Kinetics screening of the *N*-alkylation of organic superbases using a continuous flow microfluidic device: basicity versus nucleophilicity

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Supplementary Information

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Experimental section

All compounds were purchased from commercial sources. All chemicals were in the highest purity available and were used as received without further purification.

The high pressure syringe pump (pumping force up to 1926 N) was fitted with two 8 mL stainless steel syringes which are driven simultaneously. As a micromixer, for all bases except BEMP **10**, we utilized a multilaminating distributive micromixer chip (NanoMixer®, Upchurch, now part of IDEX Health and Science Company, Oak Harbor, WA, USA) and a capillary reactor with an internal diameter and length of 75 µm and 300 cm respectively. For BEMP **10**, which is less reactive, we used a mixing MicroTee (Upchurch) and a capillary reactor size of 200 µm internal diameter and 400 cm length. The capillary tubular reactor is kept in a water bath at the desired temperature (20 °C). The mixing time of the two micromixers is in the order of 1 ms. For the different flow rates, a certain volume (4 µL for **1**, **2** and **6**, 1µL for **3**, 10 µL for **4** and **10**, 100 µL for **9** and **11**) of reaction medium was collected at the outlet of the tubular reactor and quenched in 1000 µL methanol: water: trifluoroacetic acid (50:50:0.1, v/v/v). A 20 µL volume (40 µL for **3,** 100 µL for **9** and **11**) of quenched sample was diluted again to 1000 µL (500 µL for **10**) of methanol: water: trifluoroacetic acid (50:50:0.1, v/v/v). This sample was later analyzed by mass spectrometry.

When bis-alkylated products were formed the kinetics was checked using Chemical Kinetics Simulator (http://www.almaden.ibm.com/st/computational_science/ck/?cks) which uses a general, rigorously accurate stochastic algorithm to propagate a reaction based on the algorithms published by D. T. Gillespie (D. T. Gillespie, *J. Comput. Phys.* 1976, 22, 403-434).

The electrospray and tandem mass spectra were recorded on a Micromass Quattro II triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an ESI source. Nitrogen was used as the nebulizing and drying gas at flow rates of 10-15 and 250-300 $L.h^{-1}$ respectively. The samples were infused into the ESI source by using a syringe pump (Harvard Apparatus Biomedical Dispensing system, Les Ulis, France) at the flow rate of 0.5 $mL.h^{-1}$. The ESI source potentials were: capillary 3.5 kV and cone at 25 V. The mass spectrometer scan time was fixed at 4.00 seconds and mass scan range was set depending to the component mass. Data acquisition and processing were carried out using Mass Lynx 4.0 software supplied with the instrument. Data acquisition was conducted in multichannel analyzer (MCA) mode and the spectra were accumulated over ten scans.

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Table S1 Capillary length and diameters, flow rates and their corresponding residence times

All bases except **3**, **9**, **10**, **11**		Bases **9** and **11**		Base **10**		Base **3**	
Diameter (µm)	Length (cm)	Diameter (µm)	Length (cm)	Diameter (µm)	Length (cm)	Diameter (µm)	Length (cm)
75	300	75	300	200	400	75	300
Flow rate (µL. min^{-1})	Residence time (s)	Flow rate (µL. min^{-1})	Residence time (s)	Flow rate (µL. min^{-1})	Residence time (s)	Flow rate (µL. min^{-1})	Residence time (s)
7.95	100	79.5	10	1.05	7200	0.147	5400
8.83	90	88.3	9	1.14	6600	0.166	4800
9.94	80	99.4	8	1.26	6000	0.189	4200
11.4	70	113.5	7	1.40	5400	0.221	3600
13.3	60	132.5	6	1.57	4800	0.265	3000
15.9	50	159.0	5	1.80	4200	0.331	2400
19.9	40	198.7	4	2.09	3600	0.442	1800
26.5	30	265.0	3	2.51	3000	0.662	1200
39.7	20	397.4	2	3.14	2400	1.325	600
79.5	10			4.19	1800		
				6.28	1200		
				12.57	600		
				75.40	100		

Table S2 Statistical analysis for a typical experiment, **6** MTBD

Flow rate (μL. min $^{-1}$)	79.5	39.7	26.5	19.9	15.9	13.3	11.4	9.94	8.83	7.95
Residence time (s)	10	20	30	40	50	60	70	80	90	100
Prototonated base intensity	171121776	166128304	137760320	120183920	109969864	98773216	94798280	90620816	68258928	81462160
Alkylated base intensity	65108196	72729936	89120312	96560016	115232768	123657328	132512424	141252832	138692384	164635536
Sum of the protonated and alkylated base intensities	236229972	238858240	226880632	216743936	225202632	222430544	227310704	231873648	206951312	246097696
Chemical yield (%)	27.6	30.4	39.3	44.6	51.2	55.6	58.3	60.9	67.0	66.9
Sum / average	1.04	1.05	1.00	0.95	0.99	0.98	1.00	1.02	0.91	1.08

Table S3 Summary of regression analysis for the investigated bases

Base	Acronym	Conc. (mM)	Max. conv. (%)	Intercept	R^2	k ($mol^{-1}.L.\ s^{-1}$)
2	Barton's base	478.2	30	0.996	0.982	1.4×10^{-2}
3	TMGN	155.4	8	0.997	0.986	1.2×10^{-4}
6	MTBD	470.1	67	1.087	0.993	4.8×10^{-2}
7	DBN	46.0	72	1.14	0.995	5.5×10^{-1}
8	DBU	46.8	53	0.948	0.975	2.5×10^{-1}
9	DABCO	46.3	73	0.888	0.986	8.3
10	BEMP	46.3	18	0.995	0.985	8.0×10^{-4}
11	P_2Et	4.6	79	1.377	0.984	72

Table S4 Summary of the experiments using **3** TMGN

Entry	Kinetic conditions	TMGN ($mmol.L^{-1}$)	MeI ($mmol.L^{-1}$)	k ($mol^{-1}.L.\ s^{-1}$)	Set-up
a	2^{nd} order	93.4	96.4	1.2×10^{-4}	Batch[a]
b	2^{nd} order	46.6	48.2	1.2×10^{-4}	Continuous[b]
c	2^{nd} order	155.6	160.6	1.2×10^{-4}	Continuous[c,d]
d	1^{st} order	155.8	1606	1.0×10^{-4}	Continuous[c,d]

[a]Kinetics followed up to 25 h, maximum conversion. [b]Mixing device: MicroTee, capillary reactor 4 m×200 µm. [c]Mixing device: NanoMixer® capillary reactor 3 m×75 µm. [d]With DMF dried over molecular sieves.

