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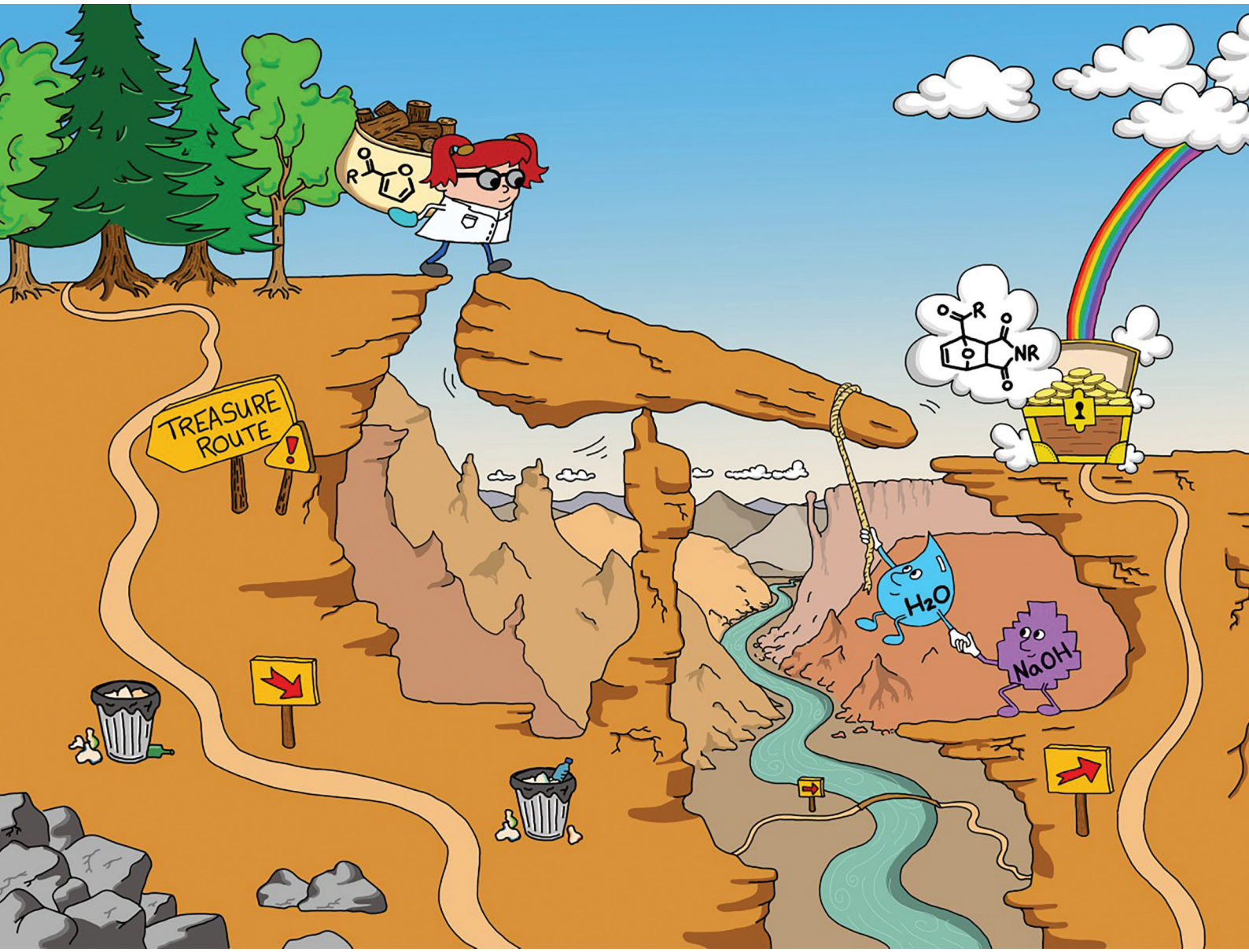

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Furoic acid and derivatives as atypical dienes in Diels–Alder reactions†

