Electronic Supplementary Material (ESI) for Chemical Communications.

Unexpected Rapid P-Stereomutation of Phosphine Oxides Catalysed by Chlorophosphonium Salts

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Supporting Information

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1. General Experimental

All reactions were carried out under a nitrogen atmosphere in Schlenk-type reaction vessels. Dry degassed solvents were stored in Young-type flasks over molecular sieves 4 Å. Air and moisture sensitive liquids and solutions were transferred *via* syringe. The water content in all solutions as monitored by titration on an Aquamax KF instrument was less than 5 ppm v/v.

Reagents and solvents were purchased from commercial suppliers and used as supplied unless otherwise stated. DCM, and toluene were degassed and dried by passing through a Grubbs type Pure Solv-400-3-MD solvent purification system supplied by Innovative Technology Inc. Oxygen-free nitrogen was obtained from BOC gases and was passed through a column filled with dry molecular sieves 4 Å. *(S)*-**1b** was received from our industry partners Celtic Catalysts.

NMR spectra were recorded at 25 °C and 60 °C on Varian VNMRS 300, 500 and 600 spectrometers. Assignments were based on standard ^{1}H, ^{31}P Peak integrations were determined by using a MestreNova software package. All NMR samples of potentially air-sensitive compounds were made up under a nitrogen atmosphere in dry degassed $CDCl_3$.

High-performance liquid chromatography was performed on an Agilent Technologies 1200 series instrument equipped with an IA column. HPLC grade solvents were purchased from Aldrich and Lennox Supplies Ireland and used as supplied. All samples were filtered through an Acrodisc CR 13 mm syringe filter with 0.2 µm PTFE prior to injection.

2. Self-Racemization of Scalemic Phosphine Oxide

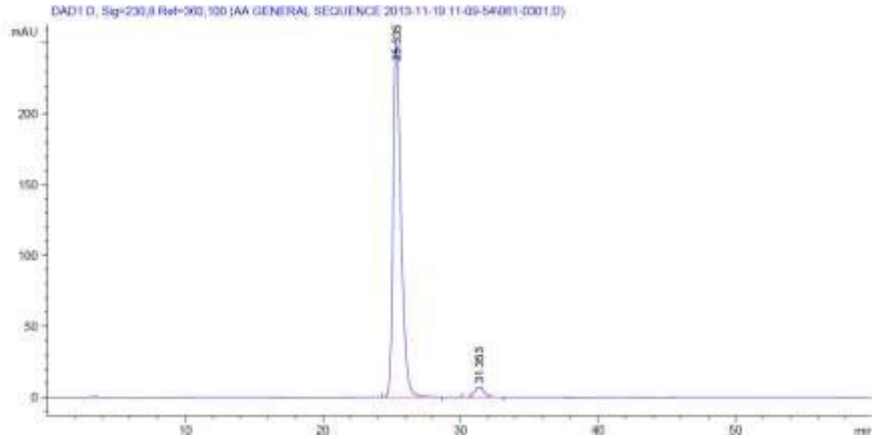
2.1 Effect of the Amount of 2b (0.5 mol%) on stereomutation of *(S)*-1b

(S)-**1b** (93% *ee*, 0.046 g, 0.2 mmol) was placed in a flame-dried and degassed Schlenk flask fitted with a stirring bar and septum. *(S)*-**1b** was melted using a flameless heat gun, evacuated and flushed with nitrogen and allowed to cool. DCM (5 mL) was added to dissolve *(S)*-**1b**. Stock solution of oxalyl chloride (0.2 M), (0.05 mL, 0.001 mmol, 0.005 equiv.) was quickly added to *(S)*-**1b** at room temperature (20.3 °C), stirred for 5 min and a portion (0.010 mL) of the reaction mixture was syringed to an HPLC vial which was charged with 1 mL of quench mixture *n*-heptane and EtOH (95:5 v/v). HPLC analysis (CHIRALPAK® IA column, 80:20 Heptane/EtOH, 1 mL/min), Rt: 25.3 min, major *(S)*, 31.4 min minor (*R*), revealed it to have 93% *ee* prior to the addition of oxalyl chloride. The reaction mixture was sampled for HPLC analysis in a similar manner at time intervals 5, 10, 20, 40, 60, 80, 100 min.

Table S1: The logarithmic (ln ee^t/ee^0) and absolute *ee* values of *(S)*-**1b** obtained after adding 0.5 mol.% of **2b** to *(S)*-**1b** at *ca* 20 °C in DCM[(a),(b)]

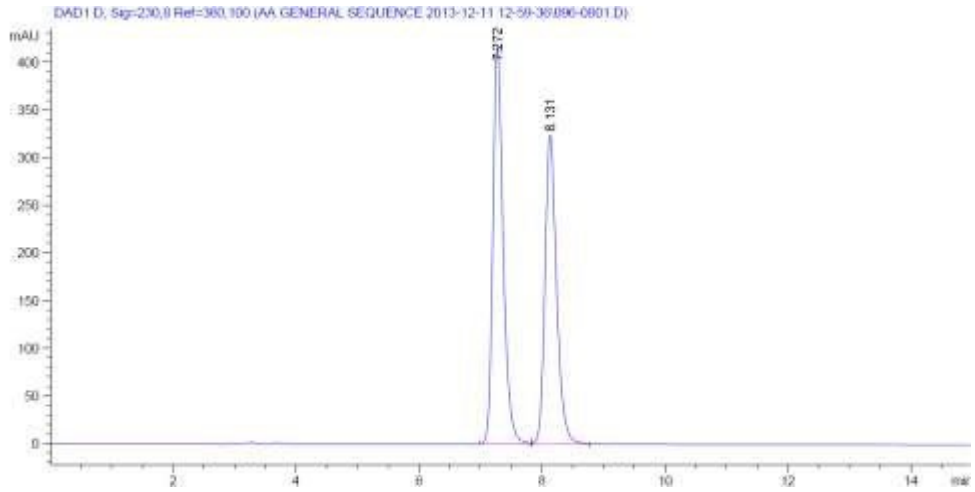
Time/min	% *ee*	ln(ee^t/ ee^0)
5	69.7	–0.28
10	56.8	–0.49
20	40.6	–0.82
40	21.1	–1.47
60	10.8	–2.14
80	6.7	–2.62
100	4.4	–3.06

