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Supporting Information

Biocatalytic ketone reductions using BioBeads for miniaturized high throughput experimentation

Jia Shen Chew, Thi Thanh Nha Ho and Chi-Lik Ken Lee*

*Corresponding author's email: ken.lee@ntu.edu.sg

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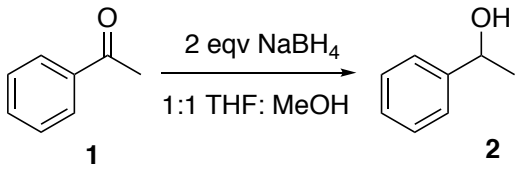
General Information

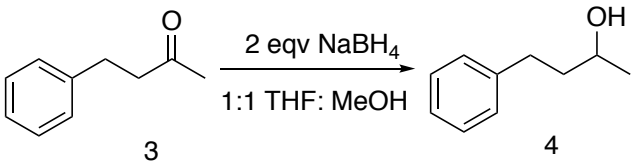
Ketoreductases (Kred) and other corresponding reagents were purchased from Codexis. Native reactions were carried out as stated by procedures from Codexis Screening Kit[1] and the respective Kred Recycled Mix P and N prepared fresh on the day of use. Polystyrene beads (35-45 mesh size) were coated with the respective reagents (1) Kred, (2) Mix P or Mix N which contains β-NADP-Na_2 or β-NAD-Na_2, the necessary buffer reagents and glucose/glucose dehydrogenase co-factor recycling reagent), according to the ratios similar for native reactions. Reactions performed with BioBeads only required the subsequent addition of deionised (DI) water, isopropanol (IPA) and the carbonyl substrate. The preparation methods for BioBeads were similar to ChemBeads.[2,3] For the enzymatic reactions, commercially available solvents were used. Reagents were of analytical grade, obtained from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance III 400 MHz BBFO1 spectrometer at 25°C. $CDCl_3$ was used as solvent with internal reference $SiMe_4$. Chemical shifts for ^{1}H and ^{13}C NMR spectra were recorded as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03) respectively. Multiplicities were given as: s (singlet), d (doublet), q (quartet), or m (multiplets). The number of protons (n) for a given resonance was indicated by nH. Mass spectra (MS) were obtained on the ThermoFinnigan LCQ Fleet mass spectrometer. MS were reported in units of mass to charge ratio (m/z). The conversion yields (% conversion) and enantiomeric excess (% *ee*) were determined by high performance liquid chromatography (HPLC) analysis using Shimadzu LC-20AT and LC- 2010CHT HPLC workstations with either Chiralcel OD-H or Chiralpak IB or Chiralcel OJ-H columns). Confirmation of *R* and *S* enantiomers were determined by comparing the retention times (t_R) against previous reports.[4-8] Flash chromatography separations were performed on Merck 60 (0.040 - 0.063mm) mesh silica gel. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F_{254} silica gel plates. Visualization was performed using a UV lamp.

General Procedures to Racemic 2, 4, 6

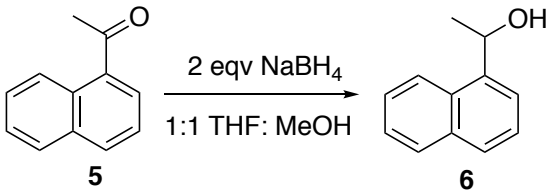
To a 4 mL vial containing a solution of ketone (25 mg, 1 eqv) in THF (1 mL) at 0°C was added $NaBH_4$ (2 eqv) in portions followed by cold MeOH (1 mL). The reaction was stirred at room temperature for 1 hr. After the completion of the reaction by TLC, saturated brine (2 mL) was added and the mixture was extracted with ethyl acetate (2 × 1 mL) before being further washed with H_2O (2 × 1 mL). The organic layer was concentrated in *vacuo* and purified by silica gel chromatography.



(±)-*1-phenylethan-1-ol,* **2.** Colourless oil (16.5 mg, 65% yield).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.21 (m, 5H), 5.01 – 4.79 (q, *J* = 8 Hz, 1H), 2.04 (s, 1H), 1.49 (d, *J* = 8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 145.91, 128.59, 127.56, 125.48, 70.49, 25.23. MS (ESI): Found *m/z* 104.90. Calcd for C_8H_8 [M-H_2O] = 104.15. HPLC analysis: Chiralcel OD-H column; Hex:IPA = 90:10; 1.0 mL/min; 210 nm; 23°C; t_R of *R* isomer = 5.96 min; t_R of *S* isomer = 6.69 min. Previous reports[4,5,7] : Chiralcel OD-H column; Hex:IPA = 98:2; 1.0 mL/min; t_R of *R* isomer = 15.31 min; t_R of *S* isomer = 19.87 min.



(±)-*4-phenylbutan-2-ol,* **4.** Colourless Oil (22.3 mg, 88% yield) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 3.87 (m, 1H), 2.85-2.68 (m, 2H), 1.86-1.80 (m, 2H), 1.28-1.27 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 142.11, 128.43, 125.84, 67.50, 40.88, 32.17, 23.63. MS (ESI): Found *m/z* 134.72. Calcd for $C_{10}H_{14}$ [M-H_2O] = 134.22. HPLC analysis: Chiralpak IB column; Hex:IPA = 95:5; 0.8 mL/min; 210 nm; 23°C; t_R of *R* isomer = 8.51 min; t_R of *S* isomer = 10.8 min. Previous reports[6]: Chiralpak IB column; Hex:IPA = 95:5; 0.8 mL/min; t_R of *R* isomer = 8.9 min; t_R of *S* isomer = 10.9 min.



