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Asymmetric Direct Aldol Reaction Assisted by Water and Proline-derived Tetrazole Catalyst

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General: ^{1}H-NMR spectra were measured on a Varian Gemini-300 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, and m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C-NMR spectra were recorded on a Varian Gemini-300 (75 MHz) spectrometer at ambient temperature. Chemical shifts are recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.07 ppm). All aldol reactions were carried out using a test tube stopped by a septum rubber under an atmosphere of air. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254 0.25 mm) were used. In some instances, the products were purified by preparative column chromatography on silica gel (E. Merck Art. 9385).

Organic substrates chloral, chloral monohydrate, **2**, **3, 6** and other ketones in Table 1 were all commercially available and used without any purification except that **2** and **3** were used after bulb-to-bulb distillation. Product **15** ($[\alpha]^{29}_{D}$ = +6.21° (*c* 1.03, $CHCl_3$ for 99% ee; chiral GC analysis data (column: β–DM(astec. Ltd)): retention times: t_R = 24.5 min (*S*) and t_R = 26.8 min (*R*) using N_2 as a carrier gas pressure of 80 hPa (injection temperature: 180 °C; column temperature: 80 °C)) is known compound (reference: Barili, P. L.; Catelani, G.; Giorgi, R.; Mastrorilli, E.; Rousini, C. *Enantiomer*, **1998**, *3*, 357). The relative configuration (*syn* or *anti*) and the absolute configuration of **4**, **5**, and **14** were determined based on the X-ray single crystal analyses of (2*R*, 1'*R*)-*syn*-**4**, and (2*S*, 1'*R*)-*anti*-**5**, and by ^{1}H-NMR spectroscopy. In general, the hydroxy-attached methyne proton of 2-(1'-hydroxy-1-substituted)cyclohexan-1-one and -cyclopentan-1-one in the *syn* form gives more down-field shift, while that in the *anti* form gives relatively up-field shifts. See also: (a) Heathcock, H. C. In *Asymmetric Synthesis*; Morrison, J.D.,Ed.; Academic: Orland,

1984; Vol. 3, Part B, pp111-212. (b) Kiehlmann, E.; Menon, B. C.; McGillivray, N. *Can. J. Chem*. **1973**, *51*, 3177 (c) Kiehlmann, E.; Loo, P.-W. *Can. J. Chem*. **1969**, *47*, 2029. (d) Yanagisawa, A.; Matsumoto, H.; Nakashima, K.; Asakawa, H.; Yamamoto, H. *J. Am. Chem. Soc*. **1997**, *119*, 9319 (e) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc*. **1999**, *121*, 4982.

General Procedure for the Direct Aldol Reaction of Chloral Monohydrate. The reaction with cyclopentanone in the presence of tetrazole catalyst **1** is representative. To a mixture of tetrazole **1** (3.5 mg, 0.025 mmol) in acetonitrile (1.0 mL) was added cyclopentanone (88.5 μL, 1.0 mmol) and chloral monohydrate (82.7 mg, 0.5 mmol) at 23 °C under air in a closed system. The reaction mixure was stirred at 30 °C for 48 h. The reaction mixture was quenched with aq. NaCl. The organic layer was extracted with EtOAc, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/Et_2O, 4:1) to give product **4** in an isolated yield of 83%.

Spectral and Analytical Data of New Compounds:

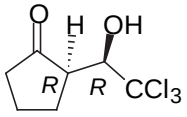
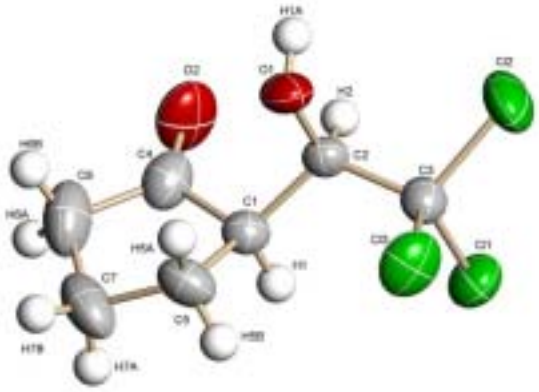


Figure. The X-ray single crystal structure of (2*R*, 1'*R*)-**4**.