(a) ee^t = *ee* value of *(S)*-**1b** obtained after mixing with 0.5 mol.% of **2b** at *ca* 20 °C in DCM for the time indicated. The *ee* of starting material *(S)*-**1b** (93% *ee*) was normalized to account for added amount of racemic **2b** therefor ee^0 = 93% – 0.5% = 92.5% in this example; (b) total reaction mixture concentration 0.04 M



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.335	BB	0.5961	9976.81445	250.77612	96.6590
2	31.353	BB	0.7387	344.84491	7.14953	3.3410

Figure S1: HPLC trace of *(S)*-**1b** prior to racemisation, CHIRALPAK® IA column, 95:5 *n*-heptane/EtOH, 1 mL/min.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.272	BV	0.1773	4903.66650	416.74316	53.3679
2	8.131	VB	0.2021	4284.74951	324.37390	46.6321

Figure S2: HPLC trace of part-racemised **1b** (0.5 mol.% **2b**, 20 °C, 80 min) 6.7% ee

Similar procedure was followed to study the effect of the other amounts of **2b** on stereomutation of *(S)*-**1b**.

2.2 Effect of the Amount of 2b (1 mol.%) on Stereomutation of *(S)*-1b

Table S2: The logarithmic (ln ee^t/ee^0) and absolute *ee* values of *(S)*-**1b** were obtained after mixing with 1 mol.% of **2b** at *ca* 20 °C in DCM. The initial *ee* of *(S)*-**1b** was normalized to account for initial added amount 1 mol.% of **2b** therefore ee^0 = 93% – 1% = 92%

Time/min	% *ee*	ln(ee^t/ee^0)
5	67.9	–0.31
10	53.2	–0.55
20	26.8	–1.24
40	10.4	–2.18
60	2.5	–3.63
80	1.0	–4.53

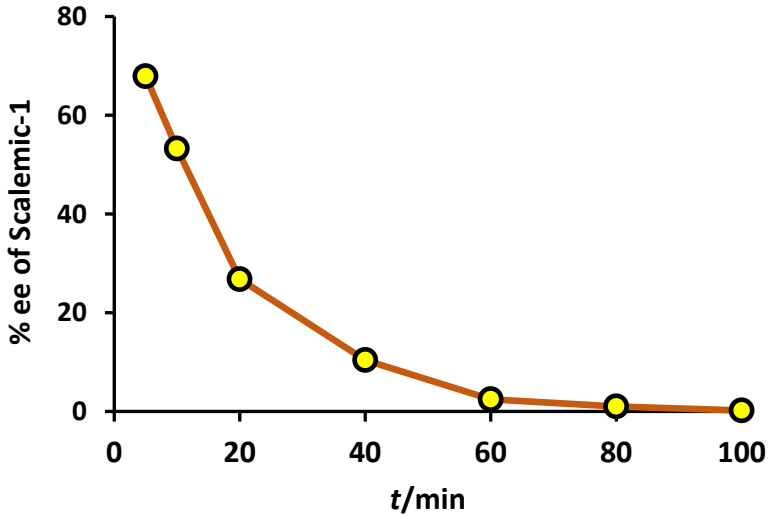


Figure S3: The *ee* values of *(S)*-**1b** as a function of time for reaction using 1 mol.% of **2b.**

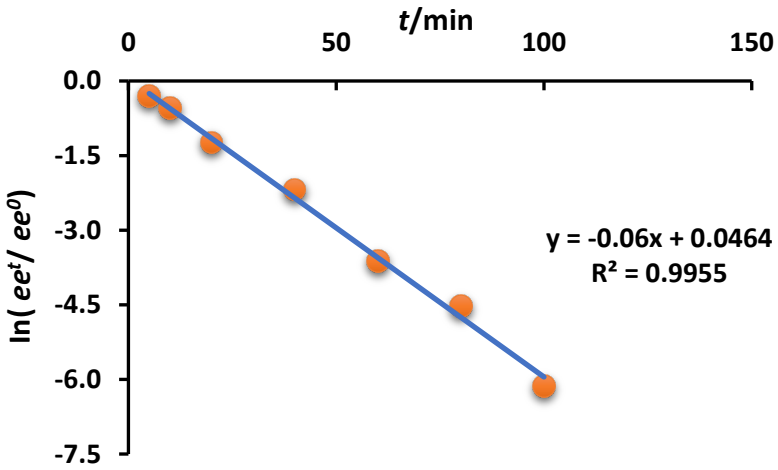


Figure S4: Log plot for reaction of *(S)*-**1b** using 1 mol.% of **2b.**

2.3 Effect of the Amount of 2b (5 mol. %) on Stereomutation of *(S)*-1b

Table S3: The logarithmic (ln ee^t/ee^0) and absolute *ee* values of *(S)*-**1b** obtained after mixing with 5 mol.% of **2b** at *ca* 20 °C in DCM. The *ee* of starting material *(S)*-**1b** (93% *ee*) was normalized to account for added amount of **2b** therefore ee^0 = 93% – 5% = 88%

Time/min	% *ee*	ln(ee^t/ee^0)
5	16.3	–1.7
8	10.1	–2.2
10	7.9	–2.4
12	5.1	–2.9
15	2.8	–3.5
25	1.0	–4.5
40	0.6	–5
60	0.2	–6.1

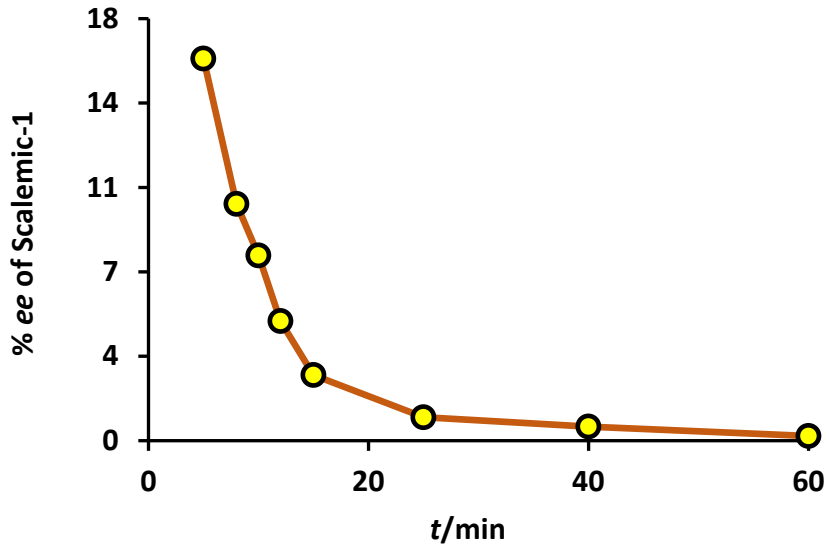


Figure S5: The *ee* values of *(S)*-**1b** as a function of time for reaction using 5 mol.% of **2b.**