5 **6**

(±)-*1-(naphthalen-1-yl)ethan-1-ol*, **6.** Colourless Oil (18.2 mg, 72% yield) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-7.96 (m, 1H), 7.96 – 7.82 (m, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.59 – 7.37 (m, 3H), 5.62 (q, *J* = 6.4 Hz, 1H), 2.49 (s, 1H), 1.69 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.46, 133.86, 130.34, 128.94, 127.93, 126.06, 125.59, 123.25, 122.07, 67.06, 24.40. MS (ESI) Found *m/z* 154.90. Calcd for $C_{12}H_{10}$ [M-H_2O] 154.21. HPLC analysis: Chiralcel OJ-H; Hex:IPA = 90:10; 1.0 mL/min; 215 nm; 23 °C; t_R of *S* isomer = 11.80 min, t_R of *R* isomer = 16.35 min. Previous reports[7,8] : Chiralcel OD-H column; Hex:IPA = 90:10; 1.0 mL/min; t_R of *S* isomer = 9.47 min; t_R of *R* isomer = 14.26 min.

Preparation of BioBeads

General Coating procedure:

(For Kreds 1-19)

In a 20 mL vial were added 6.70 g of polystyrene beads, followed by the addition of 250 mg Kred powder, 410 mg of Mix P powder. An additional 6.70 g of polystyrene beads was added to cover the solid reagent layer, sandwiching the solid reagents between the two layers of polystyrene beads. The mixture was then placed inside a Resodyn Acoustic Mixer (RAM, 500 g capacity, Resodyn) and mixed for 15 min with a mechanical driver magnitude of 40–45 times the acceleration of gravity. The oscillation frequency was optimized by the RAM driver control module to mix the powder at resonance 5 frequency. After mixing, no loose powders were observed in the 20 mL vial. The bead loading was thus estimated to be 1.78% Kred and 2.92% Mix P. The stoichiometries of Kred and Mix P for miniaturized reactions were calculated based on this bead loading.

General Coating procedure:

(For Kreds 20-24)

In a 20 mL vial were added 6.28 g of polystyrene beads, followed by the addition of 250 mg Kred powder, 1250 mg of Mix N powder. An additional 6.28 g of polystyrene beads was added to cover the solid reagent layer, sandwiching the solid reagents between the two layers of polystyrene beads. The mixture was then placed inside a Resodyn Acoustic Mixer (RAM, 500 g capacity, Resodyn) and mixed for 15 min with a mechanical driver magnitude of 40–45 times the acceleration of gravity. The oscillation frequency was optimized by the RAM driver control module to mix the powder at resonance 5 frequency. After mixing, no loose powders were observed in the 20 mL vial. The bead loading was thus estimated to be 1.78% Kred and 8.89% Mix N. The stoichiometries of Kred and Mix N for miniaturized reactions were calculated based on this bead loading.

Procedures for Bioreduction of ketones using native Kred 1-24 at analytical scale (Adopted from Codexis Screening Protocol)

(For entries 1-19: screening procedure P was adopted) In each 4 mL vial, was added 10 mg of the respective native Kred. 0.6 g Kred Recycle Mix P was added to 33 mL of DI water to give the reconstituted Kred recycle mix P in the right concentration (The reconstituted Kred recycled Mix P contained 128 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$, pH 7.0). 0.9 mL of Kred Recycle Mix P solution was added into each vial. 1 mmol of the respective ketones was added to 4 mL of IPA for the preparation of substrate stock solution, whereby 0.1 mL was added into each reaction vial together with 0.05 mL THF. The reaction vials were left to shake at 30°C for 48 hr. Then the mixture was extracted with ethyl acetate (2 × 1 mL), and passed through a microcolumn. The organic layer was dried over Na_2SO_4, evaporated in *vacuo*, and injected into HPLC to determine the % conversion and % *ee*.

(For entries 20-24: screening procedure N was adopted) In each 4 mL vial, was added 10 mg of the respective native Kred. 0.3 g Kred Recycle Mix N was added to 6 mL of DI water to give the reconstituted Kred Recycle Mix N in the right concentration (The reconstituted Kred recycled Mix N contained 263 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$, 1.1mM NAD^+, 80 mM D-glucose, 4.3 Unit/mL glucose dehydrogenase, pH 7.0). 0.3 mmol of the respective ketone was added to the reconstituted Kred Recycle Mix N solution and stirred thoroughly before 1 mL of this solution was added to each 4 mL vial containing the respective Kred. 0.1 mL of IPA and 0.05 mL THF were subsequently added and the reaction vials were left to shake at 30°C for 48 hr. Then the mixture was extracted with ethyl acetate (2 × 1 mL), and passed through a microcolumn. The organic layer was dried over Na_2SO_4, evaporated in *vacuo*, and injected into HPLC to determine the % conversion and % *ee*.

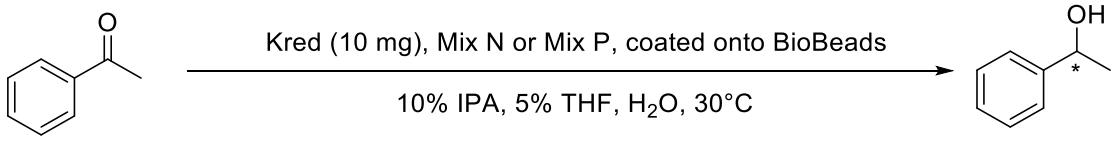
General Procedures for Bioreduction of ketones using BioBeads with Kred 1-24 at analytical scale

In each 4.0 mL vials was added 562 mg of the respective BioBeads (10 mg Kred), followed by 0.9 mL of DI water. 1 mmol of ketone was added to 4 mL of IPA for the preparation of substrate stock solution, where 0.1 mL of the eventual stock solution was added into each reaction vial, followed by 0.05 mL of THF. The reaction vials were agitated on the Torrey Pines orbital shaker at 30°C for 48 hr. The mixture was extracted with ethyl acetate (2×1 mL), and passed through a microcolumn. The organic layer was dried over Na_2SO_4, evaporated in *vacuo*, and injected into HPLC to determine the % conversion and % *ee*.