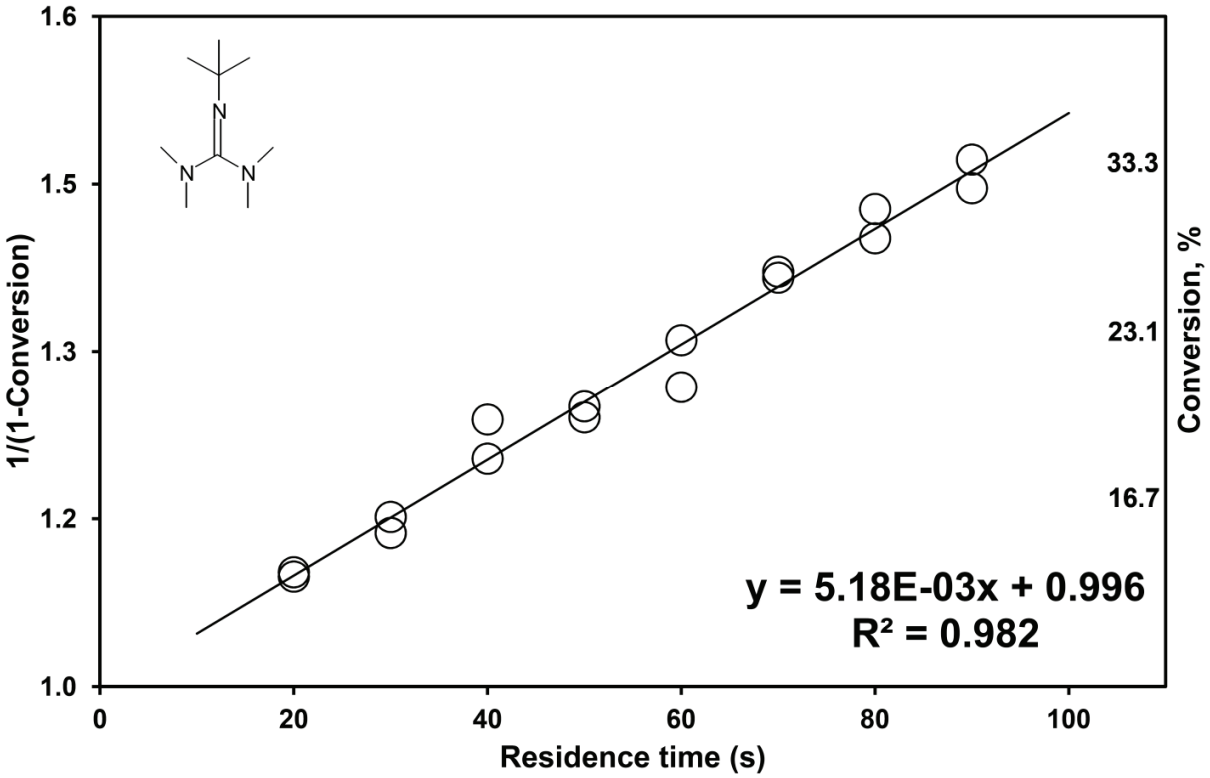

Fig. S1 Second order kinetics plot of **2** Barton's base alkylation by iodomethane in DMF at 20°C, $[B]_0$= 0.48 M

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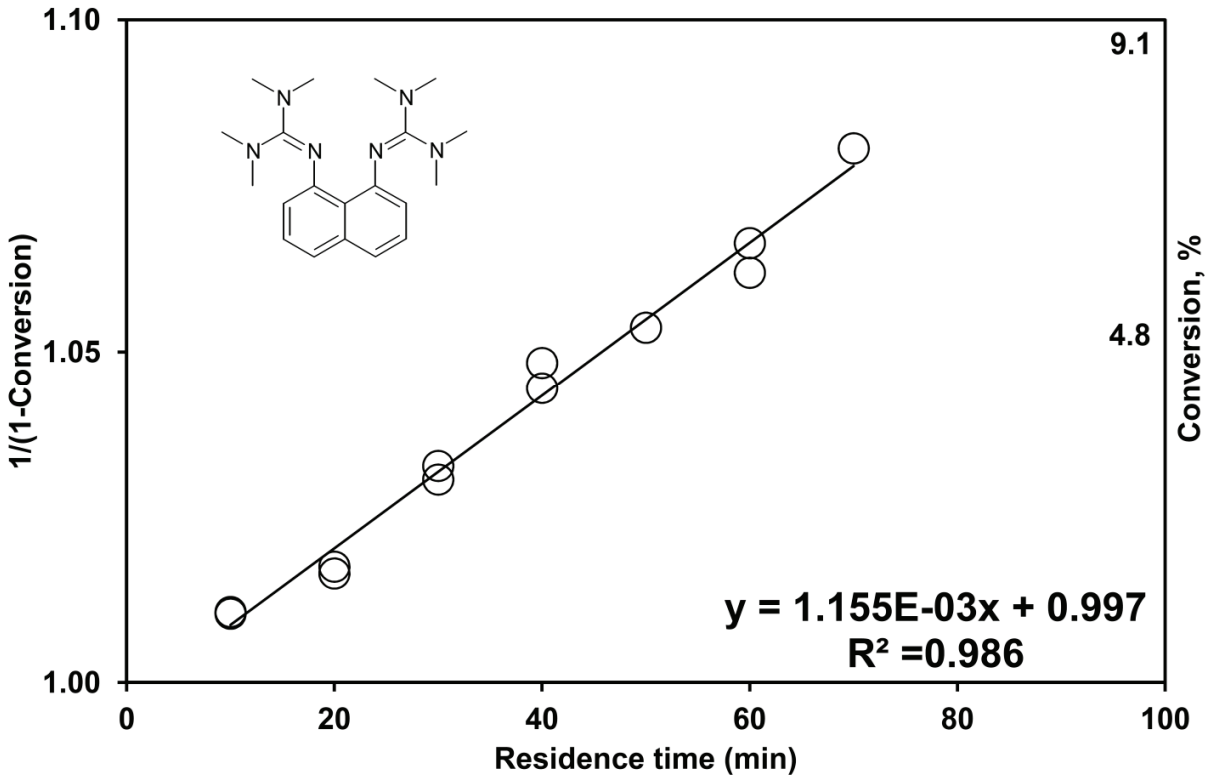

