Supplementary Information: *N*-Butylpyrrolidinone as a dipolar aprotic solvent for organic synthesis

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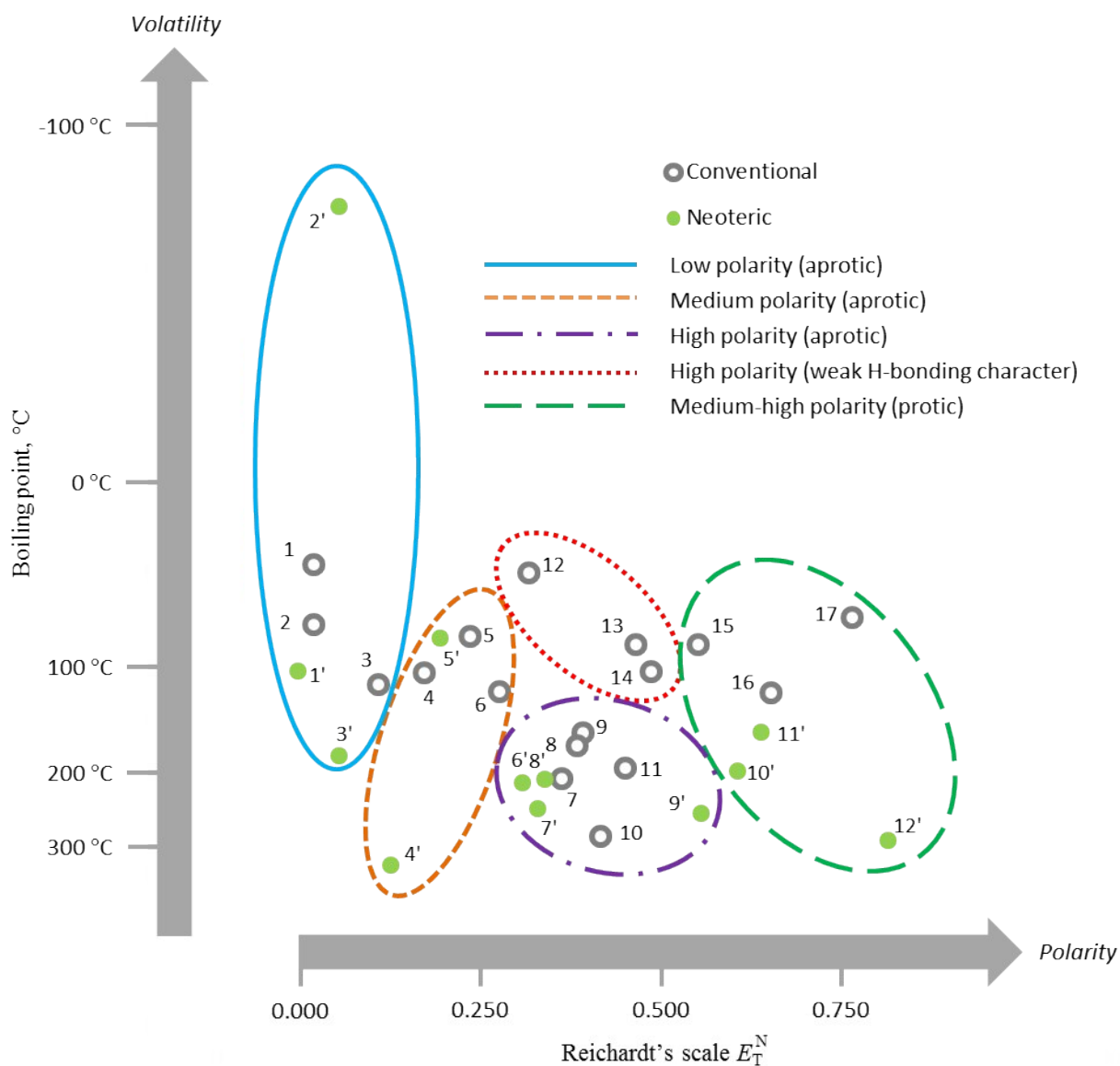
Contents

Fig. S1. Enlarged version of Figure 1 as found in the main article. Key to conventional solvents: 1, *n*-pentane; 2, *n*-hexane; 3, toluene; 4, 1,4-dioxane; 5, ethyl acetate; 6, methyl isobutyl ketone; 7, NMP; 8, DMAc; 9, DMF; 10, sulpholane; 11, DMSO; 12, dichloromethane; 13, acetonitrile; 14, nitromethane; 15, isopropanol; 16, acetic acid; 17, methanol. Key to neoteric solvents: 1', hexamethyldisiloxane; 2', supercritical CO_2; 3', limonene; 4', methyl oleate; 5', 2-methyltetrahydrofuran; 6', γ-valerolactone; 7', *N*-butylpyrrolidinone; 8',Cyrene; 9', ethylene carbonate; 10', solketal; 11', ethyl lactate; 12', glycerol. Polarity data can be found in Table S1 and ref. S1.