(2*R*, 1'*R*)-2-(1'-Hydroxy-2',2',2'-trichloroethyl)cyclopentan-1-one ((2*R*, 1'*R*)-*syn*-**4**): (IR (KBr) 3372, 2974, 2895, 2689, 1728, 1423, 1329, 1259, 1145, 1041, 925, 808 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 4.75 (1H, dd, *J* = 5.4, 1.2 Hz, C*H*-O), 3.22 (1H, bs), 2.85 (1H, t, *J* = 9.9 Hz), 2.44~2.06 (5H, m), 1.88~1.72 (1H, m); typical chemical shifts of the *anti*-product: δ 5.55 (1H, d, *J* = 5.7 Hz, -OH), 4.23 (1H, t, *J* = 5.7 Hz, C*H*-O), 2.75~1.80 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.9, 103.0, 80.6, 50.9, 37.6, 23.1, 20.7; Anal. Calcd for

$C_7H_9Cl_3O_2$: C, 36.32, H, 3.92; Found: C, 36.25, H, 3.94. $[\alpha]^{20}_D$ = +69.9° (*c* 1.01, $CHCl_3$, for the *syn* product of 99% ee), The chiral HPLC analytical data (column AD-H): retention times: t_R = 24.98 min ((2*S*, 1'*S*): *syn*, minor enantiomer) and t_R = 34.90 min ((2*R*, 1'*R*): *syn*, major enantiomer) using *i*-PrOH/hexane (1/50) as eluent at a flow rate of 1.0 mL/min; t_R = 22.86 (*anti*, major enantiomer) and t_R = 30.05 (*anti*, minor enantiomer).

Crystallographic data (excluding structure factors) for the structure of **4** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-216553. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.au.uk).

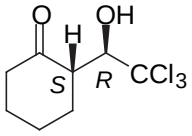
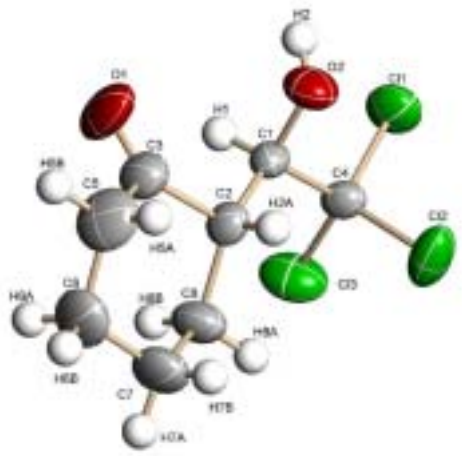
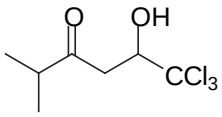


Figure. The X-ray single crystal structure of (2*S*, 1'*R*)-**5**.