Fig. S2 Second order kinetics plot of **3** TMGN alkylation by iodomethane in DMF at 20°C, $[B]_0$= 0.16 M (Higher concentration is not possible because of solubility problems)

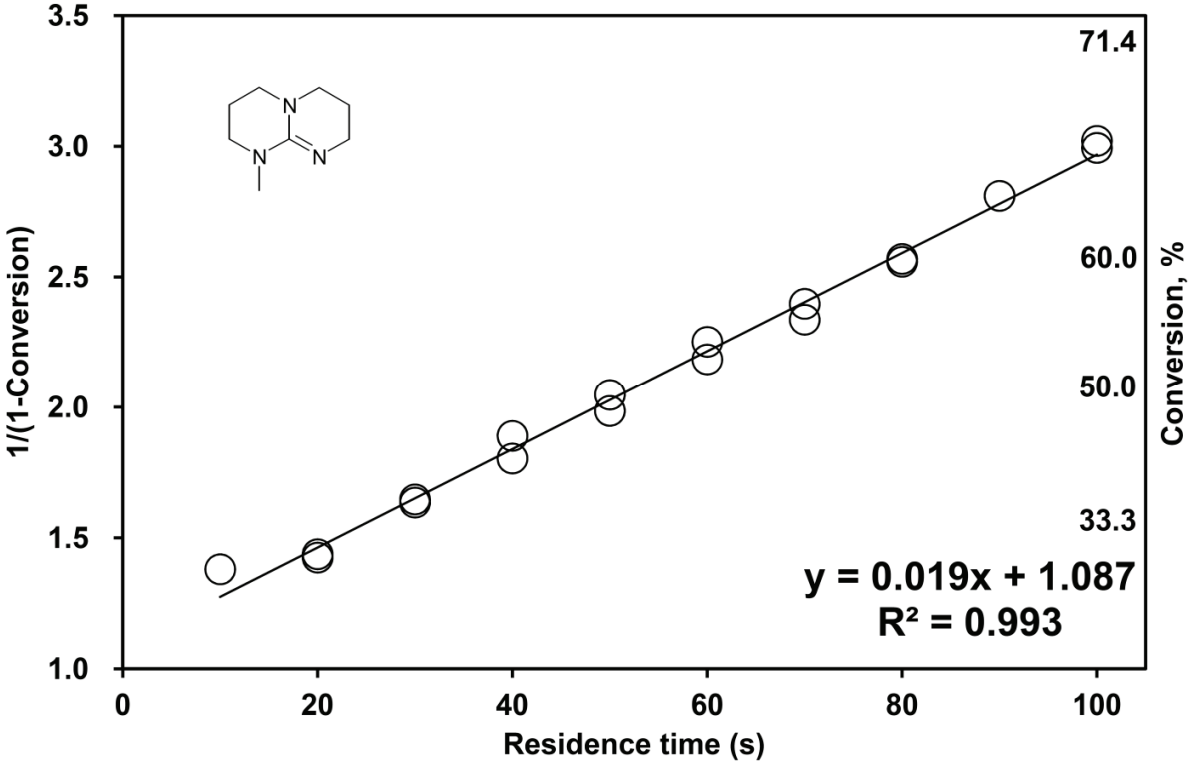

Fig. S3 Second order kinetics plot of **6** MTBD alkylation by iodomethane in DMF at 20°C, $[B]_0$= 0.47 M