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The furan Diels–Alder (DA) cycloaddition reaction has become an important tool in green chemistry, being central to the sustainable synthesis of many chemical building blocks. The restriction to electron-rich furans is a significant limitation of the scope of suitable dienes, in particular hampering the use of the furans most readily obtained from biomass, furfurals and their oxidized variants, furoic acids. Herein, it is shown that despite their electron-withdrawing substituents, 2-furoic acids and derivatives (esters, amides) are in fact reactive dienes in Diels–Alder couplings with maleimide dienophiles. The reactions benefit from a substantial rate-enhancement when water is used as solvent, and from activation of the 2-furoic acids by conversion to the corresponding carboxylate salts. This approach enables Diels–Alder reactions to be performed under very mild conditions, even with highly unreactive dienes such as 2,5-furandicarboxylic acid. The obtained DA adducts of furoic acids are shown to be versatile synthons in the conversion to various saturated and aromatic carbocyclic products.

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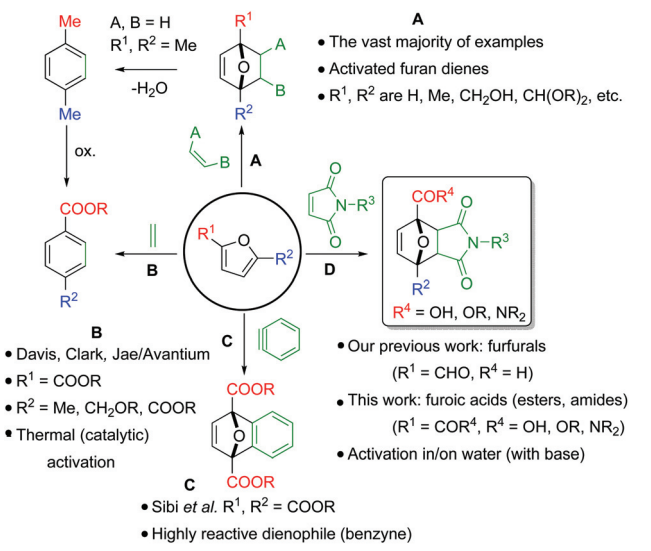
Introduction

Since its discovery in 1929,[1] the furan Diels–Alder (DA) reaction has been extensively applied in organic chemistry, with the resulting 7-oxabicyclo[2.2.1]hept-2-enes being exploited in natural product synthesis, drug discovery, bioconjugation, as well as in polymer and materials science applications.[2–7] Indeed, furan DA reactions allow versatile synthons of considerable molecular complexity to be generated in an atom-economical fashion, making it a highly attractive strategy for green chemical synthesis of cyclic compounds.[8] The reactivity of furan derivatives as dienes has been the subject of numerous theoretical and experimental studies. The general consensus is that good kinetics requires electron-rich furanic rings, as found in the parent furan and derivatives decorated with electron-donating substituents (*e.g.* alkyl-, alkoxyalkyl-, acetals *etc.*, Scheme 1A)[9–13] and accordingly most applications employ such dienes.

Conversely, Diels–Alder reactions involving electron-poor derivatives such as furoic acids (furans substituted with a COOH group) are very much underexplored.[14–21] That such highly oxygenated furanics cannot be readily used in DA-based synthesis strategies is a missed opportunity. Furoic acids are readily available *via* renewable platform molecules such as furfural and 5-hydroxymethyl furfural (5-HMF).[22] Furoic acids also offer the advantage of being stable renewable platform molecules, this in contrast to, for instance, 5-HMF and its hydrogenated derivatives (2,5-dimethyl furan, 2,5-bishydroxymethyl furan) which can readily degrade and/or polymerize.[23]



Scheme 1 Diels–Alder reactions with 2-furoic acid-derived dienes.

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Together, this makes them attractive building blocks for the atom- and redox-efficient synthesis of a large number of renewable value-added carboxylic acid- or ester-containing chemical products, including biobased aromatics.