Procedures for Bioreduction of 1 using BioBeads with Kred 1-24 at miniaturized scale In each 2.0 mL Eppendorf tube, was added 2 mg of the respective BioBeads (0.036 mg Kred), followed by 16.2 μL of DI water. 1.07 mg (1.03 μL) of acetophenone **1** was added to 35.6 μL of IPA for the preparation of substrate stock solution, where 0.9 μL of the eventual stock solution was added into each reaction tube. An additional 0.9 μL of IPA and 0.1 μL of THF was added and the reaction tubes were agitated on the Torrey Pines orbital shaker at 30°C for 48 hr. Then the mixture was extracted with ethyl acetate (2× 20 μL), combined and dried over Na_2SO_4. The organic contents were evaporated in *vacuo*, and injected into HPLC to determine the % conversion and % *ee*.

Procedures for Bioreduction of 5 using BioBeads with Kred 1-24 at miniaturized scale[8] In each 2.0 mL Eppendorf tube, was added 2 mg of the respective BioBeads (0.036 mg Kred), followed by 16.2 μL of DI water. 1.51 mg (1.35 μL) of 1-(naphthalen-1-yl)ethan-1-one **5** was added to 35.6 μL of IPA for the preparation of substrate stock solution, where 0.36 μL of the IPA-substrate stock solution was added into the reaction tube followed by the subsequent addition of 2.6 μL of IPA and 1 μL DMSO. The reaction tubes were agitated on the Torrey Pines orbital shaker at 30°C for 24 hr. Then the mixture was extracted with ethyl acetate (2×20 μL), combined and dried over Na_2SO_4. The organic contents were evaporated in *vacuo*, and injected into HPLC to determine the % conversion and % *ee*.

Bioreduction of **1** comparing native Kred and BioBeads at analytical scale



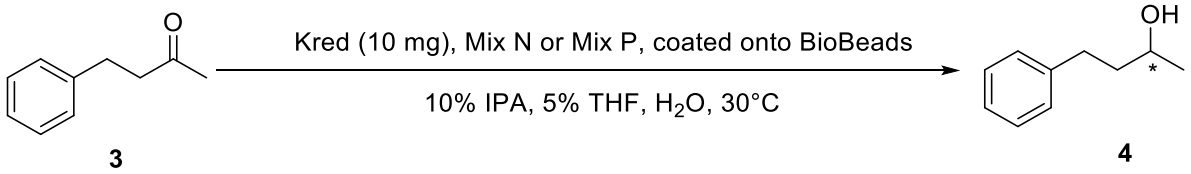
1 **2**

Table 1. Comparison of BioBeads and native reactions with acetophenone **1** as substrate.

Entry[a]	Kred	C(%)[b]	*ee (%)*[b]	Entry[a]	Kred	C(%)[b]	*ee (%)*[b]
1	P1-A04	>99(91)	>99(93)	13	P2-D11	98(98)	-1(-22)
2	P1-A12	96(91)	>99(69)	14	P2-D12	92(96)	18(-2)
3	P1-B02	98(96)	4(-2)	15	P2-G03	95(95)	77(18)
4	P1-B05	98(98)	-6(-2)	16	P2-H07	98(91)	>99(72)
5	P1-B10	98(95)	1(-3)	17	P3-B03	98(96)	1(-32)
6	P1-B12	98(96)	33(-3)	18	P3-G09	72(96)	6(-8)
7	P1-C01	96(98)	-3(1)	19	P3-H12	96(95)	-15(-45)
8	P1-H08	98(96)	-24(-4)	20	101	99(93)	53(25)
9	P2-B02	98(98)	-26(-1)	21	119	94(96)	-99(-99)
10	P2-C02	98(97)	-10(-3)	22	130	93(87)	-99(-92)
11	P2-C11	94(98)	41(26)	23	NADH-101	93(97)	25(16)
12	P2-D03	98(96)	41(-1)	24	NADH-110	90(94)	93(80)

[a]Reaction conditions: For entries 1-19, Mix P [128 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$], pH 7.0. Entries 20-24: identical conditions but using Mix N [263 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$,1.1 mM NAD^+,80 mM D-glucose and 10 Unit/mL glucose dehydrogenase], pH 7.0. Kred (10 mg), DI water (0.9 mL), IPA (0.1 mL), tetrahydrofuran (0.05 mL), 48 hr at 30°C. [b]Determined by HPLC: numbers inside parentheses represent results from native Kred; numbers outside parentheses represent results with BioBeads; positive and negative % *ee* values indicate *R* and *S* enantiomers respectively.

Bioreduction of **3** comparing native Kred and BioBeads at analytical scale



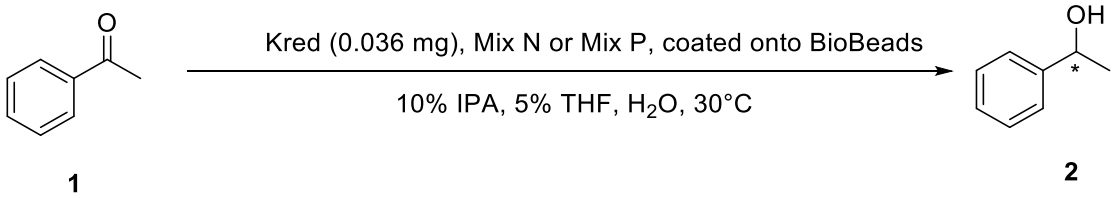
3 **4**

Table 2. Comparison of BioBeads and native reactions with 4-phenylbutan-2-one **3** as substrate.