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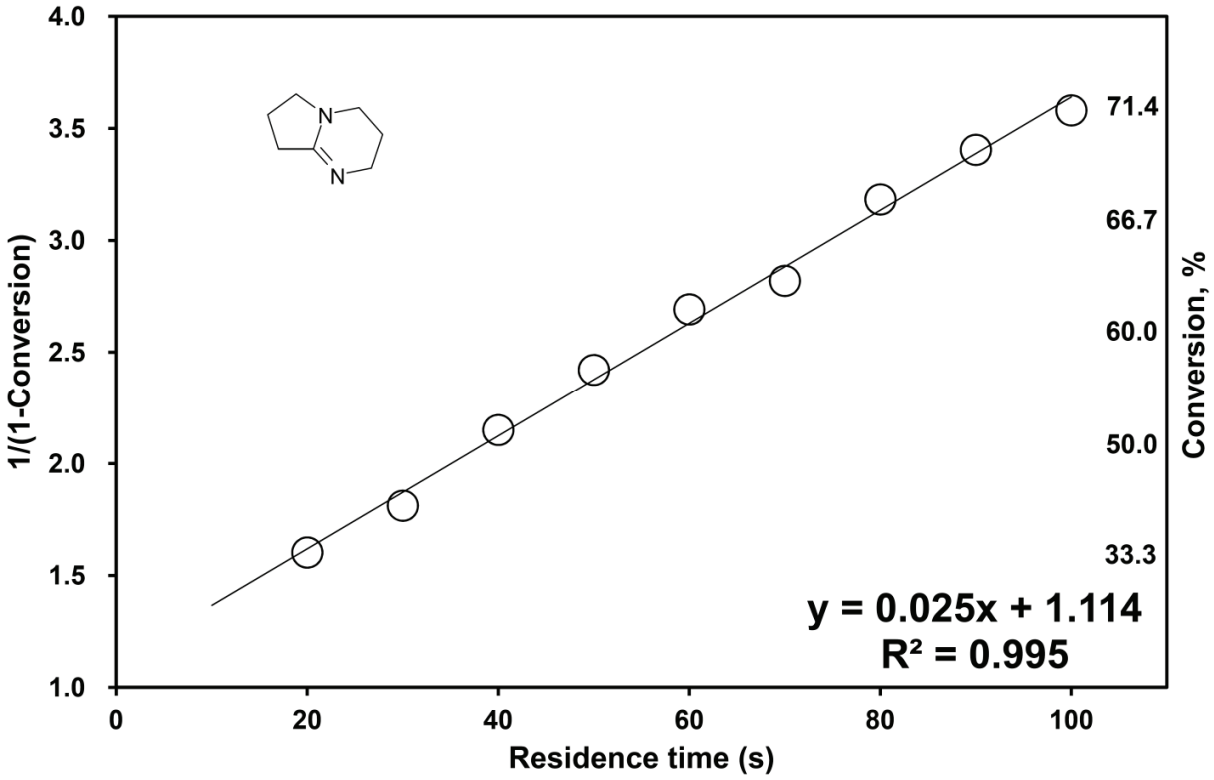

Fig. S4 Second order kinetics plot of **7** DBN alkylation by iodomethane in DMF at 20°C, $[B]_0$= 0.046 M

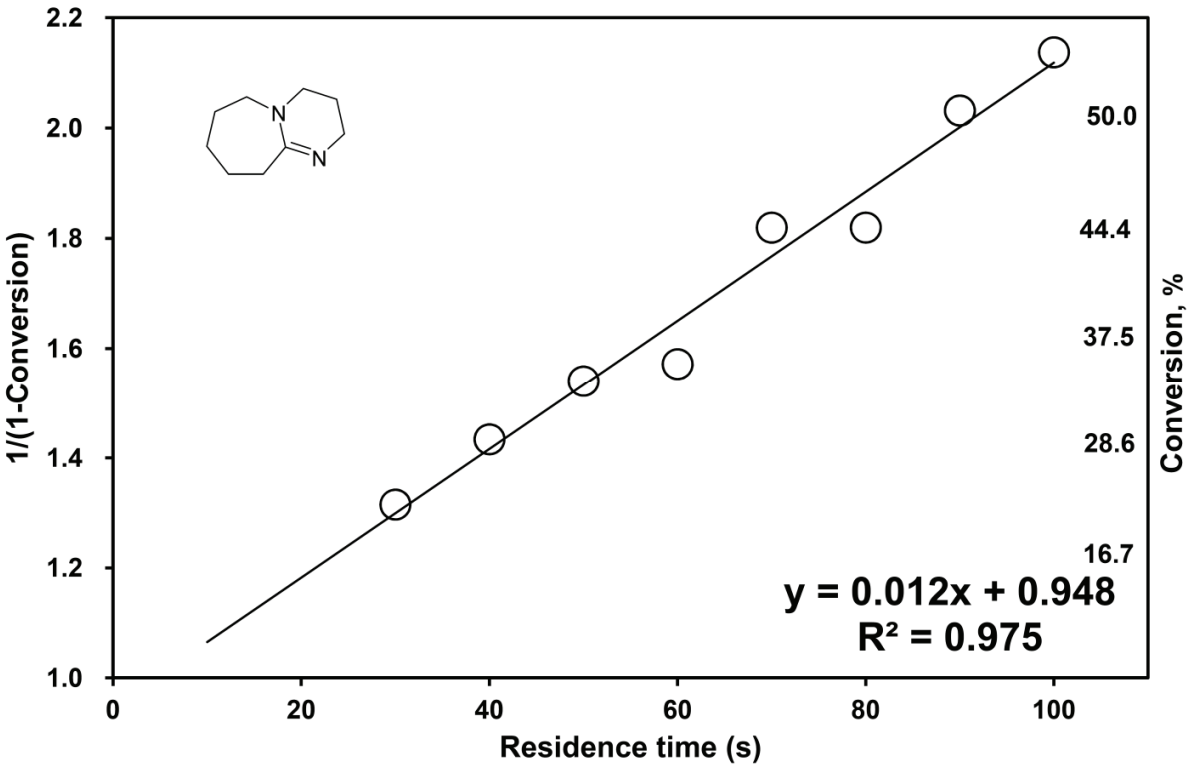

Fig. S5 Second order kinetics plot of **8** DBU alkylation by iodomethane in DMF at 20°C, $[B]_0$= 0.047 M

