A Simple and Highly Effective Water-Compatible Organocatalytic System for

Asymmetric Direct Michael Reactions of Linear Aldehydes to Maleimides

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Supporting Information

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General information: Commercial reagents were used without further purification, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence UV254 were used for thin-layer chromatography (TLC) analysis. ¹H and ¹³C NMR spectra were recorded on the varian-400. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted were designated as multiplet (m) or broad (br). The high resolution mass spectra were analyzed by using ESI-TOF high-acc from the Scripps Research Institute. All the compounds synthesized (shown in Table 1 and 2) in the manuscript are known compounds¹, except those described below. Their relative and absolute configurations of the products were determined by comparison with the known ¹H and ¹³C NMR, chiral HPLC analysis, and optical rotation values. Optical rotations were measured using a 1 mL cell with a 1 dm path length and reported as follows: $[\alpha]_D^{20}$ (*c* in g per 100 mL of solvent). HPLC analysis was performed using ChiralPak columns.

Typical procedure for the Michael addition:

To the solution of Brine (0.4 mL) was added aldehyde (0.8 mmol), maleimide (0.4 mmol), catalyst **2** (0.04 mmol) and ILS-sulfonic acid **6a** (0.0412 mmol) at room temperature. The resulting mixture was stirred at 4°C for the time indicated in Table 2 and then quenched with 1 M HCl. The products were extracted three times with CH_2Cl_2 (3×10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude Michael product. The residue was purified by flash chromatography on silica gel to afford the desired products **7a-j**.

Data of Michael addition products shown in Table 2:¹



Yield: 69%. $[\alpha]_{D}^{20} = +71$ (*c* 0.6, CHCl₃). (Lit^[1a]: $[\alpha]_{D}^{25} = +70.2$ (c 1.0, CHCl₃)). ¹H NMR (400 MHz, CDCl₃) $\delta = 9.69$ (s, 1H), 7.41 (t, *J* = 8Hz, 2H), 7.34(d, *J* = 8Hz, 1H), 7.21 (t, *J* = 8Hz, 2H), 3.30-3.25 (m, 1H), 2.97-2.90 (m, 2H), 2.53 (dd, *J* = 20Hz, 8Hz, 1H), 1.90-1.80 (m, 1H), 1.64-1.54 (m, 1H), 1.52 (s, 1H), 1.46-

1.38 (m, 2H), 1.37-1.28 (m, 2H), 1.19 (s, 1H), 0.87 (t, J = 8Hz, 3H). ¹³C NMR (100 MHz,

CDCl₃) δ =200.5, 176.6, 174.1, 130.9, 128.2, 127.7, 125.5, 51.6, 37.6, 31.4, 28.8, 24.9, 21.6, 12.8. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 15/85, 25°C, flow rate = 0.8 mL/min, λ = 254 nm; major diastereomer: t_{minor} = 18.305 min, t_{major} = 34.795 min, *ee* = 96%.

Yield: 74%.
$$[\alpha]^{20}{}_D = +52$$
 (c 0.6, CHCl₃). ¹H NMR (400 MHz,
CDCl₃) $\delta = 9.72$ (s, 1H), 7.48 (t, $J = 8$ Hz, 2H), 7.41 (t, $J = 2$ Hz,
1H), 7.28 (t, $J = 7.2$ Hz, 2H), 3.43-3.38 (m, 1H), 3.22-3.15 (m,
1H), 3.06-2.99 (dd, $J = 16$ Hz, 8Hz, 1H), 2.57-2.51 (dd, $J = 16$ Hz,
4Hz, 1H), 1.33 (d, $J = 8$ Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 201.3$, 177.6, 175.0,

131.8, 129.2, 128.7, 126.4, 47.0, 39.5, 31.6, 9.7. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 1/9, 25 °C, flow rate = 0.8 mL/min, λ = 254 nm; major diastereomer: t_{minor} = 42.84 min, t_{major} = 49.80 min, *ee* = 91%.