Unfortunately, only a handful of recent reports describe attempts to capitalize on these advantages. Instead, the vast majority of chemistry developed in this area relies on the well-established use of electron-rich furan dienes. While this conventional approach may be efficient for the individual DA step, it is often redox uneconomical overall, as exemplified for instance by the cycloaddition between 2,5-dimethyl furan and ethylene targeting renewable terephthalic acid (Scheme 1A).[24–27] This route is, in essence, the conversion of a highly oxygenated bio-derived resource (*e.g.* 5-HMF) to an oxygen-rich product (terephthalic acid) *via* a non-oxygenated hydrocarbon intermediate, *p*-xylene. The non-productive use of redox reactions featured in this approach (the so-called "redox-detour") greatly reduces the incentive for scale-up of such routes.

In contrast, as solution to this problem, the groups of Davis,[15–17] Clark[18] and Jae[19] and a patent by Avantium[20] have disclosed new routes towards terephthalic acid starting from furan carboxylic (di)acids or their esters and ethylene, but these diene/dienophile combinations require very harsh conditions and the overall yields are low (Scheme 1B). Relatedly, Sibi *et al.* was successful in the valorisation of the dimethyl 2,5-furandicarboxylate with benzyne as highly reactive dienophile (Scheme 1C).[21] Finally, the furoate ester/maleimide couple has on occasion been described in macromolecular applications,[28–31] even though the molecular version was deemed unfeasible by Boutevin *et al.*[10]

To the best of our knowledge, there is a single study thoroughly investigating the reactivity of furoic acids in Diels–Alder chemistry. Bowman *et al.* showed that reactions of 3-furoic acid with maleimides are actually favoured both kinetically and thermodynamically;[32] on the other hand, the more readily available 2-regioisomer was found to be much less reactive, with the coupling also being strongly entropically disfavoured. Interestingly, the authors note that reactivity could be tuned by solvent effects: rate and equilibrium conversions were significantly higher in water compared to reactions in dimethyl formamide.

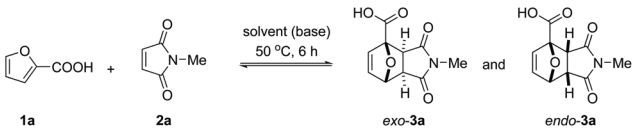
Encouraged by this precedent and following our interest in the development of synthetic applications based on the Diels–Alder chemistry of readily available oxygenated bio-based furans,[33,34] we decided to investigate 2-furoic acids as underexplored class of dienes.

Results and discussion

Reaction optimization

In line with the observations of Bowman *et al.*, the reaction between furoic acid **1a** and *N*-methyl maleimide **2a** was slow in all common organic solvents. No obvious reactivity trend (Table 1) could be discerned, although polar solvents seemed more beneficial for the reaction (MeOH, EtOH, DMSO, AcOH). Hydrogen bonding interactions with the solvent might be important as only traces of product could be detected in apolar aprotic solvents (CH_2Cl_2, $CHCl_3$; toluene being a curious exception with 5% yield). Undoubtedly, the electron-withdrawing effect of the COOH substituent on the furan ring translates into a lowered energy level for the HOMO of the diene and consequently a high activation barrier for the cycloaddition. We reasoned that the addition of a base would counteract this effect, as neutralization to the carboxylate

Table 1 Solvent effects in the cycloaddition between 2-furoic acid **1a** and maleimide **2a**



1a **2a** ***exo*-3a** ***endo*-3a**

		Yields in neutral conditions			Yields with NEt_3 (1 equiv.)		
Entry	Solvent	*exo*-**3**, %	*endo*-**3**, %	Total, %	*exo*-**3**, %	*endo*-**3**, %	Total, %
1	MeOH	10	0	10	34	6	40
2	EtOH	8	Trace	8	49	1	50
3	AcOH	6	0	6	n.a.	n.a.	n.a.
4	DMSO	7	Trace	7	35	1	36
5	DMF	3	0	3	25	2	27
6	MeCN	3	0	3	28	5	33
7	AcOEt	4	0	4	28	3	31
8	THF	3	Trace	3	27	1	28
9	Acetone	Trace	0	Trace	27	5	32
10	$CHCl_3$	2	0	2	50	0	50
11	CH_2Cl_2	Trace	0	Trace	41	6	47
12	Toluene	5	0	5	38	2	40
13	H_2O	56	7	63	83	3	86