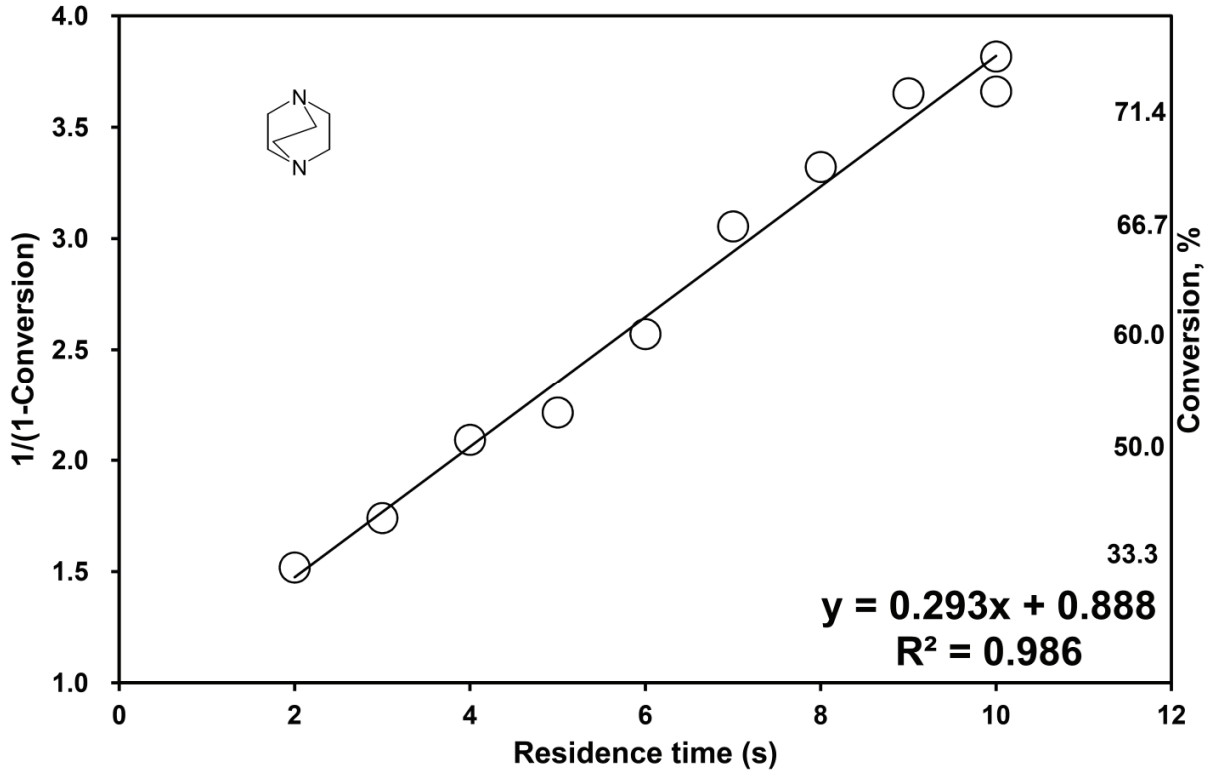

Fig. S6 Second order kinetics plot of **9** DABCO alkylation by iodomethane in DMF at 20°C, $[B]_0$= 0.045 M

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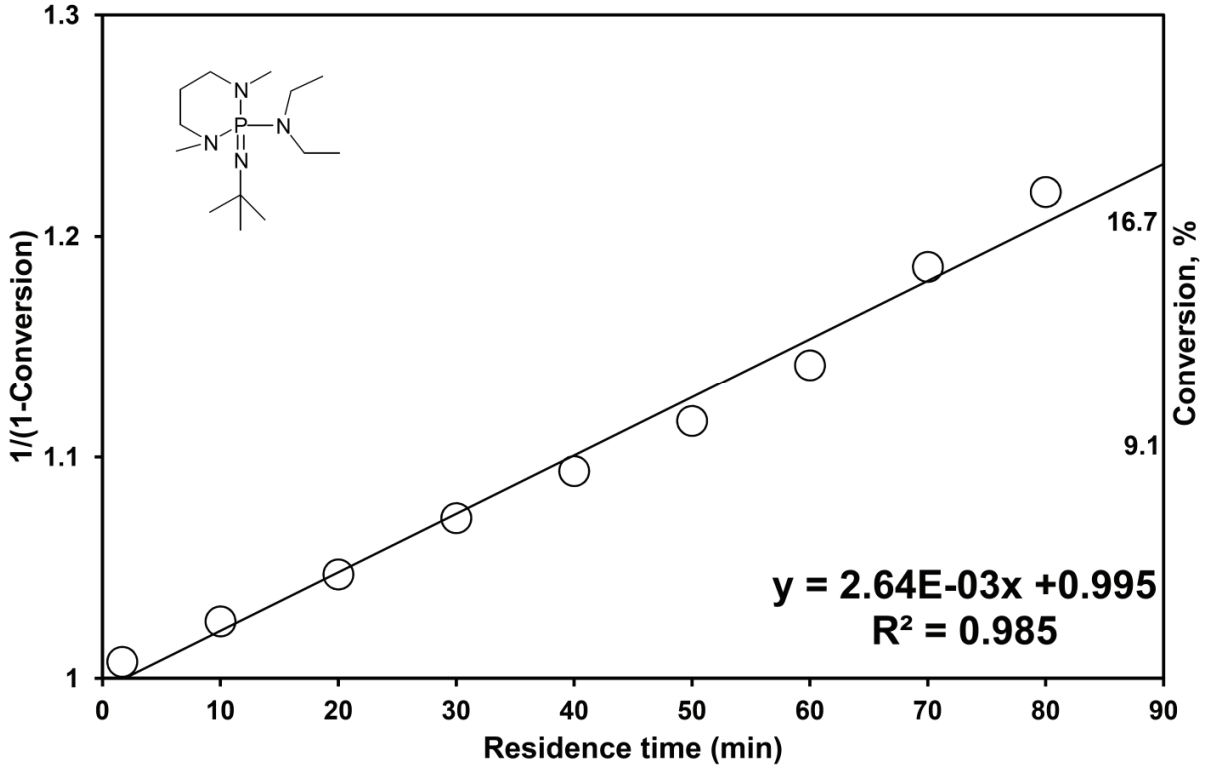

