *N*-alkyl isatine also gave tetrahydrofuran ring.[9]

The addition of the enolate to benzaldehyde should be favored in a protic solvent, due to the strong solvation of the O-anion of aldol type adduct via hydrogen bonding; thus we expected that the reaction of enolate of **1a** with aldehydes in alcohols could result in the formation of tetrahydrofurans. Indeed treatment of a solution of **1a** and benzaldehyde in ethanol with potassium *tert*-butoxide gave 2-phenyl-3-benzoyltetrahydrofuran (**4b**) in moder-

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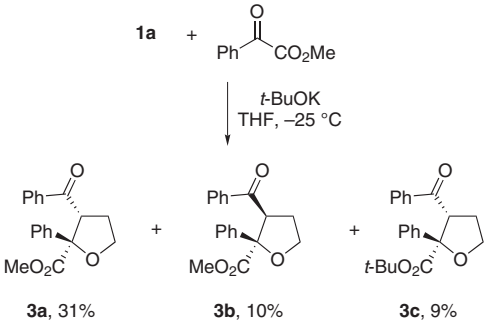
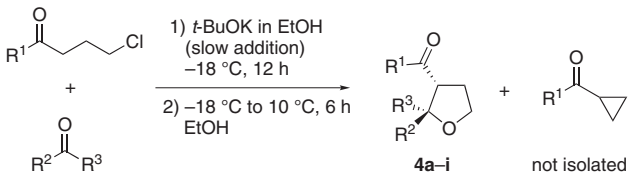


Scheme 2

ate yield. Tentative optimization of the reaction conditions provided a possibility to synthesize a series of substituted 3-aroyl tetrahydrofurans via reaction of aryl 3-chloropropyl ketones according to Scheme 3. Results are presented in Table 1.



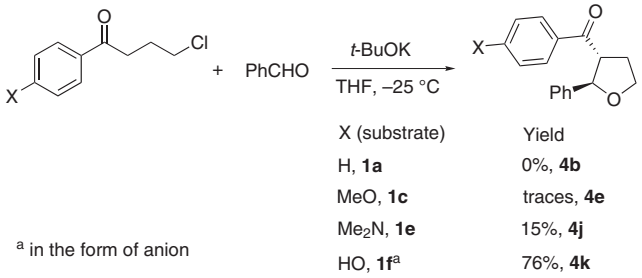
Scheme 3

Table 1 Formation of Substituted Tetrahydrofurans under Protic Conditions (Anhydrous EtOH)

Entry	R^1 (substrate)	R^2	R^3	Yield (%)
1	*p*-ClC_6H_4, **1b**	Ph	H	**4a** (32)
2	Ph, **1a**	Ph	H	**4b** (44)
3	Ph, **1a**	*n*-C_9H_{19}	H	**4c** (23)[a]
4	Ph, **1a**	Ph	CO_2Me	**4d** (76)[b]
5	*p*-$MeOC_6H_4$, **1c**	Ph	H	**4e** (76)
6	*p*-$MeOC_6H_4$, **1c**	*n*-C_9H_{19}	H	**4f** (32)[a]
7	*p*-$MeOC_6H_4$, **1c**	Me	H	**4g** (51)[c]
8	*p*-$MeOC_6H_4$, **1c**	2-thienyl	H	**4h** (75)
9	Me, **1d**	Ph	H	**4i** (40)[a,d]

[a] Unidentified by-products were observed.
[b] Complete transesterification into ethyl ester was observed.
[c] Mixture of isomers, *trans*:*cis* = 9:1.
[d] Aldol-type condensation of the methyl group of ketone with benzaldehyde leads to the cinnamyl substituted tetrahydrofuran. In the product: R^1 = styryl, mixture of *E*/*Z* isomers (5:2).

The results indicate that the reaction proceeds better with more nucleophilic enolates and more electrophilic electrophiles. In order to verify this supposition, reaction with benzaldehyde of 4-chlorobutyrophenones containing electron-donating substituents in the phenyl ring in the presence of potassium *tert*-butoxide in THF was tested. The results are presented in Scheme 4.