Entry[a]	Kred	C(%)[b]	*ee (%)*[b]	Entry[a]	Kred	C(%)[b]	*ee (%)*[b]
1	P1-A04	96(96)	98(91)	13	P2-D11	98(99)	54(7)
2	P1-A12	96(96)	98(83)	14	P2-D12	98(99)	9(-2)
3	P1-B02	94(98)	96(38)	15	P2-G03	96(98)	73(52)
4	P1-B05	95(99)	98(58)	16	P2-H07	98(97)	-20(-2)
5	P1-B10	98(97)	99(92)	17	P3-B03	98(99)	-2(-18)
6	P1-B12	98(96)	33(85)	18	P3-G09	96(98)	-71(-73)
7	P1-C01	99(99)	-1(-2)	19	P3-H12	99(99)	-5(-6)
8	P1-H08	98(99)	62(3)	20	101	88(60)	-25(-58)
9	P2-B02	98(99)	-3(-2)	21	119	51(40)	-25(8)
10	P2-C02	98(99)	-6(-2)	22	130	99(58)	-3(34)
11	P2-C11	97(97)	80(74)	23	NADH-101	99(58)	-99(-97)
12	P2-D03	97(99)	18(-1)	24	NADH-110	97(97)	64(59)

[a]Reaction conditions: For entries 1-19, Mix P [128 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$], pH 7.0. Entries 20-24: identical conditions but using Mix N [263 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$,1.1 mM NAD^+,80 mM D-glucose and 10 Unit/mL glucose dehydrogenase], pH 7.0. Kred (10 mg), DI water (0.9 mL), IPA (0.1 mL), tetrahydrofuran (0.05 mL), 48 hr at 30°C. [b]Determined by HPLC: numbers inside parentheses represent results from native Kred; numbers outside parentheses represent results with BioBeads; positive and negative % *ee* values indicate *R* and *S* enantiomers respectively

Bioreduction of **1** comparing native and BioBeads at miniaturized scale



1 **2**

Table 3. Comparison of miniaturized BioBeads reaction with native reaction with acetophenone **1** as substrate

Entry[a]	Kred	C(%)[b]	ee (%)[b]	Entry[a]	Kred	C(%)[b]	ee (%)[b]
1	P1-A04	>99(90)	>99(>99)	13	P2-D11	97(98)	-1(30)
2	P1-A12	96(90)	>99(98)	14	P2-D12	92(89)	18(14)
3	P1-B02	98(>99)	4(28)	15	P2-G03	95(98)	77(85)
4	P1-B05	98(82)	-6(-14)	16	P2-H07	98(87)	>99(74)
5	P1-B10	98(92)	1(9)	17	P3-B03	98(98)	1(3)
6	P1-B12	97(97)	33(69)	18	P3-G09	72(61)	6(24)
7	P1-C01	96(69)	-3(37)	19	P3-H12	96(97)	-15(-9)
8	P1-H08	98(97)	-24(-10)	20	101	99(99)	53(39)
9	P2-B02	98(90)	-26(-13)	21	119	94(77)	-99(-40)
10	P2-C02	98(96)	-10(-7)	22	130	93(96)	-99(-99)
11	P2-C11	94(88)	41(66)	23	NADH-101	93(99)	25(23)
12	P2-D03	98(57)	41(50)	24	NADH-110	94(>99)	>99(61)

[a]Reaction conditions: For entries 1-19, Mix P [128 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$], pH 7.0. Entries 20-24, identical conditions but using Mix N [263 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$, 1.1 mM NAD^+, 80 mM D-glucose and 10 Unit/mL glucose dehydrogenase], pH 7.0. Kred, DI water (100 μL), IPA (0.89 μL), tetrahydrofuran (0.5 μL), 48 hr at 30°C. [b]Determined by HPLC: numbers inside parentheses represent results from BioBeads (0.036 mg Kred); numbers outside parentheses represent results from BioBeads (10 mg Kred); positive and negative % *ee* values indicate *R* and *S* enantiomers respectively.

Bioreduction of **5** comparing native and BioBeads at miniaturized scale

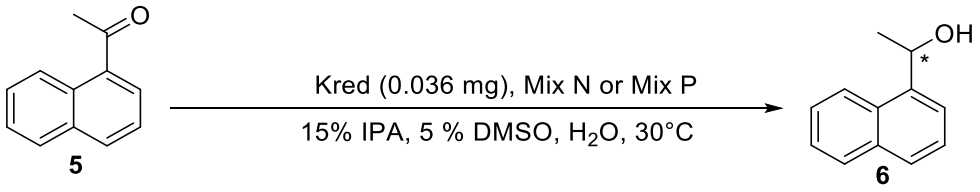
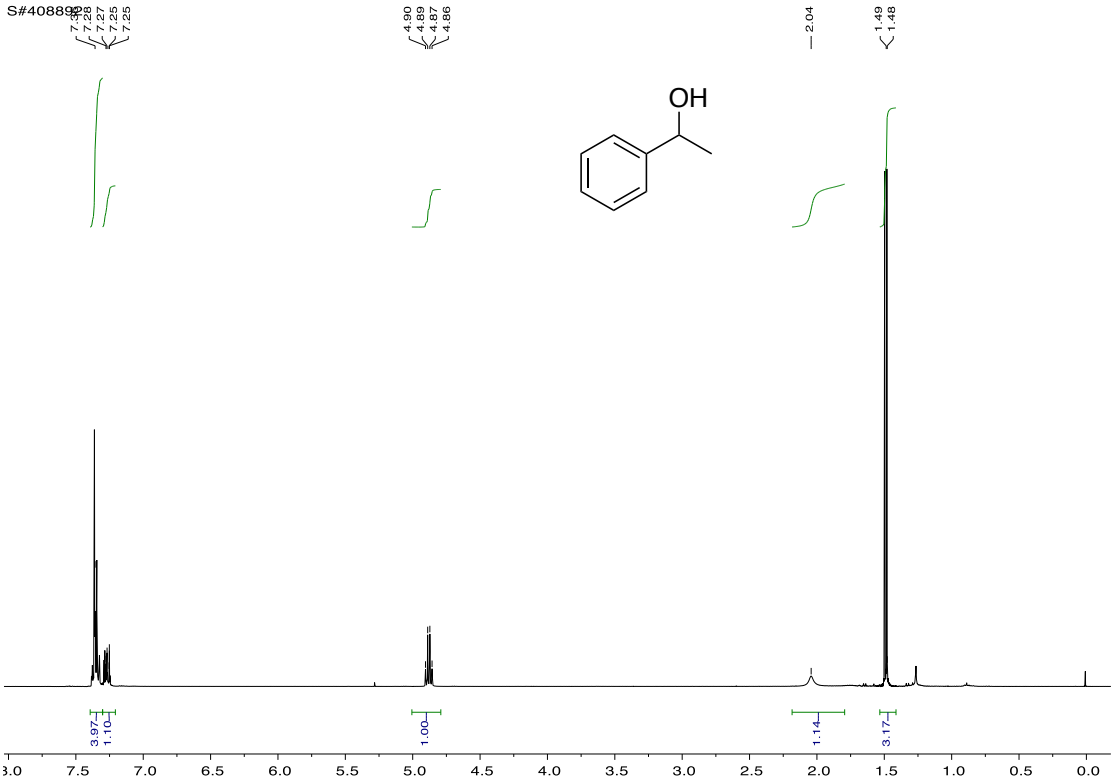


