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**Electronic Supplementary Information
for
Organic Co-Solvents in aqueous DNA-Based Catalysis**

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dimethyl 2-(4-methyl-1-(1-methyl-1H-imidazol-2-yl)-1-oxopentan-3-yl)malonate (7b)

A colorless oil was obtained after column chromatography (SiO_2 , EtOAc/Heptane 4:6). ^1H NMR (400 MHz, CDCl_3) δ 7.16 (d, $J = 5.0$, 1H), 7.02 (d, $J = 14.5$, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.65 (d, $J = 42.2$, 1H), 3.40 (dd, $J = 10.2$, 1.7, 2H), 3.24 – 3.14 (m, 1H), 0.90 (m, 6H). δ ^{13}C (101 MHz, CDCl_3) 192.6, 168.7, 168.0, 143.3, 129.2, 128.7, 54.5, 53.8, 44.6, 37.9, 36.1, 33.9, 30.3, 21.0, 18.6. HRMS: m/z : 310.1525 (Calcd. 310.1529)

Ee's were determined by HPLC analysis (Chiralcel-AD, heptane/iPrOH 98:2, 0.5 mL/min). Retention times: 44.9 and 55.0 mins

dimethyl 2-(1-(1-methyl-1H-imidazol-2-yl)-1-oxooctan-3-yl)malonate (7c)

A slightly yellow oil was obtained after column chromatography (SiO_2 , EtOAc/Heptane 4:6). ^1H NMR (300 MHz, CDCl_3) δ 7.12 (m, 1H), 7.02 (m, 1H), 4.13 – 3.88 (m, 6H), 3.88 – 3.54 (m, 5H), 3.40 – 3.01 (m, 4H), 1.90 – 1.01 (m, 6H), 1.01 – 0.52 (m, 3H). δ ^{13}C (101 MHz, CDCl_3) 192.7, 167.1, 167.0, 129.2, 127.4, 60.5, 52.7, 52.6, 47.3, 41.3, 40.7, 37.3, 32.0, 25.4, 22.8, 14.2. HRMS: m/z : 338.1835 (Calcd. 338.1842)

Ee's were determined by HPLC analysis (Chiralcel-ODH, heptane/iPrOH 90:10, 0.5 mL/min). Retention times: 23.9 and 26.0 mins

3-(5-methoxy-1H-indol-3-yl)-4-methyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (9b)

A yellow oil was obtained after column chromatography (SiO_2 , EtOAc/Heptane 1:1). ^1H NMR (400 MHz, CDCl_3) δ 8.02 (s, 1H), 7.16 (d, $J = 8.7$, 1H), 7.13 (s, 1H), 7.02 (d, $J = 13.3$, 2H), 6.93 (s, 1H), 6.79 (d, $J = 8.8$, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.63 (dd, $J = 25.2$, 11.2, 2H), 3.44 (dd, $J = 14.4$, 3.8, 1H), 2.09 (dt, $J = 12.8$, 6.3, 1H), 1.74 (s, 1H), 0.94 (t, $J = 7.4$, 6H). δ ^{13}C (101 MHz, CDCl_3) δ 192.8, 153.9, 131.4, 129.0, 128.9, 126.9, 122.8, 118.1, 112.0, 111.7, 101.6, 56.2, 56.1, 42.1, 38.6, 33.1, 20.7, 20.5. HRMS: m/z : 325.1782 (Calcd. 325.1790)

Ee's were determined by HPLC analysis (Chiralcel-AD, heptane/iPrOH 98:2, 0.5 mL/min). Retention times: 26.6 and 34.0 mins

3-(5-methoxy-1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl)octan-1-one (9c)

A colorless oil was obtained after column chromatography (SiO_2 , EtOAc/Heptane 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.88 (br, 1H), 7.20 (d, $J = 7.7$, 1H), 7.12 (s, 1H), 7.05 (d, $J = 18.9$, 2H), 6.96 (s, 1H), 6.81 (d, $J = 8.7$, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.72 – 3.61 (m, 2H), 3.57 – 3.44 (m, 1H), 1.86 – 1.68 (m, 2H), 1.45 – 1.06 (m, 6H), 1.04 – 0.65 (m, 3H). δ ^{13}C (50 MHz, CDCl_3) 192.4, 153.7, 131.3, 128.8, 127.4, 126.7, 121.8, 111.9, 111.6, 105.0, 101.2, 55.9, 45.5, 36.1, 36.0, 32.4, 31.9, 27.2, 22.6, 14.1. HRMS: m/z : 353.4983 (Calcd. 353.4580)