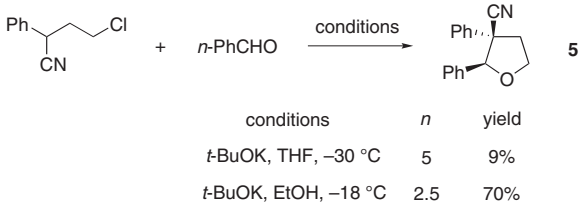


Scheme 4

Thus indeed highly nucleophilic enolates reacted with benzaldehyde in aprotic medium giving tetrahydrofurans, whereas less nucleophilic enolates under these conditions gave cyclopropanes. The higher nucleophilicity of enolates accelerates both of the competing reactions: intramolecular substitution leading to cyclopropanes and addition to benzaldehyde. However, it favors formation of tetrahydrofurans due to deceleration of dissociation of the aldol-type adducts thus increasing the addition equilibrium.

A favorable effect of protic solvents on the addition equilibrium and therefore formation of tetrahydrofurans was also confirmed by the reaction of benzaldehyde with 2-phenyl-4-chlorobutyronitrile.

Deprotonation of this nitrile[10] in the presence of a 5-fold excess of benzaldehyde in THF gave the expected substituted tetrahydrofuran in low yield of 9%,[5b] whereas in ethanol with a smaller excess of benzaldehyde this product was obtained in high yield (Scheme 5).



Scheme 5

In conclusion we have shown that, contrary to the previous results, enolates of γ-chloroketones can react with aldehydes to form substituted tetrahydrofurans provided the reactions are carried out in protic media or reacting partners exhibit high nucleophilic or electrophilic activity.

All reagents were used as obtained from the commercial sources. All reactions were carried out under an atmosphere of argon in dried glassware using standard Schlenk techniques. Tetrahydrofuran was distilled from potassium–benzophenone ketyl and anhydrous grade of ethanol was used. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with $CDCl_3$ as standard (δ = 7.26 ppm and 77 ppm) on a Bruker 500 or a Varian 200 spectrometer. IR data were recorded on an FT-IR Perkin Elmer Spectrum 2000 using a film (for oils) or in KBr pellets (for solids). Mass spectrometric data were obtained by electron ionization on an AMD 604 Intectra

GmbH spectrometer in electron ionization mode or on a Mariner™ in electrospray mode. Microanalyses were performed at the Institute of Organic Chemistry, Polish Academy of Sciences.

Compound **1a** was commercially available (Aldrich). Compounds **1b** (yield: 61%, mp 28–31 °C; Lit.[11] 29–30 °C) and **1c** (yield: 75%, mp 31–32 °C; Lit.[11] 31–32 °C) were prepared in a Friedel–Crafts reaction according to the procedure described in the literature.[12] Compound **1d** was commercially available (Fluka). Compound **1e** was prepared from *N*,*N*-dimethylaniline and *N*,*N*-diethyl-4-chlorobutyramide in a Vilsmeier-type reaction[13] (yield: 8%, mp 94–95 °C; Lit.[14] 93–94 °C). Compound **1f**[15] was a side-product in the synthesis of **1c** (yield: 9%, mp 113–115 °C; Lit.[16] 114–115 °C, $AlCl_3$-catalyzed demethylation).

Reaction of 1a with Benzaldehyde (Scheme 1)

To a solution of **1a** (182 mg, 1 mmol) in THF (4 mL) at –75 °C under argon, LDA (1 mL, 2 mmol, 2.0 M solution in THF–heptane–ethylbenzene, Fluka) was added dropwise. After 1 min a solution of benzaldehyde (320 mg, 3 mmol) in THF (2 mL) was added dropwise. After next 3 min an aq solution of NH_4Cl was added, mixture was extracted with EtOAc (3 × 50 mL), washed with brine and dried with $MgSO_4$. Column chromatography with hexane–EtOAc gave **2** (210 mg, 73%) as a mixture of diastereoisomers (ca 1.3:1 according to ^{1}H NMR); oil.