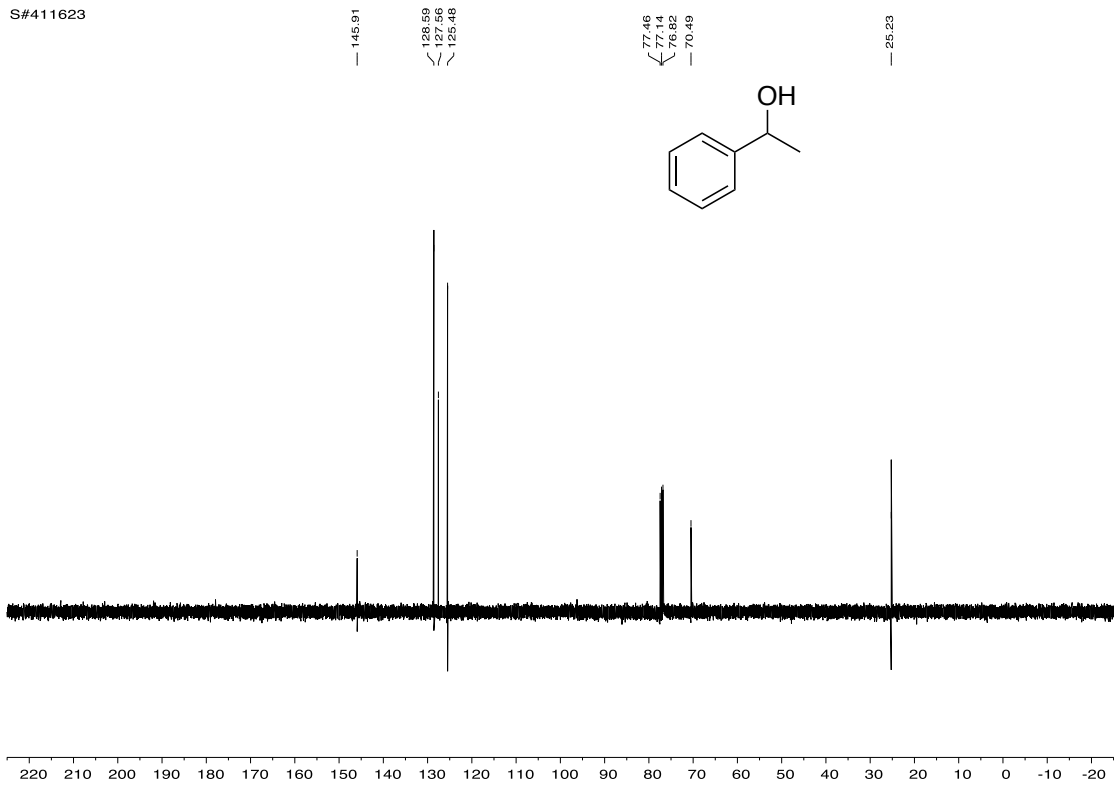
Table 4. Comparison of miniaturised BioBeads with results from Berglund *et. al* with 1-(naphthalen-1-yl)ethan-1-one **5** as the substrate.

Entry[a]	Kred	C(%)[a]	ee (%)[a]	Entry[a]	Kred	C(%)[a]	ee (%)[a]
1	P1-A04	13(14)	-84(-70)	13	P2-D11	90(99)	99(99)
2	P1-A12	3(37)	-2(-14)	14	P2-D12	69(99)	78(70)
3	P1-B02	97(99)	-99(-93)	15	P2-G03	50(99)	-74(-60)
4	P1-B05	30(17)	78(72)	16	P2-H07	33(30)	-70(-72)
5	P1-B10	94(99)	-99(-90)	17	P3-B03	95(99)	99(99)
6	P1-B12	98(99)	-99(-90)	18	P3-G09	8(8)	66(-)
7	P1-C01	79(99)	39(80)	19	P3-H12	95(99)	83(68)
8	P1-H08	53(43)	80(80)	20	101	23(17)	-99(-99)
9	P2-B02	79(99)	63(70)	21	119	31(13)	69(99)
10	P2-C02	54(99)	60(51)	22	130	3(0)	-4(-)
11	P2-C11	0(0)	-(-)	23	NADH-101	78(77)	-5(99)
12	P2-D03	62(99)	-80(-45)	24	NADH-110	99(99)	-98(-99)