Yield: 66%. $[\alpha]_D^{20} = +35.0$ (c = 0.8, CHCl₃). ¹H NMR (400 MHz, CDCl₃) $\delta = 9.77$ (s, 1H), 7.48 (t, J = 8Hz, 2H), 7.40 (t, J = 7.2Hz, 1H), 7.28 (t, J = 8Hz, 2H), 3.37-3.32 (m, 1H), 3.04-2.89 (m, 2H), 2.60-2.54 (dd, J = 20Hz, 8Hz, 1H), 2.04-1.93 (m, 1H), 1.77-1.70 (m, 1H), 1.14 (t, J = 8Hz, 3H). ¹³C NMR (100 MHz,

CDCl₃) δ = 201.5, 177.6, 175.0, 131.9, 129.2, 128.7, 126.4, 54.3, 38.4, 32.4, 19.6, 12.3. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 5/95, 25 °C, flow rate = 0.8 mL/min, λ = 254 nm; major diastereomer: t_{minor} = 20.30 min, t_{major} = 26.16 min, *ee* = 96%. HRMS (ESI-TOF high-acc) m/z calcd for C₁₄H₁₆NO₃⁺ (MH⁺): 246.1125, found: 246.1129.



1H), 1.06 (t, J = 8Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 202.0$, 178.2, 175.2, 132.2,

129.1, 128.6, 126.7, 51.4, 39.0, 31.5, 28.5, 20.7, 13.9. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 5/95, 25 °C, flow rate = 1.0 mL/min, λ = 254 nm; major diastereomer: t_{minor} = 45.44 min, t_{major} = 87.18 min, *ee* = 94%. HRMS (ESI-TOF high-acc) m/z calcd for C₁₅H₁₈NO₃⁺ (MH⁺): 260.1281, found: 260.1283.



128.7, 126.4, 52.7, 38.6, 32.4, 31.7, 27.3, 26.2, 22.3, 13.9. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 1/9, 25 °C, flow rate = 0.8 mL/min, λ = 254 nm; major diastereomer: t_{minor} = 22.30 min, t_{major} = 48.34 min, *ee* = 96%. HRMS (ESI-TOF high-acc) m/z calcd for C₁₇H₂₂NO₃⁺ (MH⁺): 288.1594, found: 288.1595.



Yield: 60%. $[\alpha]_{D}^{20} = +29.6 (c \ 0.3, \text{CHCl}_3)$. ¹H NMR (400 MHz, CDCl₃) $\delta = 9.75 (s, 1\text{H}), 7.44-7.35 (m, 3\text{H}), 7.27-7.22 (m, 1\text{H}), 3.33-3.29 (m, 1\text{H}), 3.05-2.98 (m, 1\text{H}), 2.60-2.54 (dd, <math>J = 20\text{Hz}, 4\text{Hz}, 1\text{H}), 1.96-1.87 (m, 1\text{H}), 1.73-1.67 (m, 1\text{H}), 1.59-1.52 (m, 2\text{H}), 1.25 (s, 1\text{H}), 1.02 (t, <math>J = 8\text{Hz}, 3\text{H})$. ¹³C NMR (100 MHz, 100 MHz)

CDCl₃) δ = 201.4, 177.2, 174.6, 134.7, 132.9, 130.1, 128.9, 126.8, 124.7, 52.7, 38.5, 32.6, 28.5, 20.9, 14.0. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 1/9, 25 °C, flow rate = 0.8 mL/min, λ = 254 nm; major diastereomer: t_{minor} = 33.06 min, t_{major} = 46.76 min, *ee* = 95%. HRMS (ESI-TOF high-acc) m/z calcd for C₁₅H₁₇ClNO₃⁺ (MH⁺): 294.0891, found: 294.0895.



2H), 7.28-7.20 (m, 2H), 3.35-3.28 (m, 1H), 3.07-2.98 (m, 2H), 2.61-2.54 (m, 1H), 1.98-1.87 (m, 1H), 1.70-1.65 (m, 1H), 1.60-1.53 (m, 2H), 1.27 (d, = 8Hz, 1H), 1.03 (t, J = 4Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 201.4$, 177.3, 174.7, 132.4, 130.9, 128.0, 122.6, 52.7, 38.5, 32.6, 28.5, 21.0, 14.0. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 5/95, 25 °C, flow rate = 1.0 mL/min, $\lambda = 254$ nm; major diastereomer: $t_{major} = 87.88$ min, $t_{minor} = 99.41$ min, ee = 94%. HRMS (ESI-TOF high-acc) m/z calcd for C₁₅H₁₇ClNO₃⁺ (MH⁺): 338.0386, found: 338.0375.