Ee's were determined by HPLC analysis (Chiralcel-ODH, heptane/iPrOH 90:10, 0.5 mL/min). Retention times: 26.6 and 34.5 mins

3-(5-methoxy-1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl)-3-phenylpropan-1-one (9e)

A brownish oil was obtained after column chromatography (SiO_2 , EtOAc/Heptane 1:1). ^1H NMR (400 MHz, CDCl_3) δ 8.09 (s, 1H), 7.83 (d, $J = 16.2$, 1H), 7.70 (s, 2H), 7.40 – 7.01 (m, 5H), 6.87 (d, $J = 8.5$, 1H), 6.49 (s, 1H), 4.11 (s, 3H), 3.92–3.85 (m, 2H), 3.86 (s, 3H), 3.76 (m, 1H). δ ^{13}C (50 MHz, cdCl_3) 192.6, 142.5, 129.2, 128.2, 127.8, 127.7, 127.1, 126.2, 123.8, 121.5, 111.3, 110.6, 103.6, 101.3, 59.5, 54.8, 37.9, 28.6. HRMS: m/z : 359.1639 (Calcd. 359.1634)

Ee's were determined by HPLC analysis (Chiralcel-AD, heptane/iPrOH 80:20, 0.5 mL/min). Retention times: 19.0 and 26.8 mins.

Table S1. Full investigation of solvent scope of the Diels-Alder reaction of azachalcone (**1**) with cyclopentadiene (**2**)

Solvent	MeCN	MeOH	EtOH	iPA	DMF	DMSO	1,4-Dioxane	DCM	THF
Content	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)
30%	Full (99%)	Full (99%)	Full (99%)	Full (99%)	Full (99%)	Full (99%)	Full (99%)	- ^a	50% (99%) ^a
33%	Full (99%)	Full (99%)	Full (99%)	Full (99%)	Full (99%)	Full (99%)	Full (99%)	- ^a	34% (99%) ^a
35%	Full (98%)	Full (98%)	Full (98%)	Full (97%)	Full (98%)	Full (97%)	Full (93%)	- ^a	- ^a
40%	60% (80%)	49% (81%)	43% (79%)	40% (75%)	52% (80%)	39% (74%)	Full (82%)	- ^a	- ^a

General conditions: 0.15 mM Cu(dmbipy), 0.67 mg/ml st-DNA, 1 mM azachalcone, 3d, 15 mM cyclopentadiene. ^a DNA precipitation observed

Table S2. Full investigation of solvent scope of the Michael Addition of azachalcone (**1**) with dimethyl malonate (**4**)

Solvent	MeCN	MeOH	EtOH	iPA	DMF	DMSO	1,4-Dioxane	DCM	THF
Content	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)
5%	Full (96%)	Full (96%)	Full (96%)	Full (96%)	Full (95%)	Full (96%)	Full (94%)	15% (96%) ^a	Full (92%)
10%	Full (96%)	Full (96%)	Full (96%)	Full (96%)	Full (95%)	Full (95%)	Full (93%)	8% (94%) ^a	Full (90%) ^a
15%	Full (95%)	Full (95%)	Full (96%)	Full (96%)	Full (94%)	Full (93%)	Full (92%)	5% (86%) ^a	90% (87%) ^a
20%	Full (94%)	Full (95%)	Full (95%)	Full (95%)	Full (92%)	Full (93%)	Full (90%)	4% (61%) ^a	60% (81%) ^a

General conditions: 0.15 mM Cu(dmbipy), 0.67 mg/ml st-DNA, 1 mM azachalcone, 100 mM dimethyl malonate, 1d. ^a DNA precipitation observed