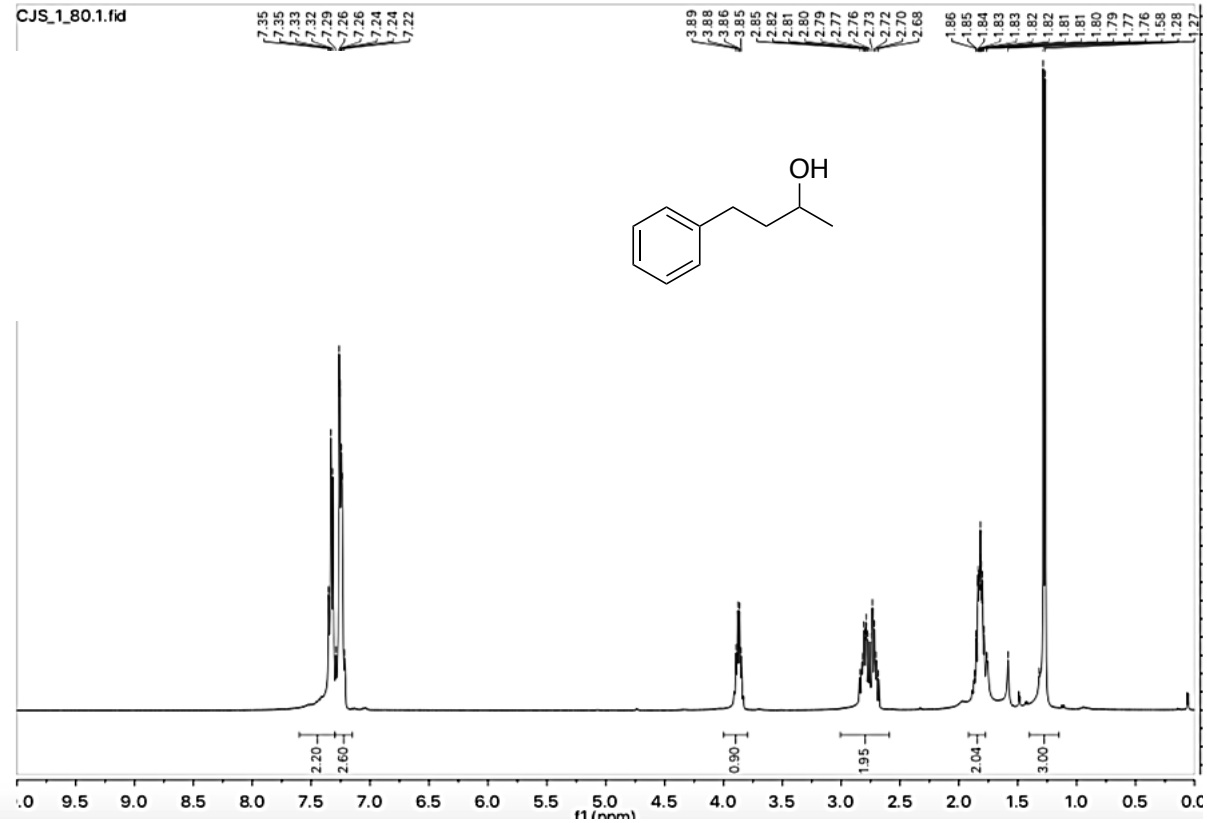
[a]Reaction conditions: For entries 1-19, Mix P [128 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$], pH 7.0. Entries 20-24, identical conditions but using Mix N [263 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$, 1.1 mM NAD^+, 80 mM D-glucose, 10 Unit/mL Glucose dehydrogenase], pH 7.0. Kred, DI water (16.2 μL), IPA (3 μL), dimethyl sulfoxide (1 μL), 24 hr at 30°C. [b]Determined by HPLC: numbers outside parentheses represent results from BioBeads (0.036 mg Kred); numbers inside parentheses represent results by Berglund *et al* [8]; positive and negative % *ee* values indicate *S* and *R* enantiomers respectively.

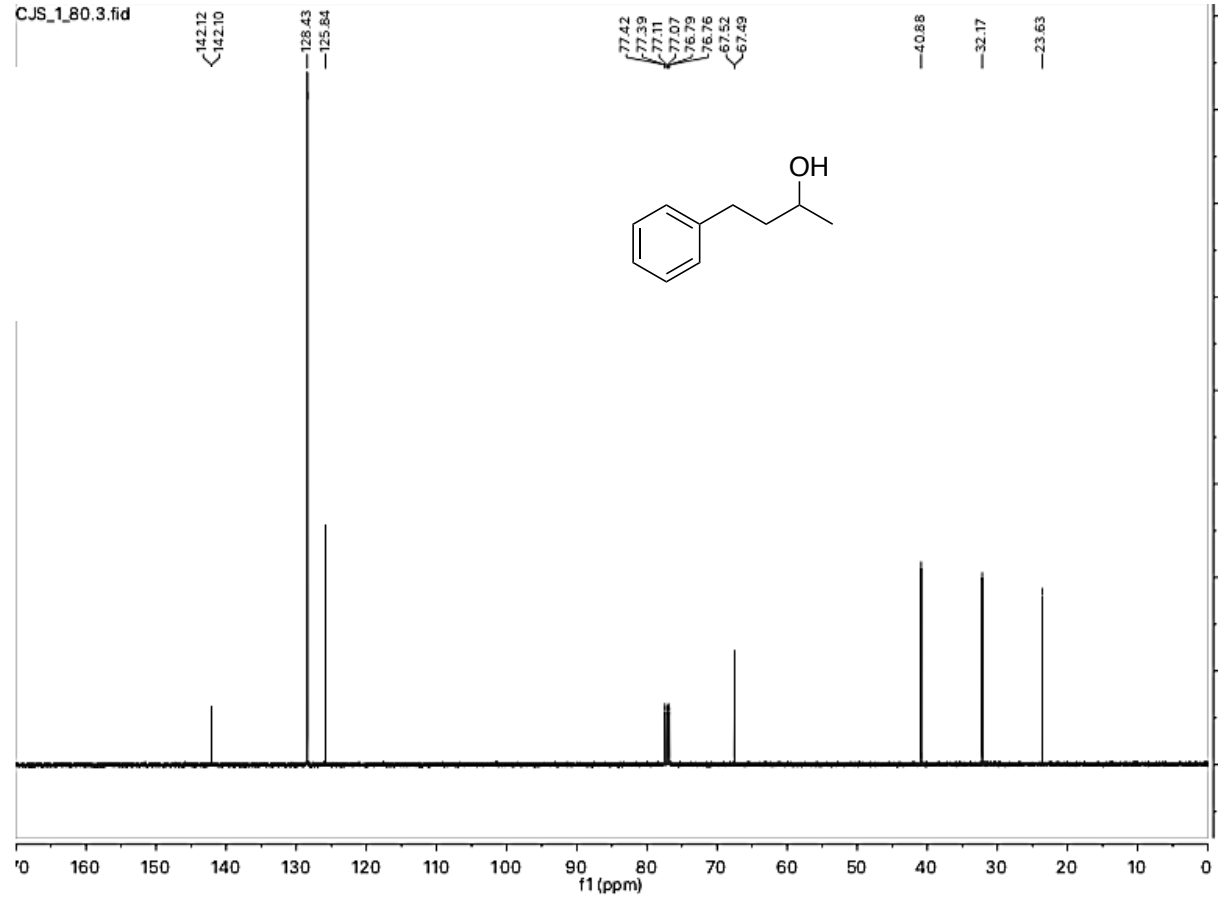
Appendix: ^{1}HNMR and ^{13}CNMR of **2**