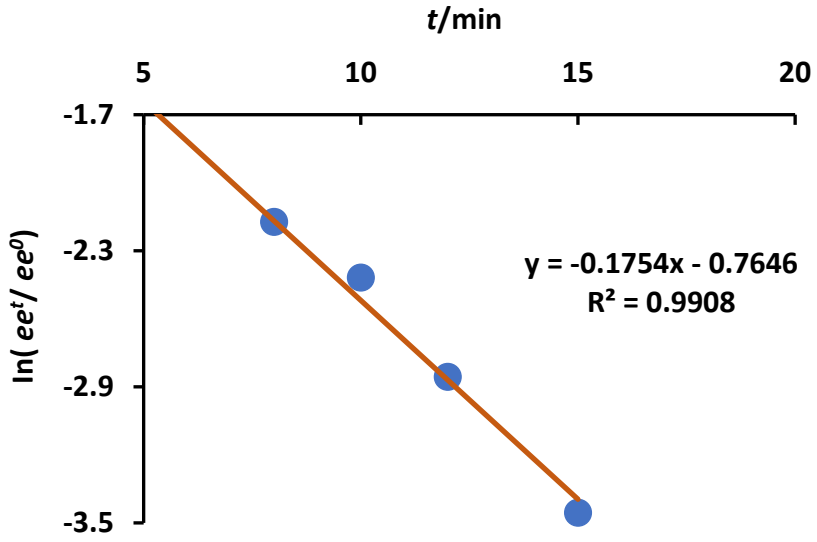


Figure S6: Log plot for reaction of *(S)*-**1b** using 5% of **2b**.

2.4 Effect of the Temperature on the Stereomutation of *(S)*-1b, (5 mol% 2b) at 0 °C

Similar procedure was followed to study the effect of temperature on stereomutation of *(S)*-**1b** as in stereomutation of *(S)*-**1b**, (5 mol.% **2b**) at 20 °C, except at 0 °C using an ice bath.

Table S4: The logarithmic (ln ee^t/ee^0) and absolute *ee* values of *(S)*-**1b** obtained after mixing with 5 mol.% of **2b** at *ca* 0 °C in DCM. The *ee* of starting material *(S)*-**1b** (93% *ee*) was normalized to account for added amount of **2b** therefore ee^0 = 93% – 5% = 88%.

Time/min	% ee	ln(ee^t/ee^0)
5	37.1	–0.9
10	22.4	–1.4
20	7.7	–2.4
40	1.3	–4.2
60	1.2	–4.3
80	0.6	–5.0
100	0.6	–5.0

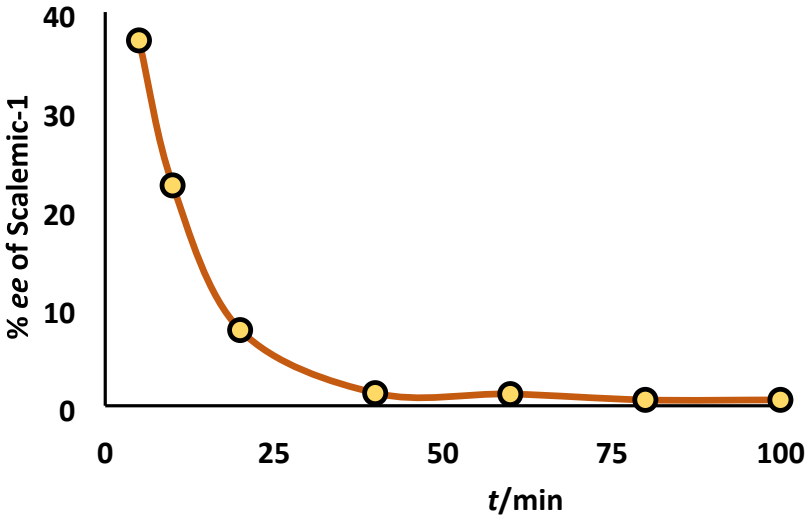


Figure S7: The *ee* values of *(S)*-**1b** as a function of time for the racemisation of *(S)*-**1b** using 5% of **2b** at 0°C in DCM

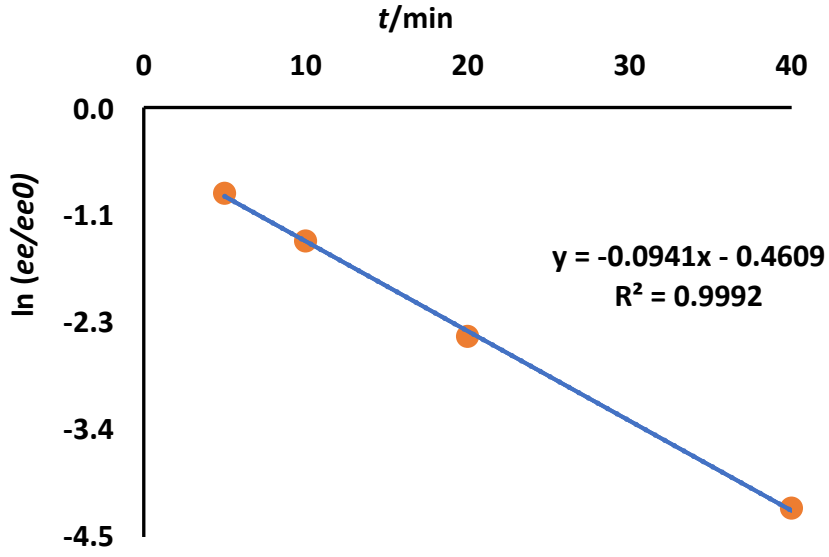


Figure S8: Log plot for reaction of *(S)*-**1b** using 5% **2b** at 0 °C in DCM.

2.5 Effect of the Temperature on the Stereomutation of *(S)*-1b (5 mol% 2b) at – 19.3 °C

Similar procedure was followed to study the effect of temperature on stereomutation of *(S)*-**1b** as in stereomutation of *(S)*-**1b**, (5 mol.% **2b**) at 20 °C, except at – 19.3°C using acetone and ice bath.