Yield: 51%. $[\alpha]_{D}^{20} = -5.1$ (*c* 0.1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) $\delta = 9.62$ (s, 1H), 7.45 (d, J = 8Hz, 2H), 7.29 (d, J = 12Hz, 2H), 3.30-3.25 (m, 1H), 3.08-3.03 (m, 1H), 2.86 (dd, J = 16Hz, 8Hz, 1H), 2.60 (dd, J = 16Hz, 4Hz, 1H), 2.00-1.93 (m, 1H), 1.55 (s, 2H), 1.34 (s, 2H), 1.06 (t, J = 16Hz, 4Hz, 1H), 2.00 (dd, J = 16Hz, 2H), 1.95 (s, 2H), 1.95

8Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ = 202.0, 178.0, 174.9, 134.5, 130.6, 129.4, 127.9, 51.5, 39.0, 31.4, 28.5, 20.7, 13.9. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 1/9, 25 °C, flow rate = 0.8 mL/min, λ = 254 nm; major diastereomer: t_{minor} = 33.03 min, t_{major} = 69.45 min, *ee* = 95%. HRMS (ESI-TOF high-acc) m/z calcd for C₁₅H₁₇ClNO₃⁺ (MH⁺): 294.0891, found: 294.0890.



Yield: 15%. $[\alpha]_{D}^{20} = -41.5$ (*c* 0.1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) $\delta = 9.64$ (s, 1H), 7.29-7.15 (m, 4H), 3.28-3.23 (m, 1H), 3.09-2.96 (m, 1H), 2.89-2.82 (dd, J = 20Hz, 12Hz, 1H), 2.63-2.57 (dd, J = 20Hz, 12Hz, 1H), 2.38 (s, 3H), 1.99-1.90 (m, 1H), 1.54 (s, 3H), 1.25 (s, 1H), 1.05 (t, J = 4Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ = 202.0, 178.3, 175.4, 138.7, 129.9, 126.5, 126.3, 51.4, 39.1, 31.5, 28.5, 21.2, 20.7, 13.9. HPLC: Chiralpak AD-H, *i*-propanol/hexane = 15/85, 25 °C, flow rate = 0.8 mL/min, λ = 254 nm; major diastereomer: t_{minor} = 25.09 min, t_{major} = 26.93 min, *ee* = 86%. HRMS (ESI-TOF high-acc) m/z calcd for C₁₆H₂₀NO₃⁺ (MH⁺): 274.1438, found: 274.1436.



Yield: 53%. $[\alpha]^{20}{}_{D}$ = +5.9 (*c* 0.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ = 9.67 (s, 1H), 7.37-7.22 (m, 5H), 3.54-3.45 (m, 2H), 3.36-3.31 (dd, *J* = 16Hz, 8Hz, 1H), 2.73-2.66 (m, 2H), 2.64-2.60 (m, 1H), 2.49-2.44 (dd, *J* = 12Hz, 4Hz, 1H), 1.66-1.56 (m, 2H), 1.26 (s, 1H), 0.91 (t, *J* = 4Hz, 3H). ¹³C NMR (100 MHz, CDCl₃)

δ = 201.0, 178.9, 176.0, 136.8, 129.1, 128.7, 127.3, 53.0, 40.6, 38.5, 32.8, 31.2, 20.8, 11.2. HPLC: Chiralpak AD-H,*i* $-propanol/hexane = 1/9, 25 °C, flow rate = 0.8 mL/min, λ = 254 nm; major diastereomer: <math>t_{major} = 19.40 \text{ min}, t_{minor} = 29.25 \text{ min}, ee = 90\%$. HRMS (ESI-TOF high-acc) m/z calcd for C₁₆H₂₀NO₃⁺ (MH⁺): 274.1438, found: 274.1440.