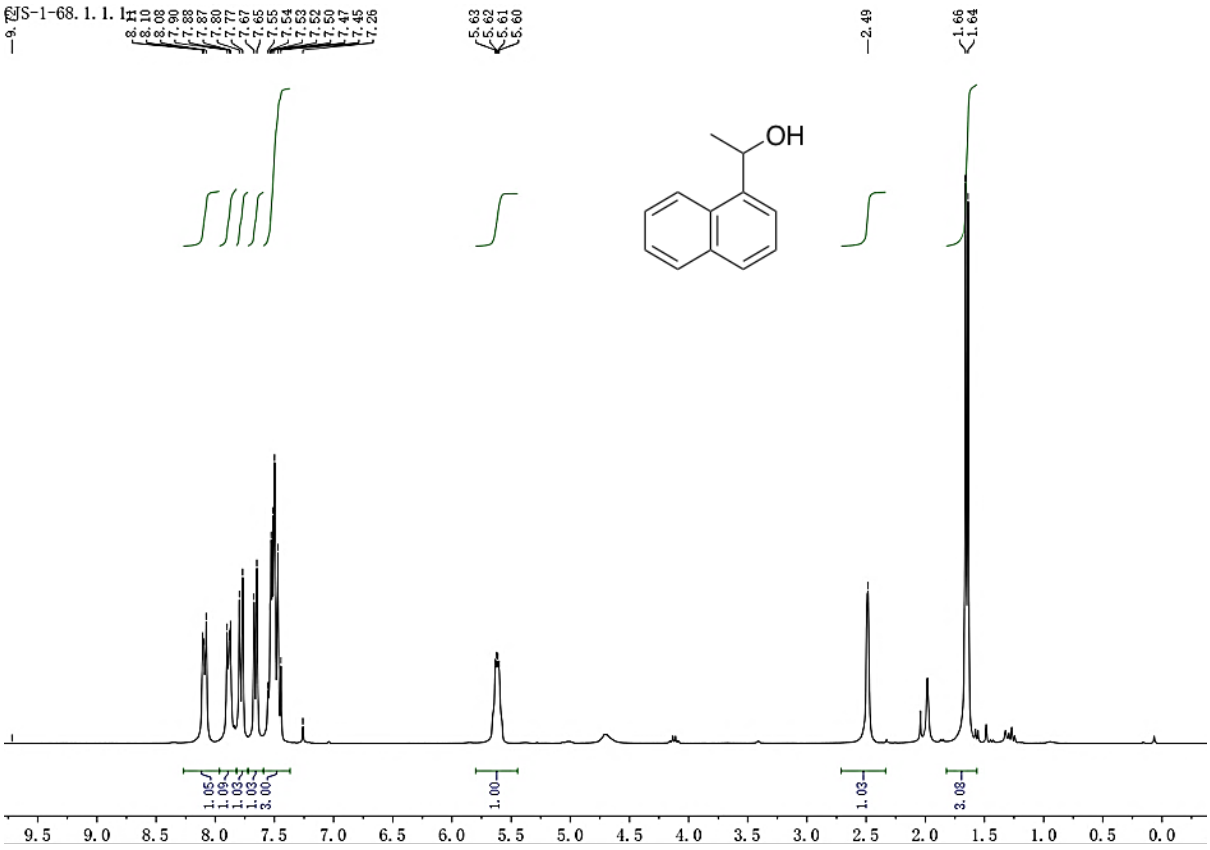


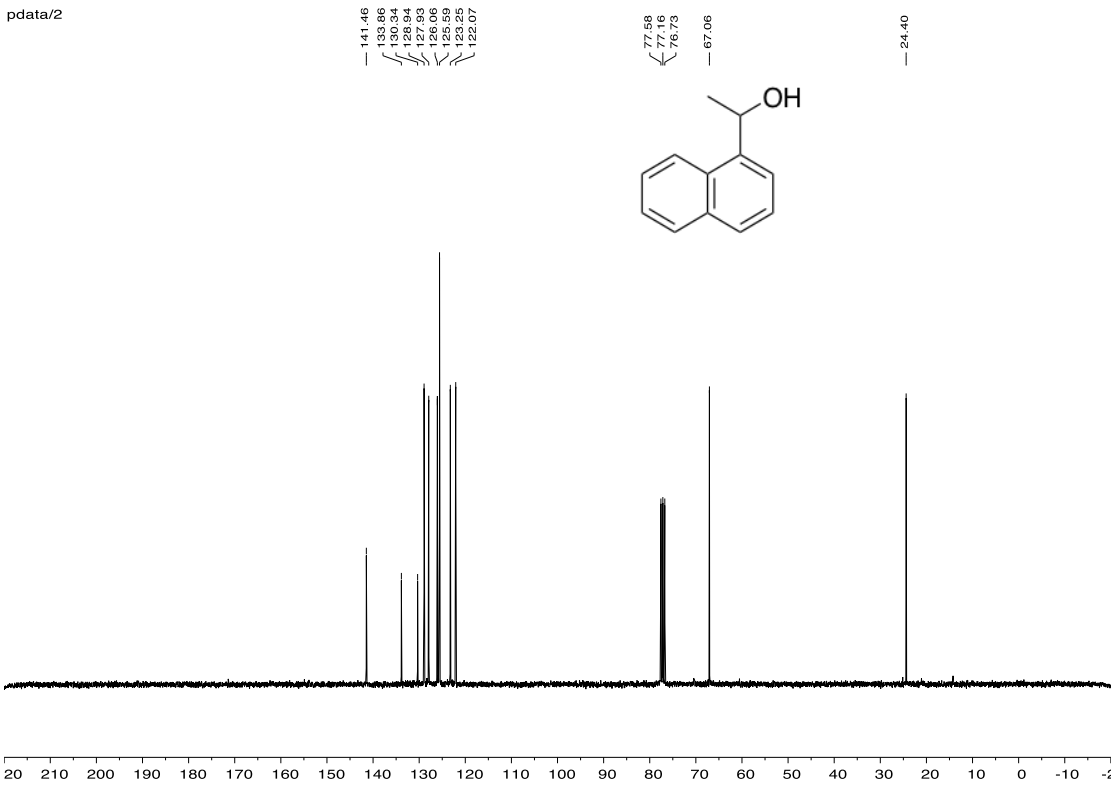
Appendix: ^{1}HNMR and ^{13}CNMR of **4**





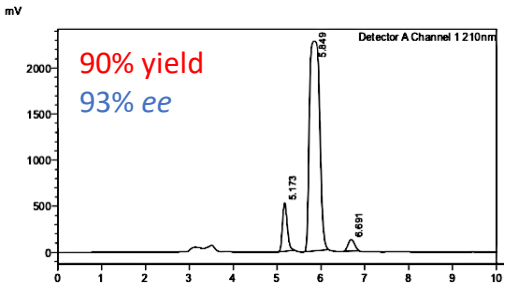
Appendix: ^{1}HNMR and ^{13}CNMR of **6**





Appendix: HPLC profiles of selected bioreductions of acetophenone **1**

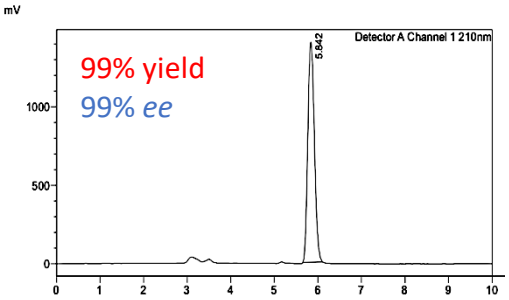
Kred P1-A04, Native



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	5.173	3993023	9.532
2	5.849	36611008	87.393
3	6.691	1288258	3.075
Total		41892290	100.000

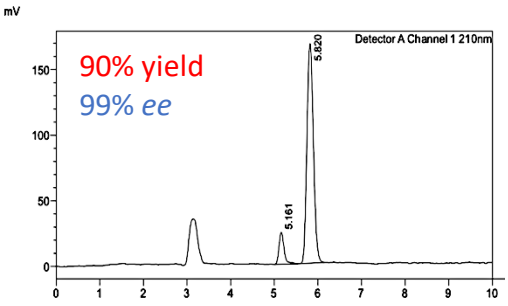
Kred P1-A04, BioBeads



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	5.842	14792605	100.000
Total		14792605	100.000

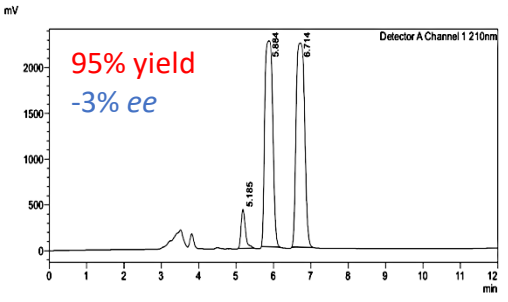
Kred P1-A04, Miniaturized