IR (neat): 3469, 3063, 3030, 2961, 1674, 1596, 1579, 1493, 1448, 1366, 1297, 1257, 1214, 1050, 1027, 1001, 971, 762, 701, 686, 552 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.00–8.09 (m, 4 H), 7.24–7.73 (m, 16 H), 5.18 (dd, *J* = 2.2, 4.3 Hz, 1 H, isomer a), 5.06 (dd, *J* = 6.0, 6.4 Hz, 1 H, isomer b), 4.23–4.35 (m, 1 H, isomer b), 4.13–4.23 (m, 1 H, isomer a), 3.34–3.68 (m, 4 H), 3.25 (d, *J* = 6.0 Hz, 1 H, isomer b), 3.17 (d, *J* = 2.2 Hz, 1 H, isomer a), 1.92–2.57 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.5 (isomer b), 203.7 (isomer a), 142.0 (isomer b), 141.2 (isomer a), 137.6 (isomer b), 136.6 (isomer a), 133.7 (isomer a), 133.6 (isomer b), 128.7, 128.6, 128.5, 128.5, 128.5, 128.4, 128.0 (isomer b), 127.7 (isomer a), 126.2 (isomer b), 125.9 (isomer a), 75.7 (isomer b), 73.5 (isomer a), 50.1 (isomer a), 49.3 (isomer b), 43.4 (isomer a), 42.6 (isomer b), 32.8 (isomer b), 29.8 (isomer a).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{17}O_2{}^{35}Cl$: 288.09171; found: 288.09122.

MS (EI): *m*/*z* (rel. intensity) = 288 (1), 270 (3), 225 (7), 182 (21), 133 (45), 120 (18), 105 (100).

Anal. Calcd for $C_{17}H_{17}O_2Cl$: C, 70.71; H, 5.93; Cl, 12.23. Found: C, 70.57; H, 5.80; Cl, 12.53.

Preparation of Tetrahydrofuran Derivatives in Ethanol (Scheme 3); General Procedure

To a solution of 3-chloropropyl ketone (1 mmol) and benzaldehyde (265 mg, 2.5 mmol) in anhyd EtOH (2 mL) at –18 °C under argon, *t*-BuOK (230 mg, 2.1 mmol) in anhyd EtOH (0.85 mL) was added dropwise via an infusion pump for 12 h. Then the mixture was slowly warmed to 10 °C within 6 h. Then an aq solution of NH_4Cl was added, the mixture was extracted with EtOAc (3 × 50 mL), washed with brine and dried with $MgSO_4$. Column chromatography with hexane–EtOAc gave the product **4**. Less polar fractions of cyclopropane derivatives and unreacted aldehydes were not separated or characterized in a routine procedure.

Reactions *p*-Substituted 4-Chlorobutyrophenones with Benzaldehyde under Aprotic Conditions (Scheme 4)

To a solution of 3-chloropropyl ketone (1 mmol) and benzaldehyde (149 mg, 1.4 mmol) in THF (4 mL) at –25 °C under argon, *t*-BuOK (2 mmol; 3 mmol in case of **1f**) in THF (2 mL) was added dropwise. After 1 h, the flask was placed in a refrigerator (–18 °C) for 24 h. Then an aq solution of NH_4Cl was added, the mixture was extracted with EtOAc (3 × 50 mL), washed with brine and dried with $MgSO_4$. Column chromatography with hexane–EtOAc gave the product **4**.

3a

Oil.

IR (neat): 3061, 2951, 2891, 1759, 1729, 1682, 1596, 1580, 1491, 1448, 1359, 1282, 1228, 1184, 1092, 1002, 769, 742, 699, 583 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00–8.04 (m, 2 H), 7.68–7.73 (m, 2 H), 7.61–7.66 (m, 1 H), 7.50–7.55 (m, 2 H), 7.39–7.44 (m, 2 H), 7.33–7.38 (m, 1 H), 4.61 (dd, *J* = 2.3, 8.2 Hz, 1 H), 4.25–4.35 (m, 2 H), 3.69 (s, 3 H), 2.23–2.32 (m, 1 H), 2.10–2.17 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.2, 172.0, 140.9, 136.0, 133.4, 128.8, 128.5, 128.5, 128.1, 125.6, 89.6, 68.0, 56.3, 52.6, 30.0.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}O_4Na$: 333.10973; found: 333.1111.

3b

Oil.

IR (neat): 2953, 2890, 1727, 1681, 1596, 1492, 1448, 1360, 1254, 1225, 1067, 1034, 736, 692, 530 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66–7.69 (m, 2 H), 7.40–7.45 (m, 1 H), 7.27–7.32 (m, 2 H), 7.23–7.26 (m, 2 H), 7.00–7.04 (m, 3 H), 5.21 (dd, *J* = 3.3, 8.0 Hz, 1 H), 4.49–4.55 (m, 1 H), 4.09–4.15 (m, 1 H), 3.79 (s, 3 H), 2.47–2.55 (m, 1 H), 2.22–2.31 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.6, 173.7, 137.8, 136.1, 132.7, 128.2, 128.2, 127.9, 127.8, 125.7, 91.1, 68.6, 53.3, 51.4, 30.0.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}O_4Na$: 333.10973; found: 333.11015.