General procedure: 2-Furoic acid **1a** (0.5 mmol), (NEt_3, 1 equiv.) and *N*-methyl maleimide **2a** (1.5 equiv.) stirred in the respective solvent (1 M) at 50 °C for 6 h; yields determined from the ^{1}H-NMR ratios of product isomers and starting material; conversion of **1a** was clean; solvolysis of **2a** was detected as side reaction, in alcoholic solvents (in the presence of NEt_3).

diminishes the electron-withdrawing capability of the COOH substituent:[35] indeed, in all solvents tested, the yields increased substantially in the presence of 1 equiv. of triethylamine. Adduct yields of nearly 50% (6 h reaction time, 50 °C) were now observed in CH_2Cl_2, $CHCl_3$ and EtOH. Correlating reactivity with solvent properties is again not straightforward; plausibly, the extent of proton transfer and charge separation play a major role here.

Next, we turned our attention to water as solvent. The rate-enhancement ability of water in Diels–Alder chemistry is well known and many arguments have been proposed to explain it.[36,37] In our system, the rate of reaction between **1a** and **2a** (63% conversion in 6 h at 50 °C, Table 1, entry 13) is one order of magnitude higher than in all organic solvents tested; in fact, the reaction of the free acid in water even proved faster than the best result obtained in an organic solvent in the presence of base (Table 1, entry 2 or entry 10).

The reaction also clearly benefited from the synergy of using aqueous solvent and the base effect: nearly quantitative yield of **1a** was obtained when the cycloaddition was performed in water in the presence of 1 equiv. of NaOH (Table 2, entry 4). The reaction efficiency correlates with the base strength (NaOH ≈ Na_2HPO_4 > NEt_3 > NaH_2PO_4); clearly, the effect of the base is not catalytic, as lowering the NaOH loading (entries 7 and 8) produced results comparable to those obtained when using the weaker base NaH_2PO_4. Finally, the effect of temperature is typical for a reversible [4 + 2] cycloaddition: at lower temperatures (20 °C, entry 10), the reaction is under kinetic control, with the major product being the *endo* adduct, while at elevated temperatures (80 °C, entry 9), the formation of *exo*-**3a** is nearly exclusive (see also Fig. 1, bottom); noteworthy, the total yield diminishes with increasing temperature due to the unfavourable entropy contribution.

The reaction profiles depicted in Fig. 1 illustrate the significant enhancement of the rate of the cycloaddition in the presence of stoichiometric base: compared to the additive-free

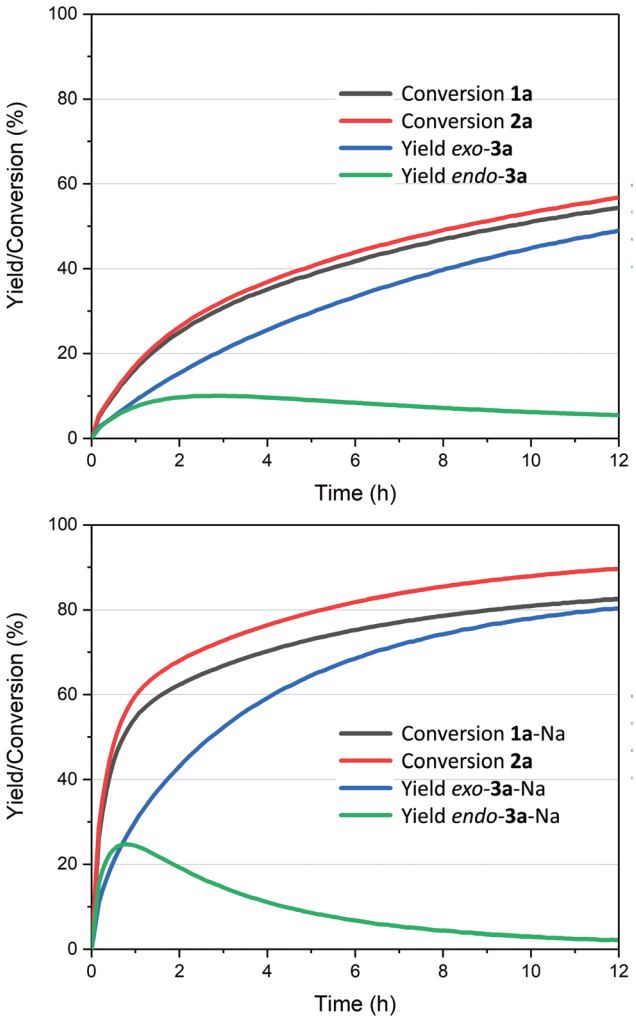
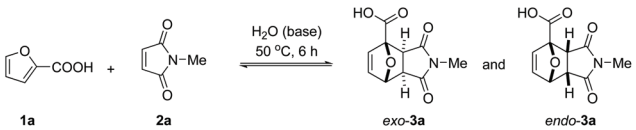