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	5.161	195290	10.190
2	5.820	1721156	89.810
Total		1916446	100.000

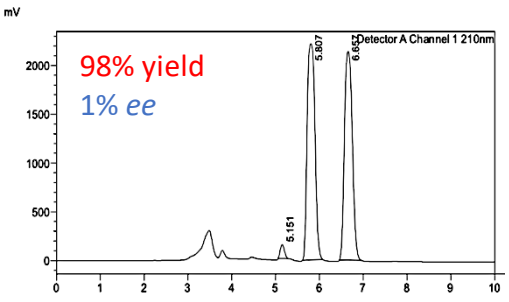
Kred P1-B10, Native



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	5.185	3432236	4.791
2	5.884	33024642	46.094
3	6.714	35189696	49.116
Total		71646574	100.000

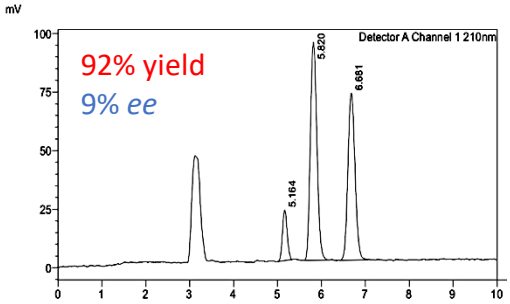
Kred P1-B10, BioBeads



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	5.151	938935	1.705
2	5.807	27432143	49.826
3	6.657	26684483	48.468
Total		55055561	100.000

Kred P1-B10, Miniaturized



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	5.164	162006	8.416
2	5.820	962842	50.017
3	6.681	800192	41.568
Total		1925040	100.000

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