Fig. S7 Second order kinetics plot of **10** BEMP alkylation by iodomethane in DMF at 20°C, $[B]_0$= 0.046 M

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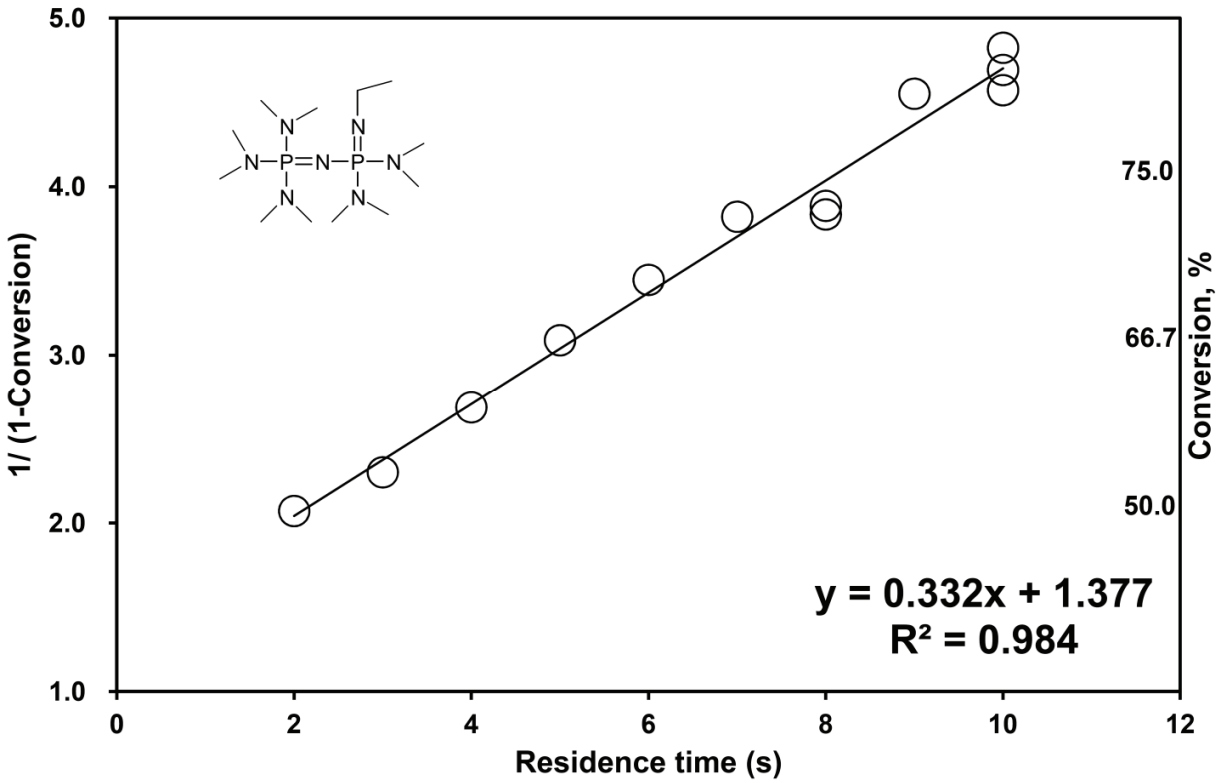

Fig. S8 Second order kinetics plot of **11** P_2Et alkylation by iodomethane in DMF at 20°C, $[B]_0$= 0.0045 M