Table S5: The logarithmic (ln ee^t/ee^0) and absolute ee values of *(S)*-**1b** obtained after mixing with 5 mol.% of **2b** at ca –19 °C in DCM. The *ee* of starting material *(S)*-**1b** (93% *ee*) was normalized to account for added amount of **2b** therefore ee^0 = 93% – 5% = 88%.

Time/min	% *ee*	ln(ee^t/ee^0)
10	51.5	–0.5
20	42.4	–0.7
40	24.7	–1.3
60	13.4	–1.9
80	10.2	–2.2
100	6.2	–2.7

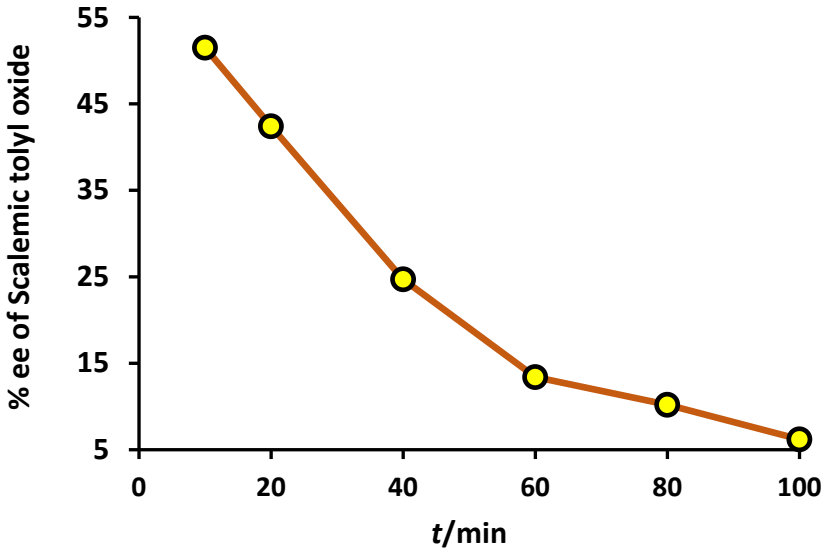


Figure S9: The *ee* values of *(S)*-**1b** as a function of time for the racemisation of *(S)*-**1b** using 1% of **2b** at *ca* –19 °C in DCM

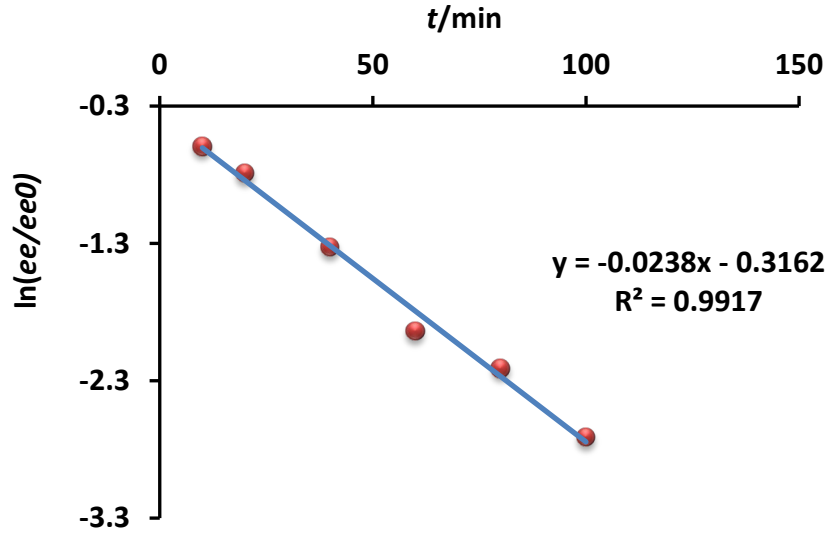


Figure S10: ee^t = *ee* value of *(S)*-**1b** obtained after mixing with 5% of **2b** at *ca* –19 °C in DCM for the time indicated.

Table S6: Rate constants for the racemisation of *(S)*-**1b** (k, s^{-1}) with 5 mol.% **2b** at various temperatures in DCM (°C)

Entry	Temp. °C	$k \times 10^{-3}$ s^{-1}
1	–19.3	0.40 ± 0.050
2	0	1.6 ± 0.089
3	20.3	2.9 ± 0.045

2.6 Effect of the Solvent on the Stereomutation

(S)-**1b** (93% *ee*, 0.046 g, 0.2 mmol) was placed in a flame-dried and degassed Schlenk flask fitted with a stirring bar and septum. *(S)*-**1b** was melted using a flameless heat gun, evacuated and flushed with nitrogen and allowed to cool. Toluene (5 mL) was added to dissolve the oxide. Stock solution of oxalyl chloride (0.2 M, 1.1 mmol) in toluene (5 mL), (0.05 mL, 0.01 mmol, 0.05 equiv.) was quickly added to *(S)*-**1b** at room temperature (*ca*. 20 °C), stirring under nitrogen in toluene and after 5 min, (0.010 mL) of the reaction mixture was syringed to an HPLC vial which was charged with 1 mL of quench mixture n-heptane and EtOH (95:5 v/v). HPLC analysis (CHIRALPAK® IA column, 80:20 heptane/EtOH, 1 mL/min). The reaction mixture was sampled for HPLC analysis in similar manner at time intervals 40, 100, 240, 360, 480, 600 min.

Table S7: The logarithmic (ln ee^t/ee^0) and absolute *ee* values of *(S)*-**1b** obtained after mixing with 5 mol.% of **2b** at *ca* 20 °C in toluene. The ee^0 of starting material *(S)*-**1b** (93% *ee*) was normalized to account for added amount of **2b** therefore ee^0 = 93% – 5% = 88%.