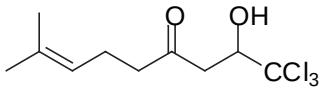


(2*S*, 1'*R*)-2-(1'-Hydroxy-2',2',2'-trichloroethyl)cyclohexan-1-one ((2*S*, 1'*R*)-*anti*-**5**): IR (KBr) 3406, 2940, 2860, 1705, 1446, 1406, 1304, 1252, 1132, 1070, 1026, 914, 814, 742 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 6.55 (1H, d, *J* = 9.6 Hz, -OH), 4.00 (1H, dd, *J* = 9.6, 1.5 Hz, C*H*-O), 3.21~3.05 (1H, m), 2.54~2.36 (2H, m), 2.32~1.92 (4H, m), 1.90~1.64 (2H, m); typical chemical shifts of the *syn*-product: δ 5.02 (1H, dd, *J* = 5.7, 2.1 Hz, C*H*-O), 3.11~3.01 (1H, m), 3.01 (1H, d, *J* = 5.7 Hz), 2.58~2.32 (3H, m), 2.19~2.07 (1H, m), 2.02~1.93 (1H, m), 1.90~1.61 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8 (major), 209.5 (minor), 103.3 (minor), 87.2 (major), 77.4, 52.2 (minor), 48.6 (major), 43.8 (major), 42.2 (minor), 35.5, 28.6 (major), 28.1 (minor), 27.5, 25.4 (major), 24.9 (minor); HRMS (FAB): Exact Mass Calcd for $C_8H_{11}C_{l3}O_2+H^+$: 244.9903. Found: 244.9887. $[\alpha]^{20}_D$ = -26.2° (*c* 0.68, $CHCl_3$, for the *anti*

product of 97% ee), The chiral HPLC analytical data (column AD-H): retention times: t_R = 16.02 min ((2*R*, 1'*S*): *anti*, minor enantiomer) and t_R = 20.56 min ((2*S*, 1'*R*): *anti*, major enantiomer) and t_R = 26.48 min (*syn*, major enantiomer) and t_R = 32.75 min (*syn*, minor enantiomer) using *i*-PrOH/hexane (1/50) as eluent at a flow rate of 1.0 mL/min. Crystallographic data (excluding structure factors) for the structure of **5** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-216552. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.au.uk).

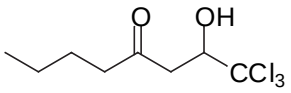


6,6,6-Trichloro-5-hydroxy-2-methylhexan-3-one (**7**): IR (film) 3492, 2982, 2930, 1719, 1467, 1285, 1366, 1275, 1107, 1057, 808, 766cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.67 (1H, ddd, *J* = 8.7, 4.2, 2.1 Hz), 3.82 (1H, d, *J* =4.2 Hz), 3.13 (1H, dd, *J* = 17.1, 2.1 Hz) , 2.97 (1H, dd, *J* = 17.1, 8.7 Hz) , 2.68 (1H, septet, *J* = 6.9 Hz), 1.16 (6H, d, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 102.5, 78.8, 42.1, 41.7, 17.9, 17.8; HRMS (FAB): Exact Mass Calcd for $C_7H_{11}C_{l3}O_2$+H^+: 233.9903. Found: 232.9899. $[\alpha]^{27}_D$ = +40.4° (*c* 1.10, $CHCl_3$ for 97% ee), The chiral HPLC analytical data (column AD-H): retention times: t_R = 17.06 min (major isomer) and t_R = 21.16 min (minor) using *i*-PrOH/hexane (1/50) as eluent at a flow rate of 1.0 mL/min.

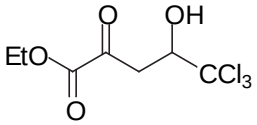


9,9,9-Trichloro-8-hydroxy-2-methyl-2-octen-6-one (**8**) IR (film) 3445, 2971, 2918, 1717, 1402, 1375, 1273, 1092, 984, 812 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 5.08 (1H, t, *J* = 7.2 Hz), 4.67 (1H, ddd, *J* = 9.0, 4.5, 2.1 Hz), 3.97 (1H, d, *J* = 4.5 Hz) , 3.09 (1H, dd, *J* = 17.4, 2.1 Hz)), 2.92 (1H, dd, *J* = 17.1, 9.0 Hz), 2.55 (2H, t, *J* = 7.2 Hz), 2.30 (2H, td, *J* = 7.2, 7.2 Hz), 1.68 (3H, s), 1.62 (3H, s) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 133.2, 122.1, 102.5,

78.6, 44.4, 43.8, 25.6, 22.2, 17.6; HRMS (FAB): Exact Mass Calcd for $C_{10}H_{15}C_{l3}O_2$+H^+: 272.0138. Found: 272.0130. $[\alpha]^{27}_D$ = +24.9° (*c* 1.20, $CHCl_3$ for 82% ee), The chiral HPLC analytical data (column AD-H): retention times: t_R = 22. 65 min (major) and t_R = 26.70 min (minor) using *i*-PrOH/hexane (1/50) as eluent at a flow rate of 1.0 mL/min.