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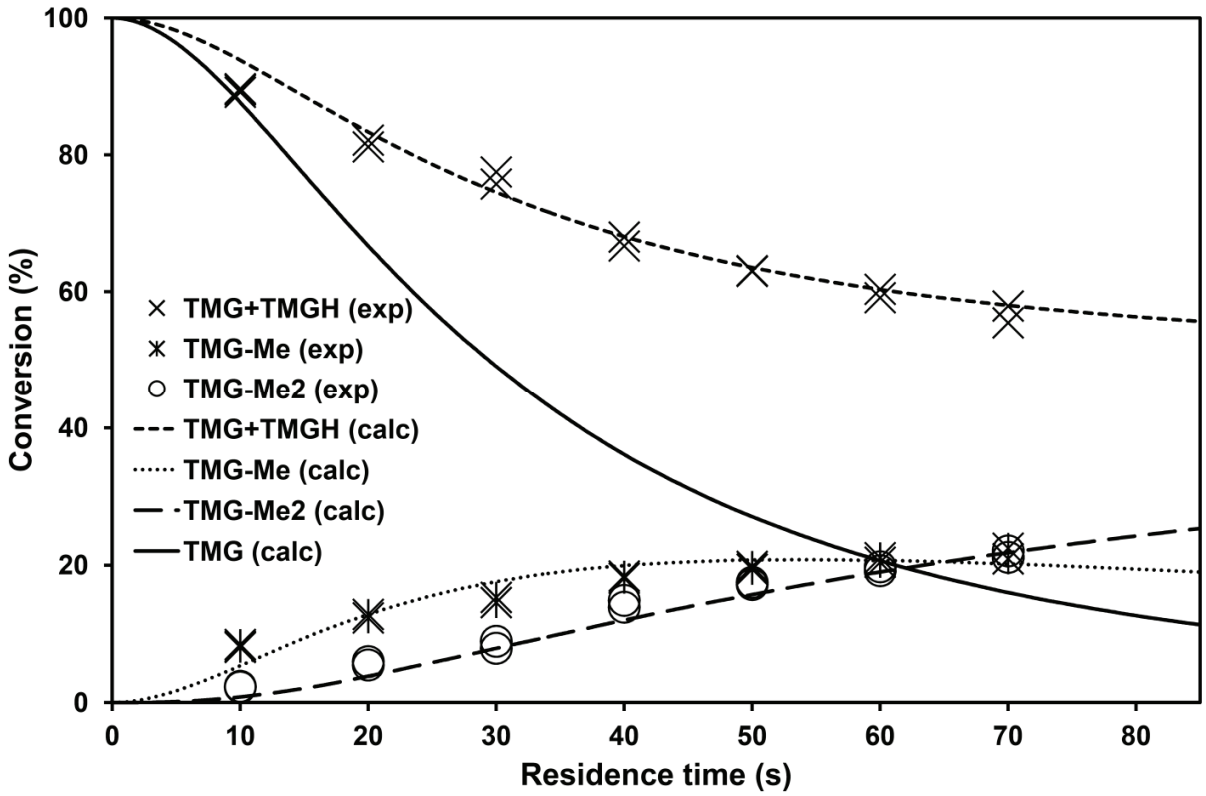
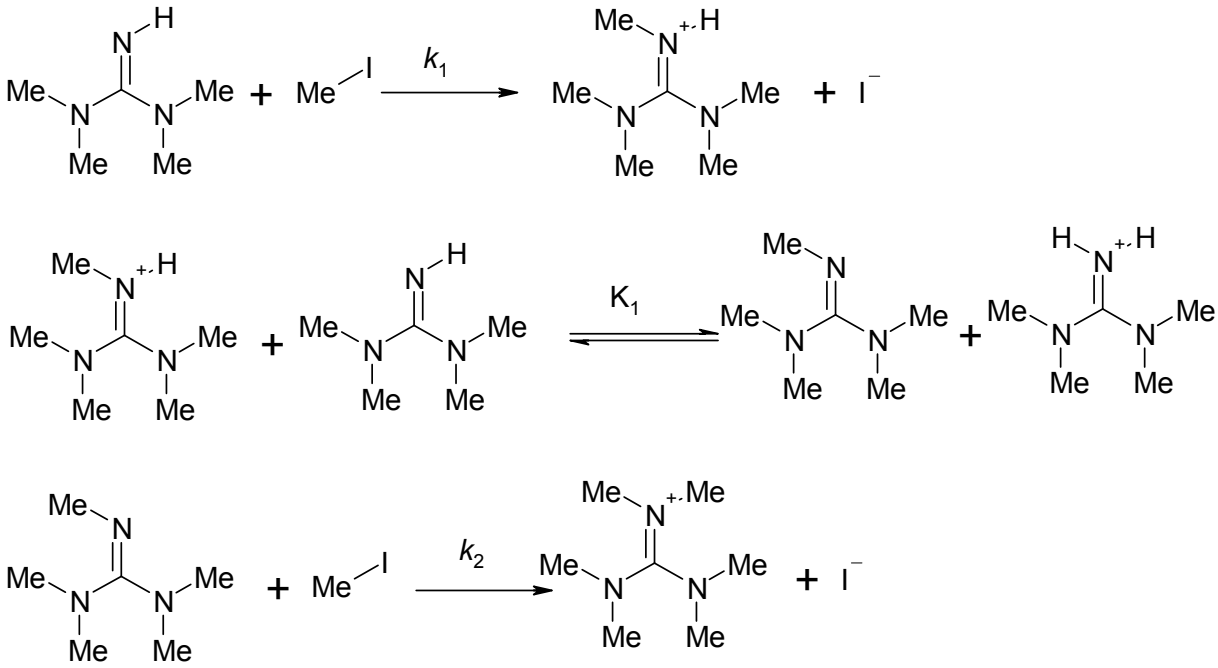


Fig. S9 Plot of experimental and calculated relative concentrations for **1** TMG alkylation by iodomethane in DMF at 20°C