3c

Mp 97–100 °C.

IR (neat): 3484, 3062, 2977, 2890, 1752, 1719, 1682, 1597, 1580, 1448, 1368, 1252, 1227, 1161, 1094, 1001, 844, 774, 750, 699, 584 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.98–8.06 (m, 2 H), 7.29–7.72 (m, 8 H), 4.52 (dd, *J* = 2.4, 8.2 Hz, 1 H), 4.13–4.39 (m, 2 H), 1.97–2.30 (m, 2 H), 1.24 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.2, 169.4, 141.4, 136.3, 133.2, 128.7, 128.4, 128.2, 127.8, 125.6, 89.8, 82.1, 67.8, 55.3, 30.1, 27.6.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{24}O_4Na$: 375.15668; found: 375.15844.

Stereochemistry was established according to COSY and NOE spectra of **3a** and **3b**.

4a

Oil.

IR (neat): 2874, 1681, 1589, 1489, 1454, 1401, 1359, 1282, 1216, 1092, 1063, 1011, 843, 758, 700, 479 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.79 (m, 2 H), 7.19–7.41 (m, 7 H), 5.20 (d, *J* = 7.3 Hz, 1 H), 4.21–4.34 (m, 1 H), 4.01–4.15 (m, 1 H), 3.80–3.93 (m, 1 H), 2.22–2.55 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.6, 141.3, 139.8, 134.8, 129.9, 128.9, 128.5, 127.8, 125.8, 83.3, 68.5, 54.9, 32.0.

MS (EI): *m*/*z* (rel. intensity) = 288 (3), 286 (9), 259 (26), 257 (61), 182 (8), 180 (20), 141 (33), 139 (100).

Anal. Calcd for $C_{17}H_{15}O_2Cl$ (286.076): C, 71.21; H, 5.27; Cl, 12.36. Found: C, 71.17; H, 5.30; Cl, 12.51.

4b
All data are consistent with those described in the literature.[8a]

4c
Oil.

IR (neat): 2926, 2855, 1682, 1597, 1581, 1448, 1366, 1217, 1069, 1002, 702, 662 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.92–8.00 (m, 2 H), 7.43–7.64 (m, 3 H), 4.13–4.24 (m, 1 H), 3.95–4.08 (m, 1 H), 3.81–3.95 (m, 1 H), 3.56–3.69 (m, 1 H), 2.26–2.41 (m, 1 H), 2.06–2.23 (m, 1 H), 1.07–1.85 (m, 16 H), 0.80–0.92 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.5, 136.8, 133.2, 128.7, 128.4, 82.0, 67.5, 51.5, 35.0, 31.9, 31.9, 29.6, 29.5, 29.5, 29.3, 26.3, 22.7, 14.1.

MS (EI): *m*/*z* (rel. intensity) = 302 (8), 259 (5), 175 (56), 162 (48), 148 (22), 105 (100), 77 (20).

Anal. Calcd for $C_{20}H_{30}O_2$ (302.458): C, 79.42; H, 10.10. Found: C, 79.27; H, 10.09.

4d
Oil.

IR (neat): 3062, 2980, 2891, 1756, 1725, 1682, 1596, 1580, 1448, 1363, 1279, 1228, 1177, 1091, 1001, 858, 771, 742, 699, 584 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.95–8.06 (m, 2 H), 7.27–7.72 (m, 8 H), 4.57 (dd, *J* = 2.4, 8.2 Hz, 1 H), 4.25 (dd, *J* = 3.6, 8.2 Hz, 1 H), 4.16–4.37 (m, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 2.00–2.34 (m, 2 H), 1.11 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.1, 171.1, 140.9, 136.0, 133.2, 128.7, 128.4, 128.3, 128.0, 125.5, 89.5, 67.9, 61.4, 56.0, 30.0, 13.8.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}O_4Na$: 347.1254; found: 347.1242.

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.22. Found: C, 70.88; H, 5.87.

4e
Oil.