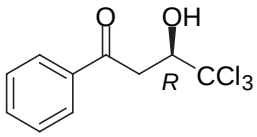


8,8,8-Trichloro-7-hydroxyoctan-5-one (**9**): IR (film) 3441, 2961, 2871, 1713, 1462, 1374, 1271, 1109, 1043, 992, 812cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.67 (1H, dd, *J* = 9.0, 2.1 Hz), 3.78 (1H, bs), 3.09 (1H, dd, *J* = 17.1, 2.1 Hz) , 2.92 (1H, dd, *J* = 17.1, 9.0 Hz) , 2.52 (2H, t, *J* = 7.5 Hz), 1.61 (2H, tt, *J* = 7.2, 7.2 Hz), 1.34 (2H, qt, *J* = 7.5, 7.5 Hz), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 102.4, 78.7, 44.2, 43.6, 25.6, 22.2, 13.8; HRMS (FAB): Exact Mass Calcd for $C_9H_{15}C_{l3}O_2$+H^+: 247.0059. Found: 247.0080. $[\alpha]^{26}_D$ = +29.4° (*c* 1.10, $CHCl_3$ for 82% ee), The ee was determined by converting it to the trifluoroacetate derivative (trifluoroacetic anhydride, Py, cat. DMAP, $ClCH_2CH_2Cl$, rt) and subsequently by chiral GC analysis using the chiral column γ-TA (astec). The chiral GC analytical data (column γ -TA): retention times: : t_R = 40.89 min (minor) and t_R = 42.69 min (major) at the column temperature of 108~113°C (injection temperature: 130°C, 0.1 °C/min) at a carrier gas (N_2) pressure of 100hPa.

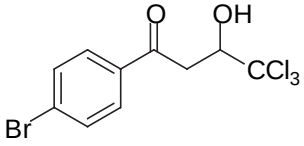


Ethyl 5,5,5-trichloro-4-hydroxy-2-oxopentanoate (**10**): IR (KBr) 3440, 2992, 2926, 1809, 1724, 1626, 1448, 1400, 1365, 1304, 1184, 1124, 1007, 893, 852 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.75 (1H, ddd, *J* =7.2, 4.5, 4.5 Hz), 4.38 (2H, q, *J* =7.2 Hz) , 3.462 (1H, d, *J* = 4.5 Hz), 3.457 (1H, d, *J* = 7.2 Hz), 3.30 (1H, d, *J* = 4.8 Hz), 1.40 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 160.1, 102.1, 78.2, 63.1, 41.8, 14.0; Anal. Calcd for $C_7H_9Cl_3O_4$: C, 31.91, H, 3.44; Found: C, 31.82, H, 3.30. $[\alpha]^{20}_D$ = +8.35° (*c* 1.07, $CHCl_3$ for 88% ee), The chiral HPLC analytical data (column AD-H): retention times: t_R = 9.65 min

(minor) and t_R = 15.38 min (major) using *i*-PrOH/hexane (1/9) as eluent at a flow rate of 1.0 mL/min.