Fig. 1 Kinetic traces for the cycloadditions between 2-furoic acid **1a** and maleimide **2a** (1 : 1 ratio at 0.5 M) in water (top), with the addition of 1 equiv. NaOH (bottom); see ESI† for details; *cf.* Tables 2 and 3: reactions run at 1 : 1.5 ratio **1** : **2** and 1 M concentration.

Table 2 DA reaction between 2-furoic acid **1a** and maleimide **2a** in aqueous solution: effect of base



Entry	Additive	Amount, equiv.	Temp., °C	Time, h	*exo*-**3**, %	*endo*-**3**, %	Total, %
1	None	n/a	50	6	56	7	63
2	None	n/a	50	16	76	3	79
3	NaOH	1	50	6	90	5	95
4	NaOH	1	50	16	94	3	97
5	Na_2HPO_4	1	50	6	89	6	95
6	NaH_2PO_4	1	50	6	71	8	79
7	NaOH	0.5	50	6	75	6	81
8	NaOH	0.25	50	6	67	7	74
9	NaOH	1	80	6	81	3	84
10	NaOH	1	20	6	25	35	60

General procedure: 2-Furoic acid **1a** (0.5 mmol), (additive) and *N*-methyl maleimide **2a** (1.5 equiv.) stirred in aqueous solution (1 M) at the indicated temperature for the indicated time; yields determined from the ^{1}H-NMR ratios of product isomers and starting material.

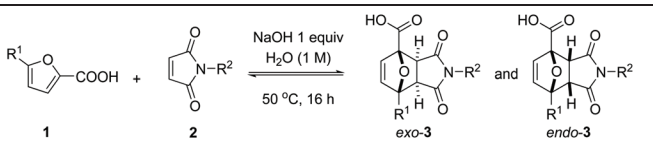
reaction (Fig. 1, top), the NaOH-mediated conversion is approx. 5 times faster, in the first 30 min. In addition, the system is nearly at equilibrium within 12 h, which is not the case for the base-free experiment. Importantly, the conversion of **1a** was clean in both cases, with no side products originating from the diene detected. On the other hand, some hydrolysis of **2a** (towards maleic acid) does occur, to a low extent, and if the NaOH stoichiometry is increased beyond the 1 : 1 ratio, the sodium salt of *N*-methyl maleamic acid is formed (see also note[52]).

Reaction scope

The choice of water as reaction solvent allows the convenient isolation of DA adducts **3** by precipitation. To maximize conversion and simplify purification, we performed the title reaction between **1a** and **2a** under more concentrated conditions (2 M) and with 1 : 1 stoichiometry; the precipitated product was isolated by filtration in a 63% yield. Unreacted starting materials were recovered from the filtrate and reused without loss of reaction efficiency (see ESI† for details). This example is an excellent showcase of the green chemistry principles: renewable raw materials use, 100% atom-economy, eco-friendly solvent, simple isolation, no additives and no waste.