Time/min	% *ee*	ln(ee^t/ee^0)
40	82.7	–0.12
100	75	–0.22
240	64.4	–0.37
360	54.8	–0.53
480	46.06	–0.71
600	39.1	–0.87

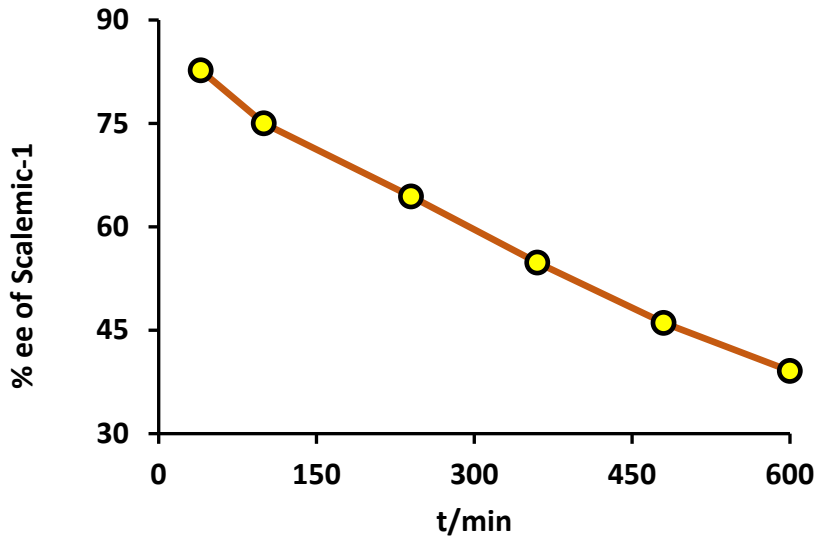


Figure S11: The *ee* values of *(S)*-**1b** as a function of time for the racemisation of *(S)*-**1b** using 5% of **2b** at *ca* 20°C in toluene

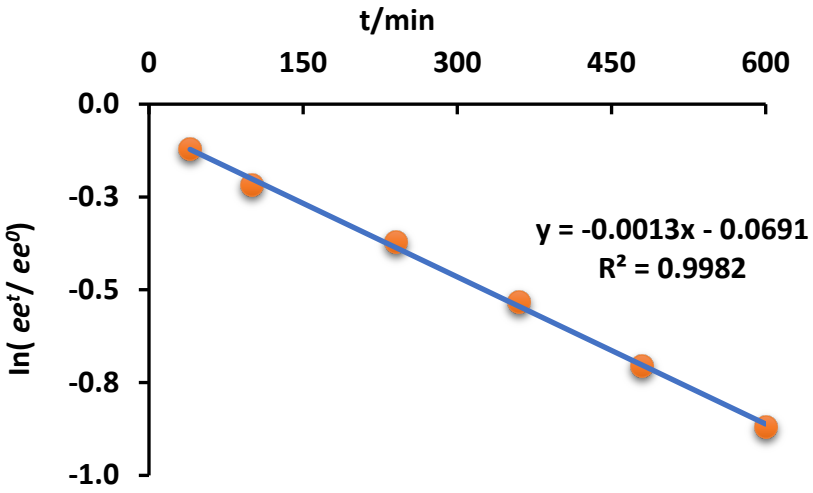


Figure S12: Log plot for reaction of *(S)*-**1b** obtained after mixing with 5% of **2b** at *ca* 20 °C in toluene for the time indicated.

2.7 Effect of Pentachloroacetonate Counterion on the Stereomutation of *(S)*-1b

Preparation of enolate phosphonium salt, EPS, **7** stock solution: a flame-dried and degassed Schlenk flask fitted with a stirring bar and septum was charged with (methyl(phenyl)(*o*-tolyl)phosphine (PMTP) stock solution (5 mL, 0.5 mmol, 0.10 M, 1.0 equiv.). The flask was then immersed in an ethyl acetate/ liquid nitrogen bath and cooled to –82 °C. Hexachloroacetone (HCA) stock solution (5.2 mL, 0.5 mmol, 0.10 M, 1.1 equiv.) was added dropwise *via* syringe. When all the HCA had been added, the reaction was stirred at –82 °C for 1 h under nitrogen. Formation of EPS **7** was confirmed by ^{31}P NMR as shown in Figure S13.

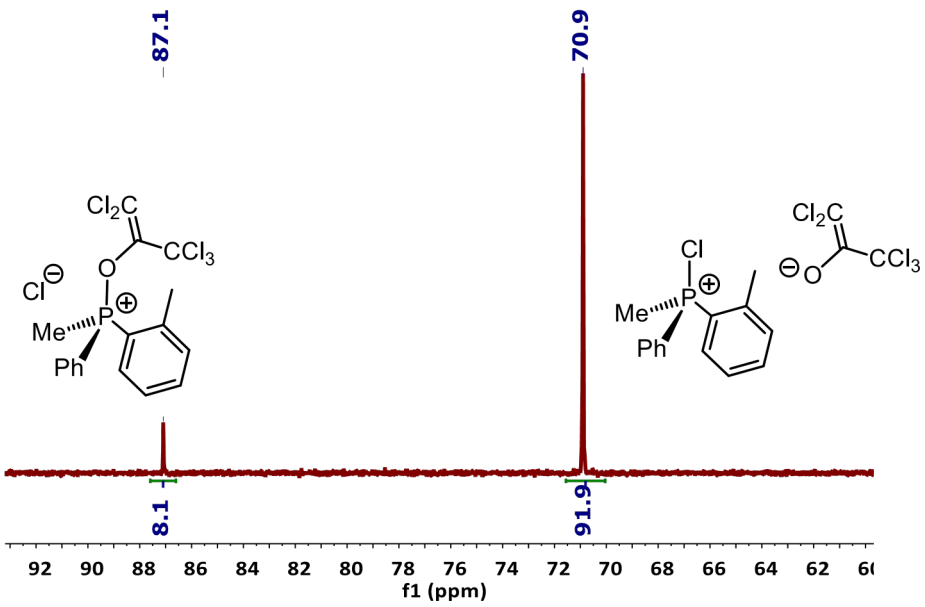


Figure S13: ^{31}P NMR spectrum of P-chlorinated EPS **7** prepared from PMTP and HCA.

(S)-**1b** (93% *ee*, 0.046 g, 0.2 mmol) was placed in a flame-dried and degassed Schlenk flask fitted with a stirring bar and septum. The *(S)*-**1b** was melted using a flameless heat gun, evacuated and flushed with nitrogen and allowed to cool. DCM (5 mL) was added to dissolve the oxide. Stock solution of **7** (0.1 M, 0.4 mmol) in toluene, (0.1 mL, 0.01 mmol, 0.05 equiv.) was quickly added to the *(S)*-**1b**, stirring under nitrogen and after 5 min, (0.010 mL) of the reaction mixture was syringed to an HPLC vial which was charged with 1 mL of quench mixture *n*-heptane and EtOH (95:5 v/v). HPLC analysis (CHIRALPAK® IA column, 80:20 heptane/EtOH, 1 mL/min). The reaction mixture was sampled for HPLC analysis in similar manner at time intervals 5, 10, 20, 40, 60, 80, 100 min.