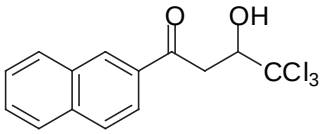


(3*R*)-4,4,4-Trichloro-3-hydroxy-1-phenylbutan-1-one ((*R*)-**11**): IR (KBr) 3389, 3060, 2932, 1688, 1404, 1354, 1287, 1091, 980, 820, 760, 687 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 8.02~7.99 (2H, m), 7.66~7.60 (1H, m), 7.53~7.48 (2H, m) , 4.88 (1H, dd, *J* = 8.7, 1.8 Hz)), 3.87 (1H, bs), 3.66 (1H, dd, *J* = 17.7, 1.8 Hz), 3.51 (1H, dd, *J* = 17.7, 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 136.2, 133.9, 128.8 (two peaks are overlapped), 128.2 (two peaks are overlapped), 102.5, 78.9, 40.7; HRMS (FAB): Exact Mass Calcd for $C_{10}H_9C_{l3}O_2$+H^+: 266.9746. Found: 266.9707. $[\alpha]^{27}_D$ = +31.0° (*c* 1.16, $CHCl_3$ for 92% ee), The chiral HPLC analytical data (column AD-H): retention times: t_R = 13.61 min (minor) and t_R = 15.74 min (major) using *i*-PrOH/hexane (1/9) as eluent at a flow rate of 1.0 mL/min. For the authentic data of (*S*)-**11**, see: Fujisawa,T.; Ito, T.; Fujimoto, K.; Shimizu, M.; Wynberg , H.; Staring, E. G. J. *Tetraahedron Lett.* **1997**, *38*, 1593.

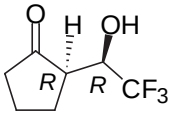


4,4,4-Trichloro-3-hydroxy-1-(4-bromophenyl)butan-1-one (**12**): IR (KBr) 3571, 3440, 2923, 1684, 1582, 1483, 1401, 1358, 1281, 1183, 1096, 1073, 1009, 984, 901, 808, 766 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 7.89~7.84 (2H, m), 7.67~7.63 (2H, m) , 4.86 (1H, dd, *J* = 8.4, 1.8 Hz)), 3.64 (1H, bs), 3.59 (1H, dd, *J* = 17.4, 2.1 Hz), 3.47 (1H, dd, *J* = 17.4, 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 135.0, 132.1 (two peaks are overlapped), 129.7 (two peaks are overlapped), 129.2, 102.4, 78.9, 40.7; HRMS (FAB): Anal. Calcd for $C_{10}H_8BrCl_3O_2$: C, 34.67, H, 2.33; Found: C, 34.66, H, 2.20. $[\alpha]^{28}_D$ = +22.7° (*c* 1.00, $CHCl_3$ for 92% ee), The chiral HPLC analytical data (column AD-H): retention times: t_R = 22.00 min (minor) and t_R = 26.35 min (major) using *i*-PrOH/hexane (1/9) as eluent at a flow rate

of 1.0 mL/min.



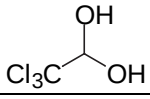
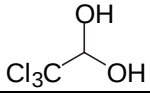
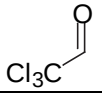
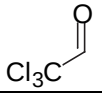
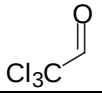
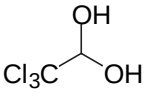
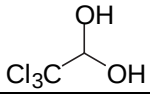
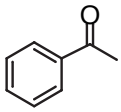
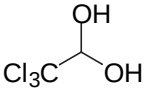
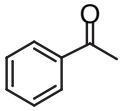
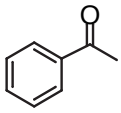
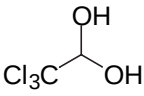
4,4,4-Trichloro-3-hydroxy-1-naphthylbutan-1-one (**13**): IR (KBr) 3482, 3058, 2919, 1682, 1628, 1468, 1399, 1364, 1287, 1215, 1179, 1115, 1103, 1017, 982, 945, 912, 887, 806, 749 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 8.50 (1H, s), 8.06~7.88 (4H, m), 7.66~7.55 (2H, m), 4.95 (1H, ddd, *J* = 8.7, 3.9, 2.1 Hz)), 3.95 (1H, d, *J* = 3.9 Hz), 3.78 (1H, dd, *J* = 17.4, 2.1 Hz), 3.65 (1H, dd, *J* = 17.4, 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 135.9, 133.6, 132.3, 130.3, 129.7, 128.9, 128.7, 127.0, 123.5, 102.6, 79.0, 40.7; HRMS (FAB): Exact Mass Calcd for $C_{14}H_{11}C_{l3}O_2$: 315.9825. Found: 315.9795. $[\alpha]^{29}_D$ = +23.9° (*c* 1.00, $CHCl_3$ for 91% ee), The chiral HPLC analytical data (column AD-H): retention times: t_R = 28.11 min (minor) and t_R = 37.5 min (major) using *i*-PrOH/hexane (1/9) as eluent at a flow rate of 1.0 mL/min.