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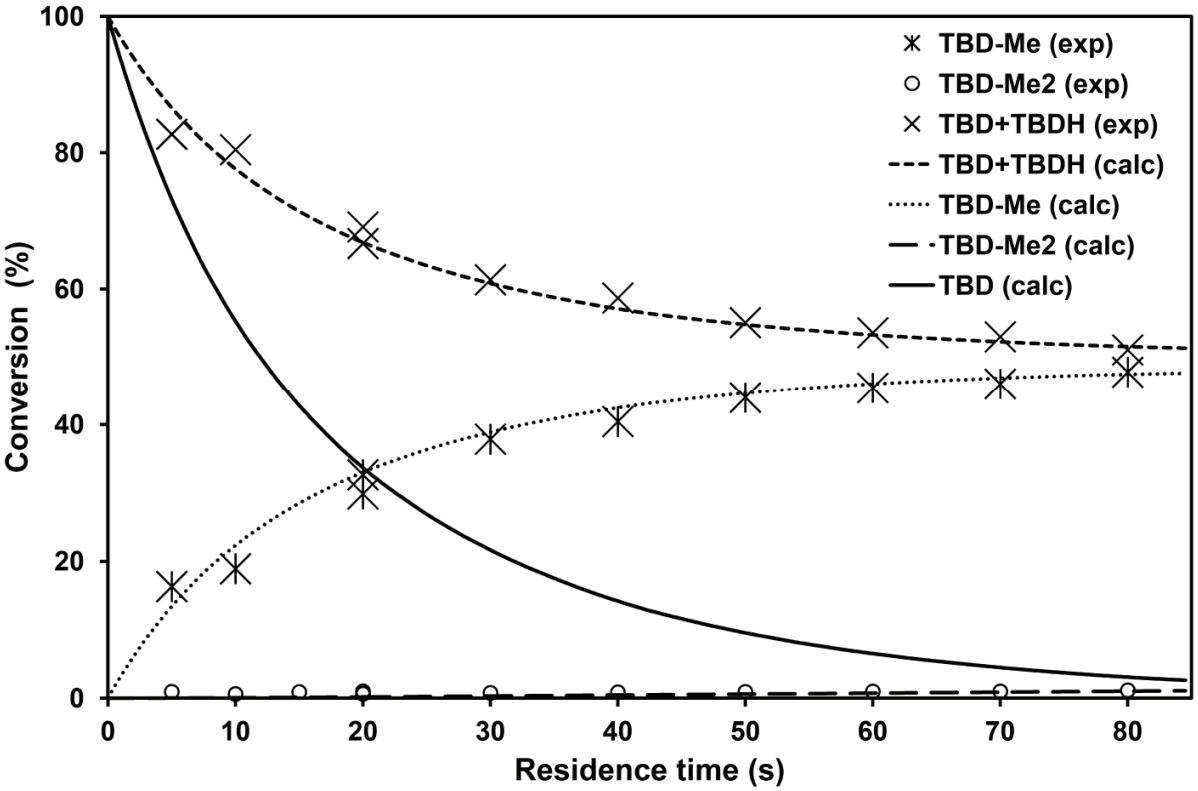
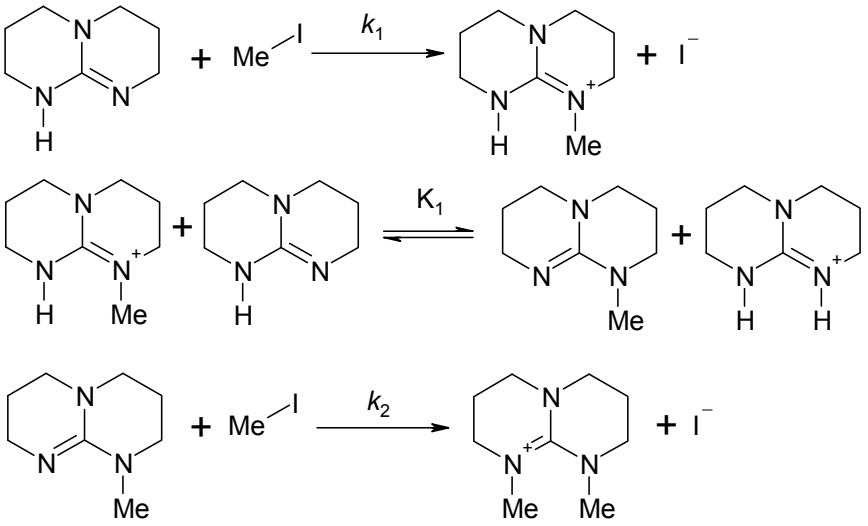


Fig. S10 Plot of experimental and calculated relative concentrations for **5** TBD alkylation by iodomethane in DMF at 20°C



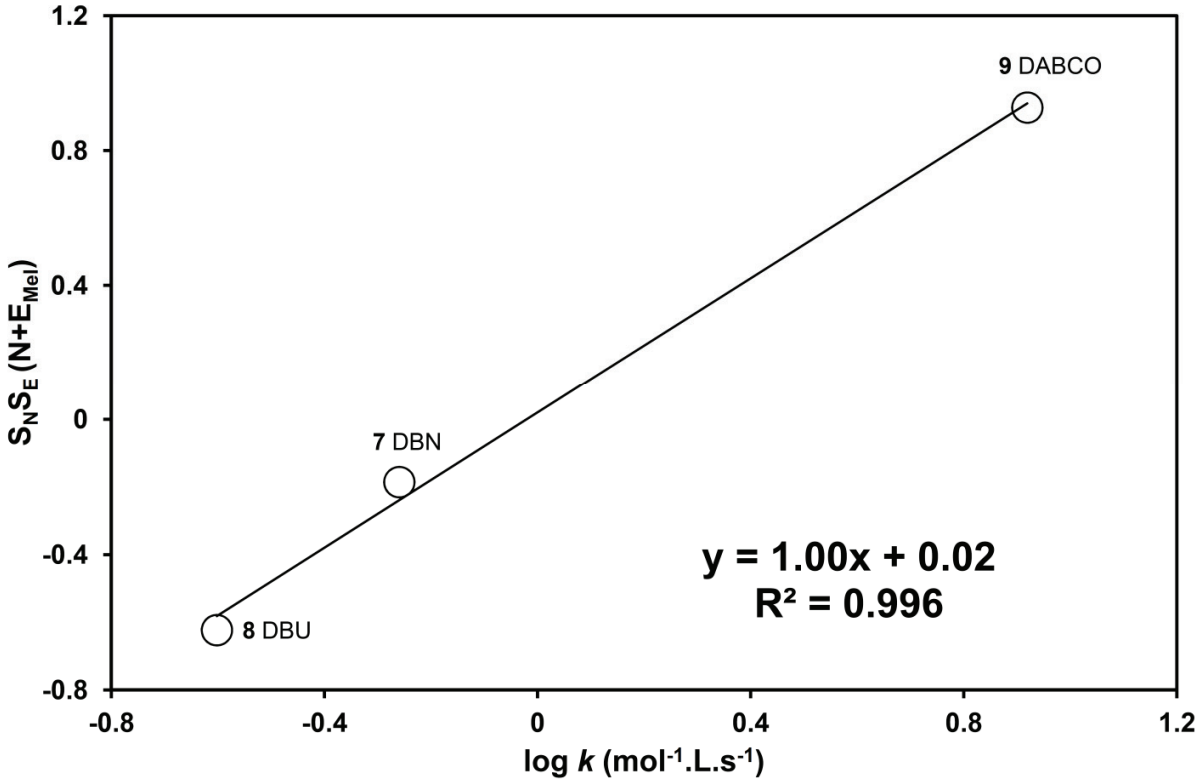


Fig. S11 Correlation of bases alkylation rate constant by iodomethane in DMF at 20°C with Mayr's equation using Mayr's *N* values