In studying the reaction scope, we chose the conditions shown in entry 4, Table 2 (with 1 equiv. NaOH), with the aim of minimizing the amount of minor adduct *endo*-**3** and simplifying the isolation of a pure product following a general protocol. Thus, after reaction, the excess maleimide can be washed away (and recovered) with an organic solvent, while acidification of the aqueous phase typically leads to the selective precipitation of *exo*-**3**. This procedure allowed for the isolation of the *exo*-adducts **3a–c** in good yields (Table 3, entries 1–3); the performance of the reactions is only modestly influenced by the nature of the maleimide substituent in the series H/Me/^{n}Pr. Higher homologues (*N*-Ph, *N*-Cy) proved problematic, however, due to poor solubility of the dienophile in the aqueous medium (entries 4 and 5); the addition of a cosolvent (MeOH) was beneficial in this case (entry 6) and although the conversion levels were moderate, synthetically useful yields of pure adducts **3d** and **3e** could be obtained without excessive adjustment of the general procedure. Next, we proceeded with the investigation of the furan diene scope, with the focus on easily accessible biomass-derived 5-substituted 2-furoic acids. We found that both the kinetics and the thermodynamics of the reaction are greatly influenced by the nature of the 5-substituent. Expectedly, electron-donating groups (Me) increase the reaction rate (entry 7, see ESI†) while electron-withdrawing groups (CH=O, COOH) showed the opposite effect, in line with the generally-accepted Frontier Molecular Orbital theory-derived interpretation of kinetics in DA reactions. Substitution at the furan 5-position, regardless of the nature of the substituent, not only influences kinetics but also the equilibrium position and likely destabilizes the DA adduct with respect to its addends, plausibly due to increased steric encumbrance in **3**.[11] The implication is that the most reactive diene in a series does not necessarily lead to the most thermodynamically

Table 3 Scope of DA reaction between 2-furoic acids and maleimides in aqueous solution



1 2 *exo*-**3** *endo*-**3**

Entry	R^1	R^2	**3**	Conv. **1**[a]	*exo*-**3**, %	*endo*-**3**, %	Isolated[b], %
1	H	Me	**3a**	98	97	1	77(92)[c]
2	H	H	**3b**	95	95	Trace	68
3	H	^{n}Pr	**3c**	96	93	3	72
4[d]	H	Ph	**3d**	51	51	Trace	21
5[d]	H	Cy	**3e**	18	16	2	n.d.
6[d,e]	H	Cy	**3e**	56	53	3	31
7	Me	Me	**3f**	93	88	5	75
8	CH_2OH	Me	**3g**	91	72	19	51[f]
9[d]	CH_2OH	Ph	**3h**	28	28	Trace	11
10[g]	CHO	Me	**3i**	<10	~5	Trace	n.d.
11[g]	COOH	Me	**3j**	20	20	0	n.d.
12[g,h]	COOH	Me	**3j**	56	56	0	n.d.

General procedure: 2-Furoic acid, NaOH (1 equiv.) and maleimide (1.5 equiv.) stirred in water (1 M) at 50 °C for 16 h. [a] Conversion determined from the ^{1}H-NMR ratios of product isomers and starting material in the crude mixture. [b] Isolated yield after acidification. [c] 40 mmol scale. [d] Poor dissolution of **2**. [e] Methanol was used as cosolvent. [f] After hydrogenation on Pd/C. [g] Extensive hydrolysis of **2a** to maleic acid. [h] With 2 equiv. of NaOH.