IR (neat): 2937, 2873, 1670, 1600, 1576, 1511, 1454, 1420, 1360, 1310, 1263, 1221, 1170, 1062, 1028, 842, 759, 701, 612, 514 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.75–7.84 (m, 2 H), 7.19–7.38 (m, 5 H), 6.82–6.91 (m, 2 H), 5.23 (d, *J* = 7.3 Hz, 1 H), 4.19–4.32 (m, 1 H), 4.01–4.15 (m, 1 H), 3.84 (s, 3 H), 3.81–3.95 (m, 1 H), 2.22–2.54 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.2, 163.6, 141.7, 130.8, 129.6, 128.4, 127.6, 125.9, 113.7, 83.3, 68.6, 55.5, 54.5, 32.3.

MS (EI): *m*/*z* (rel. intensity) = 282 (9), 254 (100), 176 (12), 135 (93), 108 (34).

Anal. Calcd for $C_{18}H_{18}O_3$ (282.339): C, 76.57; H, 6.43. Found: C, 76.46; H, 6.56.

4f
Oil.

IR (neat): 2926, 2855, 1673, 1601, 1576, 1511, 1465, 1420, 1367, 1310, 1261, 1231, 1171, 1032, 842, 612, 513 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.90–8.00 (m, 2 H), 6.91–7.00 (m, 2 H), 4.09–4.24 (m, 1 H), 3.91–4.07 (m, 1 H), 3.88 (s, 3 H), 3.80–3.91 (m, 1 H), 3.50–3.65 (m, 1 H), 2.04–2.38 (m, 2 H), 1.10–1.71 (m, 16 H), 0.78–0.92 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.0, 163.6, 130.6, 129.8, 113.8, 82.1, 67.6, 55.5, 51.1, 35.0, 32.0, 31.9, 29.6, 29.5, 29.3, 29.3, 26.3, 22.7, 14.1.

MS (EI): *m*/*z* (rel. intensity) = 332 (6), 304 (6), 289 (3), 234 (2), 205 (18), 192 (34), 177 (14), 150 (10), 135 (100).

Anal. Calcd for $C_{21}H_{32}O_3$ (332.235): C, 75.86; H, 9.70. Found: C, 76.10; H, 9.91.

4g
***trans*-Isomer**
Oil.

Described in the literature,[8b] but some data are moderately consistent.

IR (neat): 2972, 2870, 1670, 1601, 1575, 1511, 1458, 1420, 1371, 1310, 1262, 1223, 1171, 1117, 1090, 1028, 848, 612, 604, 514 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.93–7.97 (m, 2 H), 6.94–6.98 (m, 2 H), 4.17–4.26 (m, 1 H), 4.01–4.06 (m, 1 H), 3.88 (s, 3 H), 3.85–3.92 (m, 1 H), 3.49–3.57 (m, 1 H), 2.26–2.35 (m, 1 H), 2.17–2.25 (m, 1 H), 1.32 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.8, 163.7, 130.7, 129.9, 113.9, 78.3, 67.6, 55.5, 52.7, 31.8, 20.0.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}O_3$: 220.10994; found: 220.11029.

MS (EI): *m*/*z* (rel. intensity) = 220 (5), 192 (5), 177 (21), 164 (5), 152 (12), 135 (100).

***cis*-Isomer**
Oil.

IR (neat): 3425, 2975, 1716, 1672, 1601, 1575, 1512, 1460, 1421, 1379, 1310, 1258, 1233, 1172, 1114, 1085, 1027, 845, 606, 515 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.91–7.99 (m, 2 H), 6.91–7.00 (m, 2 H), 4.41–4.56 (m, 1 H), 3.98–4.24 (m, 2 H), 3.88 (s, 3 H), 3.85–3.90 (m, 1 H), 2.48–2.68 (m, 1 H), 1.94–2.11 (m, 1 H), 0.94 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.2, 163.5, 130.7, 130.5, 113.9, 76.4, 67.1, 55.5, 49.4, 28.0, 17.4.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}O_3$: 220.10994; found: 220.10903.

MS (EI): *m*/*z* (rel. intensity) = 220 (10), 205 (5), 192 (48), 177 (33), 161 (9), 150 (5), 135 (100).

Stereochemistry was established according to COSY and NOE spectra.

4h
Oil.