Table S8: The logarithmic (ln ee^t/ee^0) and absolute *ee* values of *(S)*-**1b** obtained after mixing with 5 mol.% of **7** at *ca* 20 °C in DCM. The *ee* of starting material *(S)*-**1b** (93% *ee*) was normalized to account for added amount of **3b** therefore ee^0 = 93% – 5% = 88%.

Time/min	% ee	ln(ee^t/ee^0)
5	59.5	–0.34
10	44.7	–0.63
20	32.6	–0.95
40	17.6	–1.56
60	9.7	–2.16
80	6.9	–2.5
100	4.3	–2.97

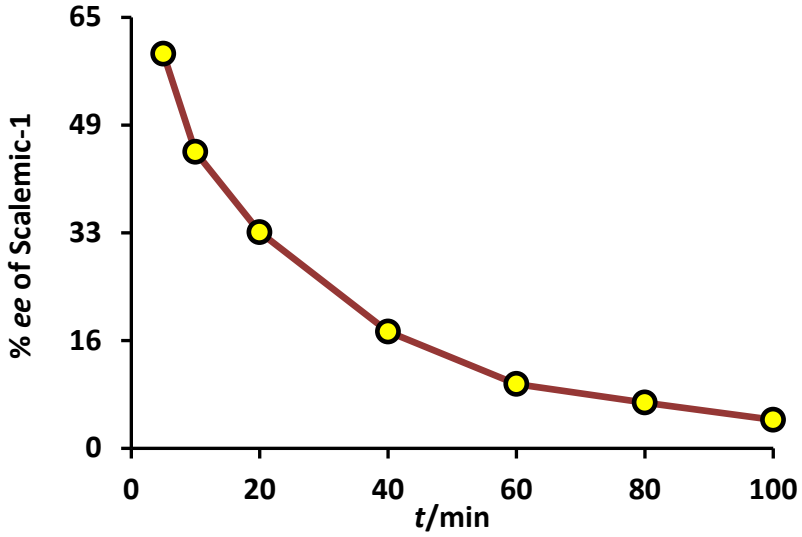


Figure S14: The *ee* values of *(S)*-**1b** as a function of time for the racemisation of *(S)*-**1b** using 5% of **7** at *ca* 20°C in DCM

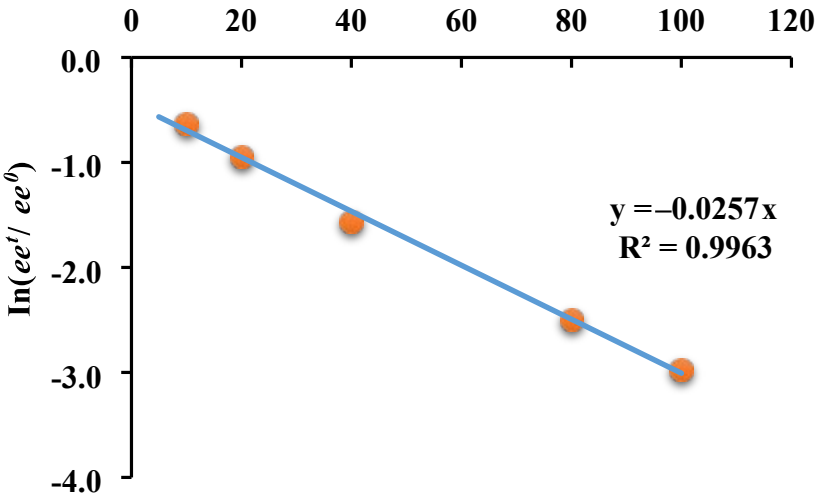


Figure S15: : Log plot for reaction of *(S)*-**1b** obtained after mixing with 5% of EPS **7** at *ca* 20 °C in DCM for the time indicated.

2.8. Cross-Racemization of Scalemic Phosphine Oxide. Effect of CPS 8 (5%) on the Stereomutation of *(S)*-1b

Oxalyl chloride neat (0.13 mL, 1.5 mmol, 1.5 equiv) was added dropwise at room temperature to a solution of trioctylphosphine oxide (0.39 g, 1.0 mmol, 1.0 equiv.) in DCM (4 mL) in 25 mL Young's tube and the reaction was allowed to stir for 2 hr. Formation of **8** (100%) was confirmed by ^{31}P NMR.

(S)-**1b** (93 % *ee*, 0.05 g, 0.2 mmol) was placed in a flame-dried and degassed Schlenk flask fitted with a stirring bar and septum. This phosphine oxide was melted using a flameless heat gun, evacuated and flushed with nitrogen and allowed to cool. DCM (5 mL) was added to dissolve the oxide **1b**. The CPS **8**, 0.25 M (0.04 mL, 0.01 mmol, 0.05 equiv.) in DCM was quickly added to the solution, stirring under nitrogen and after 5 min, (0.010 mL of the reaction mixture was syringed to an HPLC vial which was charged with 1 mL of quench mixture *n*-heptane and EtOH (95:5 v/v). HPLC analysis (CHIRALPAK® IA column, 80:20 heptane/EtOH, 1 mL/min). The reaction mixture was sampled for HPLC analysis in similar manner at interval time 5, 10, 20, 40, 60, 80, min.

Table S9: The logarithmic (ln ee^t/ee^0) and absolute *ee* values of *(S)*-**1b** obtained after mixing with 5 mol.% of **8** at *ca* 20 °C in DCM. The *ee* of starting material *(S)*-**1b** (93% *ee*).