Table S3. Full investigation of solvent scope of the Friedel-Crafts alkylation of α,β -unsaturated 2-acylimidazole (**6**) with 5-methoxyindole (**7**)

Solvent	MeCN	MeOH	EtOH	iPA	DMF	DMSO	1,4-Dioxane	DCM	THF
Content	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)	Conv (ee)
5%	Full (83%)	Full (83%)	Full (83%)	Full (83%)	Full (83%)	Full (82%)	Full (83%)	full (81%) ^a	Full (81%)
10%	Full (83%)	Full (83%)	Full (82%)	Full (83%)	Full (82%)	Full (83%)	Full (83%)	78% (75%) ^a	Full (81%)
15%	Full (81%)	Full (83%)	Full (82%)	Full (82%)	Full (83%)	Full (82%)	Full (83%)	55% (64%) ^a	Full (71%) ^a
20%	Full (81%)	Full (82%)	Full (82%)	Full (81%)	Full (82%)	Full (82%)	Full (82%)	23% (60%) ^a	Full (61%) ^a

General conditions: 0.15 mM Cu(dmbipy), 0.67 mg/ml st-DNA, 1 mM 2-acyl imidazole **6**, 5 mM 5-methoxyindole, 1d. ^a DNA precipitation observed

Figure S4. CD-spectra of st- DNA in the presence of organic solvents

Figure S7. Temporal UV measurement of the Michael reaction of azachalcone (**1**) with dimethyl malonate (**4**). The decrease of azachalcone is followed in time at 326nm

Temporal UV measurement of the Michael reaction, 0.15 mM Cu(dmbipy), 0.67 mg/ml st-DNA, 1 mM azachalcone, 100 eq. dimethyl malonate, 20 mM MOPS pH 6.5, 5°C at 326 nm — 0%, - - 5% MeCN, 10% MeCN, - · - 15% MeCN

Figure S8. Temporal conversion of the Michael addition of azachalcone(**1**) and dimethyl malonate(**4**).

Conditions; 0.15 mM Cu(dmbipy), 0.67 mg/ml st-DNA, 1 mM azachalcone, 100 eq. dimethyl malonate, 20 mM MOPS pH 6.5, 5°C, analyzed with NMR and HPLC. □ = Water ■ = 5% MeCN ■ = 10% MeCN

Figure S9. Temporal conversion of the Friedel-Crafts alkylation reaction of 5-methoxyindole (**7**) with α,β -unsaturated 2-acylimidazole (**6**).

Conditions; 0.15 mM Cu(dmbipy), 0.67 mg/ml st-DNA, 1 mM α,β -unsaturated 2-acylimidazole (**4**), 5 eq. 5-methoxyindole, 20 mM MOPS pH 6.5, 5°C, analyzed with NMR and HPLC. □ = Water ■ = 5% MeCN ■ = 10% MeCN

Figure S10. Temporal conversion of the Diels-Alder reaction of azachalcones (**1b-d**) with cyclopentadiene (**2**)

Figure S10: Temporal conversion of the Diels-Alder reaction. 0.15 mM Cu-dmbipy, 1 mM st-DNA in basepairs, 1mM enone substrate, 20 mM MOPS, pH 6.5. □ = Water ■ = 10% MeCN

Table S11. Substrate scope of DNA-Based catalytic Diels-Alder reactions with and without organic co-solvent

Enone	Nucleophile	ee (H ₂ O)	ee (10% v/v MeCN)
1b	2	96	94
1c	2	99	99
1d	2	99	93

General condition; 0.15 mM Cu(dmbipy), 1 mM st-DNA in basepairs, 1 mM enone, 20 mM MOPS pH 6.5

Table S12. Increasing substrate concentration in the Diels-Alder reaction

Substrate conc.	Water	33% MeCN
	Conv. (ee)	Conv. (ee)
1 mM	Full (99%)	Full (99%)
2 mM	Full (99%)	Full (99%)
5 mM	Full (99%)	71% (99%)
10 mM	84% (96%)	50% (93%)

General conditions: 0.15 mM Cu(dmbipy), 0.67 mg/ml st-DNA, 15 eq cyclopentadiene.

¹H-NMR spectra

References

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