Neoteric solvents:

(1') hexamethyldisiloxane

$O=C=O$

(2') scCO$_2$

(3') limonene

(4') methyl oleate

(5') 2-methyltetrahydrofuran

(6') γ-valerolactone

(7') N-butylpyrrolidinone

(8') Cyrene

(9') ethylene carbonate

(10') solketal

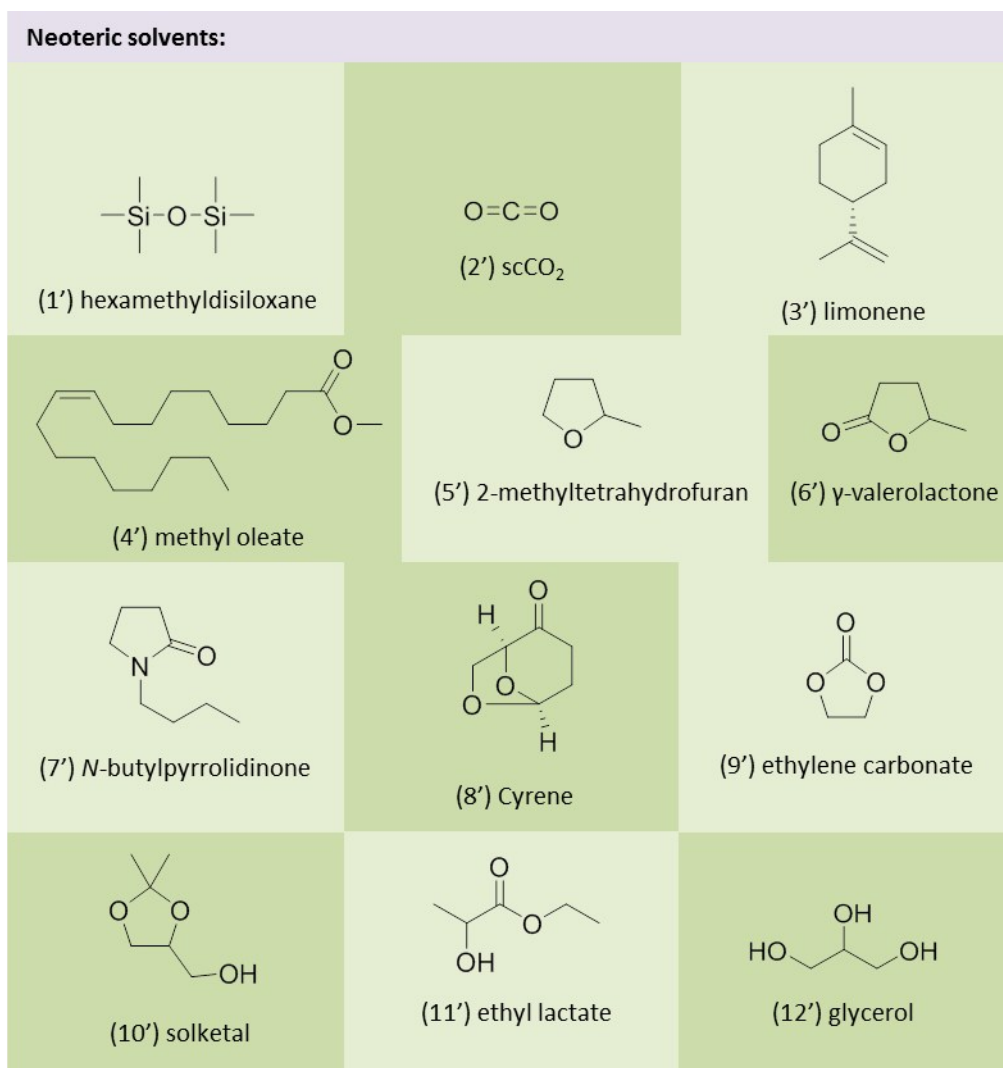(11') ethyl lactate

(12') glycerol

Fig. S2. Chemical structures of the neoteric solvents.[S2-S6]

Reichardt's polarity scale

Where values of solvent polarity according to Reichardt's normalised scale (E_T^N) were not available,[S1] they were derived using a set of equations.[S7] The Kamlet-Abboud-Taft solvatochromic parameters can be equated to $E_T(30)$ (Equation S1).

Equation S1. $$E_T(30) = 30.2 + 15.90\alpha + 12.35\pi^*$$

Equation S2. $$E_T^N = \frac{E_T(30) - 30.7}{32.4}$$

Table S1. Polarity of solvents.