Time/min	% *ee*	ln(ee^t/ee^0)
5	92.4	–0.01
10	92.1	–0.01
20	91.7	–0.02
40	90.2	–0.03
60	89	–0.05
80	88	–0.06

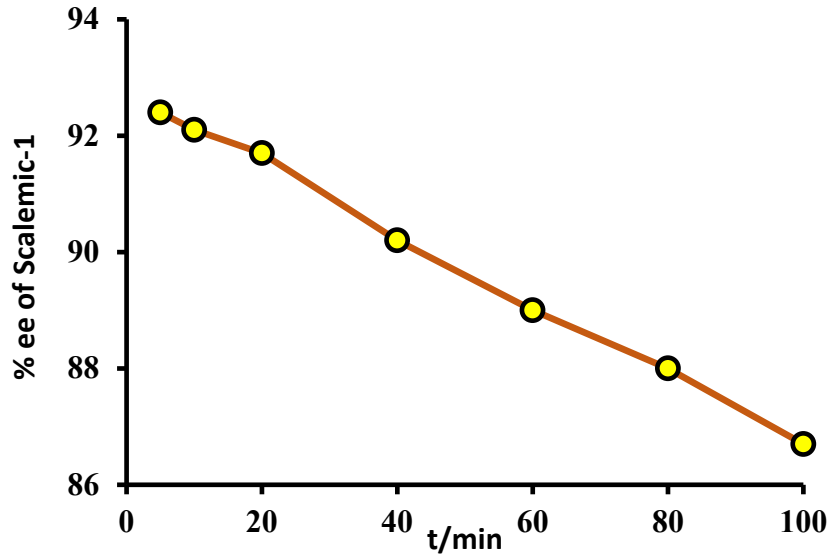


Figure S16: The *ee* values of *(S)*-**1b** as a function of time for the racemisation of *(S)*-**1b** using 5% of **8** at *ca* 20 °C in DCM for the time indicated.

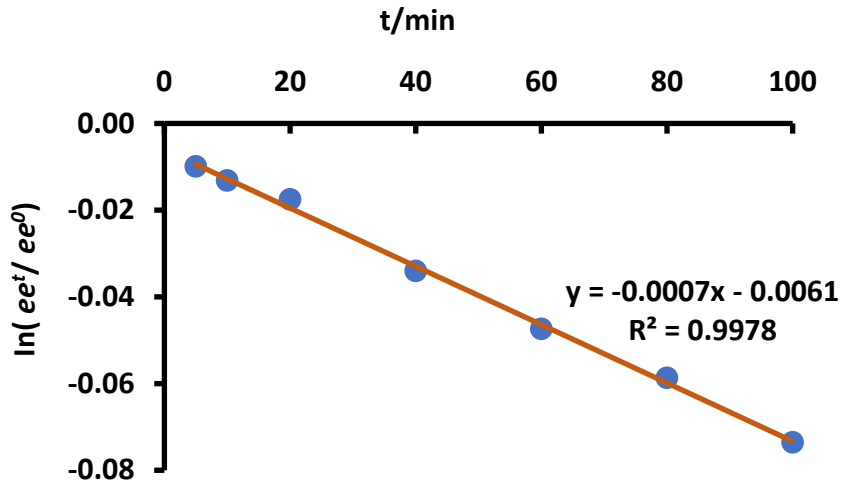
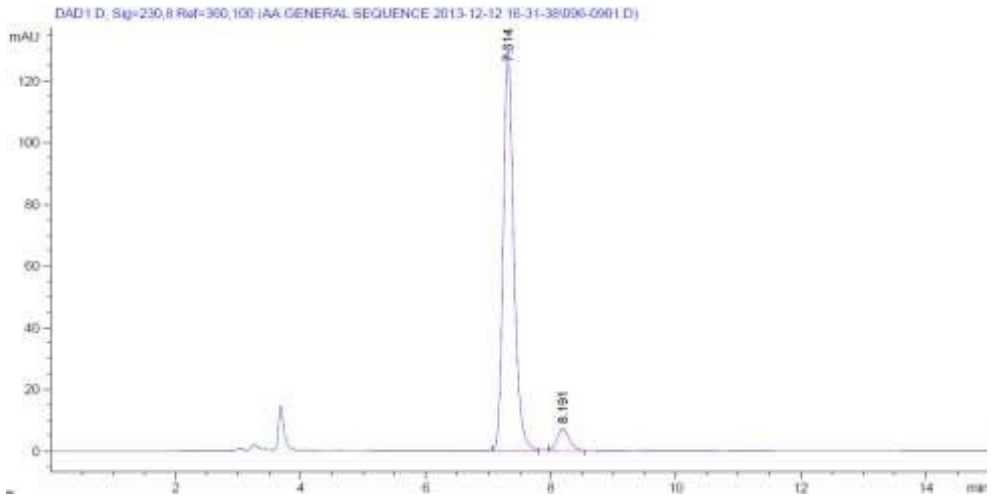


Figure S17: Log plot for reaction of *(S)*-**1b** obtained after mixing with 5% of **8** at *ca* 20 °C in DCM for the time indicated.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.314	BB	0.1773	1534.46338	130.40262	94.0159
2	8.191	BB	0.2008	97.66901	7.35989	5.9841

Figure S18: HPLC trace of the effect of **8** (5%) on the racemization of *(S)*-**1b** at *ca*. 20°C was sampled after 80 min, CHIRALPAK® IA column, 80:20 *n*-heptane/EtOH, 1 mL/min, *ee*: 88%.

3. NMR Experiments Designed for Detection of POP species 5b

3.1 ^{31}P NMR Experiment using increased concentration of reagents

Rac-**1b** (0.055 g, 0.240 mmol) was placed in a flame-dried and degassed Schlenk flask fitted with a stirring bar and septum. rac-**1b** was melted using a flameless heat gun, evacuated and flushed with nitrogen and allowed to cool. Dry $CDCl_3$ (0.6 mL) was added to dissolve **1b**. Stock solution of oxalyl chloride in $CDCl_3$ (0.22 M, 0.65 mL, 0.14 mmol, 0.6 equiv.) was added to the solution rac-**1b** at room temperature. The ^{31}P NMR spectrum indicated the presence of a new species **5b** 0.4% relative integral intensity at 80.7 ppm, 56.8% of **2b** and 42.9 % of rac-**1b**.