IR (neat): 2938, 1670, 1600, 1575, 1511, 1421, 1360, 1313, 1262, 1227, 1171, 1057, 1030, 841, 705, 611, 514 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.82–7.91 (m, 2 H), 7.21–7.27 (m, 1 H), 6.86–6.95 (m, 4 H), 5.49 (d, *J* = 6.8 Hz, 1 H), 4.16–4.28 (m, 1 H), 3.91–4.12 (m, 2 H), 3.85 (s, 3 H), 2.23–2.56 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.5, 163.7, 144.9, 130.8, 129.3, 126.7, 124.7, 124.5, 113.8, 79.5, 68.3, 55.5, 54.5, 31.8.

MS (EI): *m*/*z* (rel. intensity) = 288 (23), 260 (55), 227 (13), 176 (14), 153 (7), 135 (100), 111 (10), 108 (23), 92 (11), 77 (16).

Anal. Calcd for $C_{16}H_{16}O_3S$ (288.082): C, 66.64; H, 5.59; S, 11.12. Found: C, 66.63; H, 5.65; S, 11.17.

4i
Oil.

IR (neat): 3061, 3029, 2946, 2872, 1686, 1656, 1608, 1575, 1494, 1450, 1359, 1177, 1110, 1061, 980, 762, 699, 567, 485 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.54 (m, 11 H), 6.82 (d, *J* = 12.7 Hz, 1 H, *Z* isomer), 6.66 (d, *J* = 16.1 Hz, 1 H, *E* isomer), 6.10 (d, *J* = 12.8 Hz, 1 H, *Z* isomer), 5.08 (d, *J* = 7.2 Hz, 1 H, *E* isomer),

5.05 (d, *J* = 7.3 Hz, 1 H, *Z* isomer), 3.87–4.31 (m, 4 H), 3.41–3.55 (m, 1 H, *E* isomer), 3.16–3.29 (m, 1 H, *Z* isomer), 2.10–2.44 (4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.2 (*Z* isomer), 199.1 (*E* isomer), 143.9 (*E* isomer), 141.6 (*Z* isomer), 134.8 (*Z* isomer), 134.2 (*E* isomer), 130.7, 129.7, 129.5, 128.9, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 126.5, 126.0, 125.9, 125.6, 83.3 (*E* isomer), 83.0 (*Z* isomer), 68.6, (*E* isomer), 68.4 (*Z* isomer), 59.9 (*Z* isomer), 57.8 (*E* isomer), 31.0 (*E* isomer), 30.7 (*Z* isomer).

HRM (EI): *m*/*z* calcd for $C_{19}H_{18}O_2$: 278.13068; found: 278.13019.

MS (EI): *m*/*z* (rel. intensity) = 278 (100), 250 (21), 232 (12), 187 (34), 186 (34), 173 (26), 172 (29), 171 (40), 157 (7), 155 (11), 145 (48), 131 (88), 105 (100), 103 (84), 91 (29), 77 (93).

4j

Mp 128–130 °C.

IR (KBr): 3441, 2870, 1654, 1597, 1375, 1286, 1233, 1189, 1170, 1062, 825, 759, 733, 701, 589 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ =7.69–7.78 (m, 2 H), 7.17–7.39 (m, 5 H), 6.53–6.62 (m, 2 H), 5.25 (d, *J* = 7.4 Hz, 1 H), 4.18–4.31 (m, 1 H), 3.97–4.15 (m, 1 H), 3.79–3.92 (m, 1 H), 3.03 (s, 6 H), 2.21–2.51 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.5, 153.4, 142.0, 130.7, 128.3, 127.4, 125.9, 124.4, 110.6, 83.4, 68.6, 53.9, 40.0, 32.6.

MS (EI): *m*/*z* (rel. intensity) = 295 (26), 267 (100), 236 (11), 207 (4), 188 (7), 163 (10), 148 (80), 130 (110, 129 (11), 121 (71).

Anal. Calcd for $C_{19}H_{21}NO_2$ (295.157): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.20; H, 7.18; N, 4.59.

In the reaction of **1e**, the product of aldol addition of cyclopropyl *p*-*N*,*N*-dimethylaminophenyl ketone to benzaldehyde was also observed.

4k

Mp 129–130 °C.

IR (KBr): 3104, 1665, 1604, 1579, 1515, 1368, 1293, 1264, 1226, 1202, 1171, 1031, 1017, 983, 912, 848, 758, 703, 615, 507 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.78 (m, 2 H), 7.19–7.37 (m, 5 H), 6.74–6.82 (m, 2 H), 6.48 (br s, 1 H), 5.24 (d, *J* = 7.1 Hz, 1 H), 4.21–4.34 (m, 1 H), 4.03–4.16 (m, 1 H), 3.83–3.97 (m, 1 H), 2.20–2.55 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.5, 160.6, 141.3, 131.2, 129.4, 128.5, 127.8, 125.9, 115.4, 83.5, 68.6, 54.4, 32.2.