References:

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S7





S8













































Detector A	Ch1	254nm
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Peak#	Ret. Time	Area	Height	Area %	Height %
-1	18.234	376578	15493	28.872	38.316
2	22.115	283485	9627	21.735	23.809
3	24.139	275198	8916	21.099	22.049
· 4	36.113	369038	6399	28.294	15.826
Total		1304299	40435	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.305	117243	4938	2.079	7.229
2	34.795	5523105	63376	97.921	92.771
Total		5640347	68314	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.891	1847531	76740	41.032	50.206
2	25.499	1890434	62005	41.985	40.566
3	42.830	367573	7637	8.163	4.997
4	50.146	397107	6468	8.819	4.231
Total		4502646	152850	100.000	100.000



Detector A Ch1 254nm								
Peak#	Ret. Time	Area	Height	Area %				
1	42.838	51917	1328	4.440				
2	49.804	1117369	17507	95.560				

Total

1169285

18835

Height %

100.000

7.051

92.949

100.000



Detector	А	Chl	254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.916	1723508	43198	2.916	5.261
2	24.006	1820534	35626	3.080	4.339
3	36.449	27463276	403948	46.468	49.198
4	38.140	28094296	338298	47.536	41.202
Total		59101615	821069	100.000	100.000



Detector	А	Ch1	254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.296	64847	1943	2.159	2.881
2	26.160	2938416	65484	97.841	97.119
Total		3003263	67426	100.000	100.000



Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	45.752	2859963	40611	41.011	56.864
2	56.883	549618	7892	7.881	11.050
3	59.512	692161	10526	9.925	14.739
4	85.533	2871861	12389	41.182	17.348
Total		6973603	71419	100.000	100.000



Detector	A Ch1	254nm
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Peak#	Ret. Time	Area	Height	Area %	Height %
1	45.436	51913	844	3.011	9.738
2	87.178	1671947	7825	96.989	90.262
Total		1723860	8669	100.000	100.000



Detector	А	Ch1	254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	23.095	1858773	60162	29.355	41.642
2	27.742	1310676	31687	20.699	21.933
3	28.912	1224774	35362	19.342	24.477
4	51.825	1937851	17262	30.604	11.948
Total		6332074	144473	100.000	100.000



Detector	А	Chl	254nm
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Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.298	164298	5082	2.065	8.641
2	48.344	7792222	53736	97.935	91.359
Total		7956520	58818	100.000	100.000



Detector A	A Chl	254nm
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Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.149	7538746	115353	42.540	52.983
2	36.570	1390266	20942	7.845	9.619
3	42.822	1360395	14717	7.676	6.760
4	46.162	7432272	66704	41.939	30.638
Total		17721679	217716	100.000	100.000



	Detector	А	Ch1	254nm
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Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.055	96324	1830	2.374	4.884
2	46.764	3961376	35627	97.626	95.116
Total		4057700	37457	100.000	100.000



Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	65.994	3850206	21427	49.051	47.508
2	70.463	3883250	22588	49.472	50.083
3	89.427	52656	541	0.671	1.199
4	98.687	63202	546	0.805	1.210
Total		7849314	45101	100.000	100.000



	Detector	Α	Ch1	254nm	
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Peak#	Ret. Time	Area	Height	Area %	Height %
1	87.876	5174607	42769	96.734	98.046
2	99.410	174692	852	3.266	1.954
Total		5349299	43621	100.000	100.000



Detector	А	Ch1	254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	32.834	112348	2716	31.541	45.734
2	45.395	65499	1239	18.388	20.858
3	62.807	67338	821	18.905	13.823
4	70.080	111015	1163	31.166	19.585
Total		356199	5938	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.030	27074	733	2.470	6.731
2	69.455	1068959	10159	97.530	93.269
Total		1096033	10893	100.000	100.000



Detector A C	Ch1 254nm				
Peak#	Ret. Time	Area	Height	Area %	Height %
1	25.118	20291	660	22.062	32.170
2	27.005	20542	607	22.334	29.560
3	35.033	25106	562	27.296	27.352
4	81.609	26037	224	28.308	10.919
Total		91977	2053	100.000	100.000



Detector	Α	Chl	254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	25.091	355385	10303	93.245	93.800
2	26.930	25745	681	6.755	6.200
Total		381130	10984	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.440	319350	12050	28.174	36.420
2	20.777	251750	9728	22.210	29.402
3	29.792	307217	7876	27.104	23.805
4	57.446	255158	3432	22.511	10.373
Total		1133474	33086	100.000	100.000



Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.397	71673	2599	5.001	7.591
2	29.248	1361578	31634	94.999	92.409
Total		1433251	34233	100.000	100.000