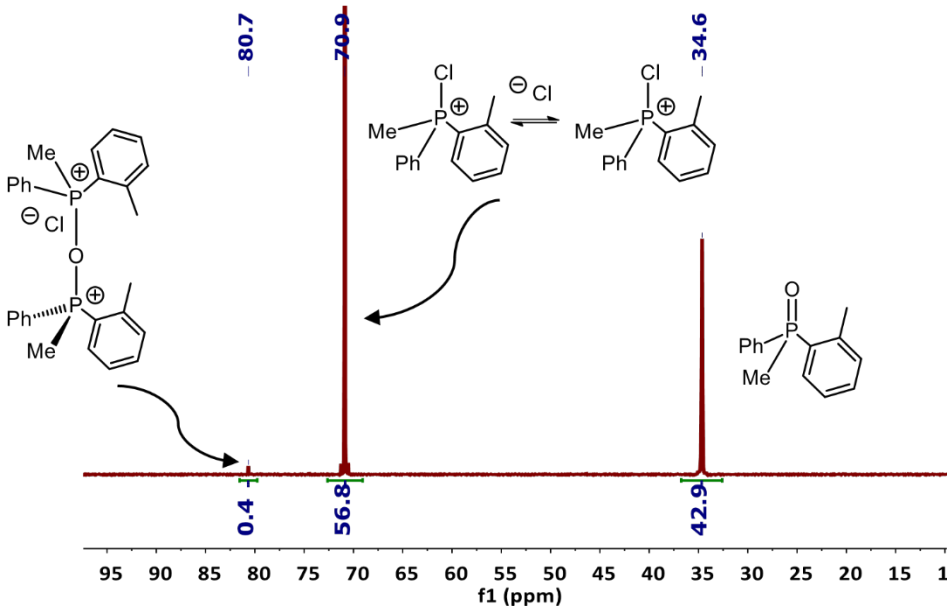


Figure S19: ^{31}P NMR spectrum of mixing rac-**1b** (1 equiv.), with oxalyl chloride (0.6 equiv.) in $CDCl_3$ at room temperature

2D EXSY NMR experiment at 25 °C

Rac-**1b** (0.4 M, 0.055 g, 0.240 mmol) was placed in a flame-dried and degassed Schlenk flask fitted with a stirring bar and septum. This oxide was melted using a flameless heat gun, evacuated and flushed with nitrogen and allowed to cool. Dry $CDCl_3$ (0.6 mL) was added to dissolve the oxide. Stock solution of oxalyl chloride (0.22 M, 1.10 mmol) in $CDCl_3$ (5 mL), (0.55 mL, 0.12 mmol, 0.5 equiv.) was added to rac-**1b** at room temperature. A 2D NMR EXSY experiment of the solution mixture containing rac-**1b** (0.1 M) and **1b** (0.1 M) was recorded at 25 °C at 600 MHz at mixing time 0.1 s.

The relative integration of the cross peak corresponding to chemical exchange between the methyl group (CH3–P) of **2b** and rac-**1b** is 0.8 % with Tm = 0.1 s and the rate constant of this interconversion is approx. 0.08 s^{-1}, Figure S20.

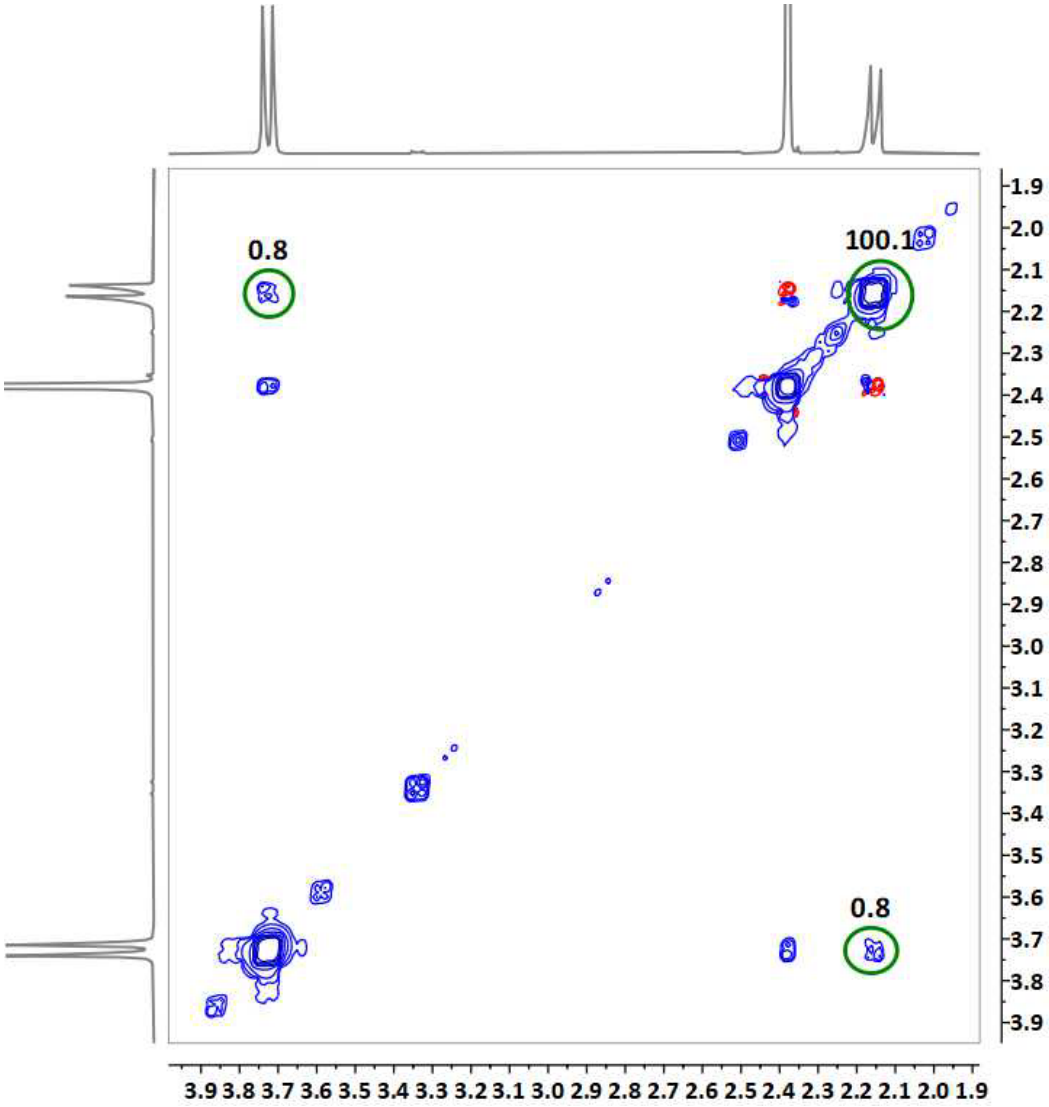


Figure S20: The ^{1}H-^{1}H 2D EXSY 600 MHz spectrum of rac-**1b** (1 equiv.) treated with oxalyl chloride (0.5 equiv.) in $CDCl_3$ at 25 °C, mixing time (0.1 s).