MS (EI): *m*/*z* (rel. intensity) = 268 (9), 240 (100), 162 (16), 147 (15), 121 (82).

Anal. Calcd for $C_{17}H_{16}O_3$ (268.312): C, 76.10; H, 6.01. Found: C, 76.30; H, 5.93.

5

Mp 102–103 °C.

IR (KBr): 3385, 3064, 3033, 2961, 2891, 2240, 1960, 1721, 1602, 1496, 1451, 1274, 1088, 1065, 1028, 996, 915, 755, 719, 699, 568, 521, 483 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.47 (m, 5 H), 7.28–7.36 (m, 3 H), 7.12–7.16 (m, 2 H), 4.99 (s, 1 H), 4.55–4.61 (m, 1 H), 4.36–4.42 (m, 1 H), 2.87–2.99 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.4, 134.6, 129.1, 128.8, 128.5, 128.1, 126.6, 126.4, 120.0, 90.1, 67.0, 55.6, 41.2.

MS (EI): *m*/*z* (rel. intensity) = 249 (30), 143 (100), 131 (3), 116 (40), 105 (15), 103 (4), 91 (6), 89 (7), 77 (13).

Anal. Calcd for $C_{17}H_{15}NO$ (249.115): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.80; H, 6.00; N, 5.52.

Stereochemistry was established according to COSY and NOE spectra of **5**.

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References

(1) (a) Roux-Schmitt, M.-C.; Seyden-Penne, J.; Wolfe, S. *Tetrahedron* **1972**, *28*, 4965. (b) Newman, M. S.; Magerlein, B. J. *Org. React. (N.Y.)* **1949**, *5*, 413.
(2) (a) McCoy, L. *J. Am. Chem. Soc.* **1958**, *80*, 658. (b) McCoy, L. *J. Am. Chem. Soc.* **1960**, *82*, 6414. (c) Zwanenburg, B.; De Kimpe, N. In *Houben-Weyl*, Vol. E17a; Thieme Verlag: Stuttgart, New York, **1997**, 45.
(3) (a) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. (b) Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631.
(4) (a) Mann, J. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 839. (b) Gronert, S.; Azizian, K.; Friedman, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3220.
(5) (a) Mąkosza, M.; Przyborowski, J.; Klajn, K.; Kwast, A. *Synlett* **2000**, 773. (b) Mąkosza, M.; Judka, M. *Chem. Eur. J.* **2002**, 4234. (c) Barbasiewicz, M.; Judka, M.; Mąkosza, M. *Russ. Chem. Bull.* **2004**, *53*, 1771.
(6) Mąkosza, M.; Judka, M. *Synlett* **2004**, 717.
(7) Mąkosza, M.; Judka, M. *Helv. Chim. Acta* **2005**, *88*, 1676.
(8) (a) Shibata, I.; Yamasaki, H.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 6909. (b) For a similar synthesis with titanium enolates, see: Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987.
(9) Smet, M.; van Osterwijck, C.; van Hecke, K.; van Meervelt, L.; Vandendriessche, A.; Dehaen, W. *Synlett* **2004**, 2388.
(10) For similar reactions of 4-chlorobutyronitrile, see also: Fleming, F. F.; Gudipati, V.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 3943.
(11) Schliemann, W.; Buege, A.; Reppel, L. *Pharmazie* **1980**, *35*, 140.
(12) Yu, J.-W.; Huang, S. K. *Org. Prep. Proced. Int.* **1997**, *29*, 214.
(13) (a) Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* **1972**, *94*, 2869. (b) See also: Zollinger, B. *Helv. Chim. Acta* **1959**, *42*, 1659.
(14) Aldrich Chemical Co., Inc.; US Patent 3476762, **1970**; *Chem. Abstr.* **1970**, *72*, 31633z.
(15) For direct synthesis of *p*-hydroxy 4-chlorobutyrophenone, see for example: Kalyanam, N.; Dave, K. G.; Likhate, M. A. *Synth. Commun.* **1988**, *18*, 2183.
(16) Janssen, P. A. J. US Patent, 2973365, **1961**; *Chem. Abstr.* **1961**, *55*, 15515.