Solvent	Code	E_T^N	Notes
n-Pentane	1	0.009	Reference S1.
n-Hexane	2	0.009	Reference S1.
Toluene	3	0.099	Reference S1.
1,4-Dioxane	4	0.164	Reference S1.
Ethyl acetate	5	0.228	Reference S1.
Methyl isobutyl ketone (MIBK)	6	0.269	Reference S1.
N-Methyl pyrrolidinone (NMP)	7	0.355	Reference S1.
N,N-Dimethyl acetamide (DMAc)	8	0.377	Reference S1.
N,N-Dimethyl formamide (DMF)	9	0.386	Reference S1.
Sulpholane	10	0.410	Reference S1.
Dimethyl sulphoxide (DMSO)	11	0.444	Reference S1.
Dichloromethane (DCM)	12	0.309	Reference S1.
Acetonitrile	13	0.460	Reference S1.
Nitromethane	14	0.481	Reference S1.
Isopropanol	15	0.546	Reference S1.
Acetic acid	16	0.648	Reference S1.
Methanol	17	0.762	Reference S1.
Hexamethyldisiloxane	1'	-0.012	*Via* equation S1 and equation S2, (α = 0.00, π^* = 0.01, reference S2).
Carbon dioxide (*40 °C and 400 bar*)	2'	0.046	Reference S1.
Limonene	3'	0.046	*Via* equation S1 and equation S2, (α = 0.00, π^* = 0.16, reference S3).
Methyl oleate	4'	0.117	Reference S4
2-Methyltetrahydrofuran (2-MeTHF)	5'	0.187	*Via* equation S1 and equation S2, (α = 0.00, π^* = 0.53, reference S5).
γ-Valerolactone (GVL)	6'	0.301	*Via* equation S1 and equation S2, (α = 0.00, π^* = 0.83, reference S5).
N-Butyl pyrrolidinone (NBP)	7'	0.323	*This work*.
Dihydrolevoglucosenone (Cyrene)	8'	0.333	Reference S6.
Ethylene carbonate	9'	0.552	Reference S1.
Solketal	10'	0.602	*Via* equation S1 and equation S2, (α = 0.59, π^* = 0.86, reference S5).
Ethyl lactate	11'	0.636	*Via* equation S1 and equation S2,

		(α = 0.69, π^* = 0.82, reference S5).		
Glycerol	12'	0.812	Reference S1.	

Linear solvation energy relationships

Relationships between reaction kinetics and solvent polarity were derived from experimental observation in the following form (Equation S3). *XYZ* is the logarithm of the reaction rate constant or the initial rate. XYZ_0, *a*, *b*, and *s* are coefficients. Linear regression with Microsoft® Excel was used to derive all correlations.

Equation S3. $XYZ = XYZ_0 + a\alpha + b\beta + s\pi^*$

Valid statistical significance of each coefficient was acccepted based on p-values (provided in brackets within Table S2), otherwise these coefficients were assumed to be zero.[S10] For the Menschutkin reaction only π^* was required to describe a satisfactory relationship with ln(k). The relationship between reaction rate and solvent polarity is not so closely correlated in the example of the Heck reaction (to give methyl cinnamate), but the most significant variable was π^*. Relationships were attempted with the three Kamlet-Taft solvatochromic parameters, both individually and in all possible combinations. The addition of more parameters, including molar volume and the Hildebrand solubility parameter, did not improve any of the correlations.

Table S2. Kamlet-Taft parameter coefficients for kinetics correlations.

XYZ	XYZ_0	α	β	π^*	R^2
Menschutkin reaction (attempted correlation with all Kamlet-Abboud-Taft parameters)					
ln(k)	-14.27	-0.04	0.61	5.17	0.9937
	(2.5E-7)	(0.94)	(0.098)	(6.3E-5)	
Menschutkin reaction (correlated with only the statistically valid variables)					
ln(k)	-14.32			5.71	0.9736
	(6.6E-9)			(5.8E-6)	
Heck cross-coupling (this work)					
ln(initial rate)	-14.37			7.28	0.7594
	(1.5E-4)			(0.011)	
Heck cross-coupling (Parker et al.[S10])					
ln(initial rate)	-13.03			6.73	0.8043
	(2.2E-5)			(2.5E-3)	

Fluorination study

A final nucleophilic substitution was attempted, with the reaction of 2-chloro-5-nitropyridine with potassium fluoride at 358 K chosen as a model system. Fluorination is also an important process for the pharmaceutical industry, with a large proportion of drug molecules possessing at least one fluorine atom.[S8] The solvent required of nucleophilic fluorinations is inevitably highly dipolar and aprotic, with conversions reducing to virtually nothing when other solvents are used, such is the strong rate dependence on the polarity of the solvent.[S9] Although the reaction proceeds to a degree, *N*-butylpyrrolidinone does not stabilise the charge separation of the intermediate species to the extent demonstrated by DMSO or NMP, and ultimately the reaction was too slow in *N*-butylpyrrolidinone to monitor accurately. The procedure was as follows: Potassium fluoride (0.261 g, 4.50 mmol) was dissolved in the chosen solvent (4 mL) and preheated at 403 K for two hours (or at the refluxing point of the solvent for low boiling solvents). The temperature was then lowered to 358 K and 2-chloro-5-nitropyridine (0.476 g, 3.00 mmol) was added as a single dose. The progression of the reaction was examined by ^{1}H-NMR spectroscopy.

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