(2*R*, 1'*R*)-2-(1'-Hydroxy-2',2',2'-trifluoroethyl)cyclopentan-1-one ((2*R*, 1'*R*)-*syn*-**14**): IR (KBr) 3410, 2986, 2892, 1749, 1406, 1338, 1115, 1041, 978, 937, 885, 848 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 4.53 (1H, m, C*H*-O), 4.02 (1H, d, *J* = 6.0 Hz, -OH), 2.47~2.30 (2H, m), 2.28~2.02 (4H, m), 1.92~1.72 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.5, 125.1 (1C, q, J_{C-F} = 280.3 Hz), 67.5 (1C, q, J_{C-F} = 31.5 Hz), 49.3, 38.0, 22.2, 20.4; Anal. Calcd for $C_7H_9F_3O_2$: C, 46.16, H, 4.98; Found: C, 46.16, H,4.97. $[\alpha]^{20}_D$ = +71.0° (*c* 0.90, $CHCl_3$, for the *syn* product of 98% ee), The chiral HPLC analytical data (column OD-H): retention times: t_R = 18.63 min ((2*S*, 1'*S*): *syn*, minor enantiomer) and t_R = 23.10 min ((2*R*, 1'*R*): *syn*, major enantiomer) using *i*-PrOH/hexane (1/50) as eluent at a flow rate of 0.5 mL/min. We were able to obtain a ca. 1.2:1 mixture of *syn*- and *anti*-**14** by adding excess water (5 equiv) to a reaction mixture. Typical chemical shifts of *anti*-**14**: ^1H NMR (300 MHz, $CDCl_3$) δ

4.87 (1H, bs, -OH), 4.10 (1H, m, C*H*-O), 2.60~2.00 (5H, m), 1.98~1.60 (2H, m). Since the measurement of the optical rotation of *syn*-**14** showed the identical sign (+) and almost the same absolute value (~70) compared with (2*R*, 1'*R*)-*syn*-**4**, we temporarily concluded the absolute configuration of *syn*-**14** to be (2*R*, 1'*R*).

Direct aldol reaction of chloral or its monohydrate in the presence of (*L*)-proline.

entry	ketone (equiv)	aldehyde	catalyst (mol%)	conditions (°C, h)	solvent	product	yield (%)	ee % of major product
1	**2** (2)		5	30, 46	$CHCl_3$	**4**	5	54 *syn*
2	**2** (2)		5	30, 46	$CHCl_3$	**4**	13	78 *syn*
3	**2** (2)		5	30, 46	MeCN	**4**	9	78 *syn*
4	**3** (10)		5	30,17	$CHCl_3$	**5**	57	89 *anti*
5	**3** (10)		5	30,17	No solvent	**5**	16	55 *anti*
6	**3** (10)		5	30,17	MeCN	**5**	8	79 *anti*
7	**3** (10)		5	30,17	DMSO	**5**	4	-
8	**3** (10)		10	30,17	$CHCl_3$	**5**	4	-
9	**3** (2)		10	30, 28	MeCN	**5**	12	96 *anti*
10	 (9)		10	40, 50	$CHCl_3$	**11**	~1	-
11	 (9)		10	40, 50	$CHCl_3$	**11**	~1	-
12	 (9)		10	40, 50	MeCN	**11**	2	-