favourable cycloaddition and hence the highest adduct yield at equilibrium. In the series R^1 = H/Me/CH_2OH, the parent reaction (formation of **3a**, R^1 = H) was found to exhibit the highest equilibrium conversion (Table 3, entry 1 *vs.* 7 and 8; see also ESI† for further details) while the relative reactivity was Me > H > CH_2OH. Despite the somewhat less favourable equilibrium, adduct **3f** (R^1 = Me) could nonetheless be isolated in a good yield (75%). Next, a high isolated yield was anticipated based on the analysis of the crude reaction mixture for adduct **3g** (R^1 = CH_2OH) but unfortunately this very polar molecule is highly water soluble, which complicated its isolation. Nonetheless, a yield of 51% of pure *exo* product was obtained after the sequential, one-pot conversion of **3g** to a more stable derivative, *i.e.* by hydrogenation over Pd/C, a method used before in furan DA chemistry.[38–41] The less water-soluble Ph-analogue could be obtained utilizing our standard protocol, albeit in a low yield and purity (11%, entry 9). As expected, the presence of a second electron-withdrawing substituent is highly detrimental for the kinetics of the reaction (and likely also for the thermodynamics[9,12,34]): adducts **3i** and **3j** (R^1 is CH=O and COOH respectively) were formed in low amounts in the crude reaction mixtures. On the other hand, with 2 equiv. of NaOH, 2,5-furandicarboxylic acid (FDCA) gave a fast equilibration to the *exo*-bis-Na salt of its adduct with **2a**. In this case, isolation after acidification was hampered by the highly polar nature, as noted previously, and facile cycloreversion of the (neutral) adduct back to the addends. Noteworthy, all these reactions feature high stereoselectivity for the *exo* adduct, typically above 15 : 1 (with the exception of adduct **3g**); the isolated products were single diastereoisomers.

We then turned our attention to other furoic acid derivatives, such as esters and amides, anticipating that the electronic properties of the furan diene would not be significantly different for the substituent series COOH/COOR/CONR$_2$. However, the physical properties, water miscibility in particular, are certainly strongly modulated by the nature of the substituent and this might impact the performance of the aqueous Diels–Alder cycloaddition. This proved indeed to be the case (Table 4). The 2-furoic acid esters tested (Me, Et, ^{i}Pr, ^{t}Bu) are liquids with poor water miscibility; however, reactions still proceeded smoothly with so-called 'on-water' activation.[42,43]

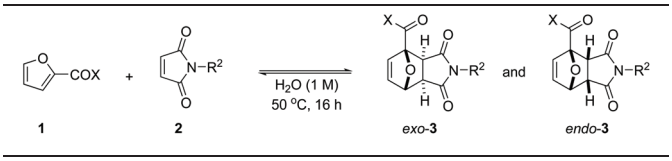
For ease of comparison, we employed reaction conditions similar to those found in the optimization of the cycloadditions with **1a** (1 mL water per mmol, 50 °C, 16 h). The reactivity differences in the ester homologous series were marginal under these conditions. Product properties did vary, however, as the adducts of the methyl ester turned out to be much more crystalline than the rest. Simple filtration of the resulting suspensions was sufficient in this case to provide good yields of pure (*exo*-) products **3k–m** (43–52%). Moreover, the adduct **3l** could be obtained in a much-improved yield (82%), simply by performing the reaction in more concentrated conditions (see ESI† for details). Notably, the reactions are clean and the filtrate containing unreacted starting materials can readily be recycled. Such crystallization from the crude reaction mixture did not occur with higher homologous esters (entries 4–6), necessitating chromatographic purification to isolate the adducts. Most likely some cycloreversion occurs in the process, leading to erosion of the final yield. Finally, 2-furamides were included in the substrate scope and also proved to be surprisingly reactive dienes (entries 7–9). The water soluble dimethylamide adduct **3r** was formed in a comparable yield to the parent compound **3a** under similar conditions (Table 2, entry 2), whereas adduct precipitation likely pushed conversions above 90% for products **3q** and **3s** by favourably shifting the thermodynamic equilibrium. Thus, the ester and amide derivatives of 2-furoic acid also show good reactivity towards maleimides and the aqueous protocol generally allows for a facile synthesis and isolation of the corresponding adducts. Again, the reactions feature high stereoselectivity towards the *exo* diastereoisomer (typically >12 : 1, with the exception of adduct **3s**).

To the best of our knowledge, none of the adducts **3** have been previously synthesized and characterized. In particular, while acknowledging the fact that the reactive diene is not FDCA itself but its Na salt, we would like to highlight the distinct nature of this adduct (Table 3) among the typical structures of furan DA adducts.[44,45]

Follow-up chemistry

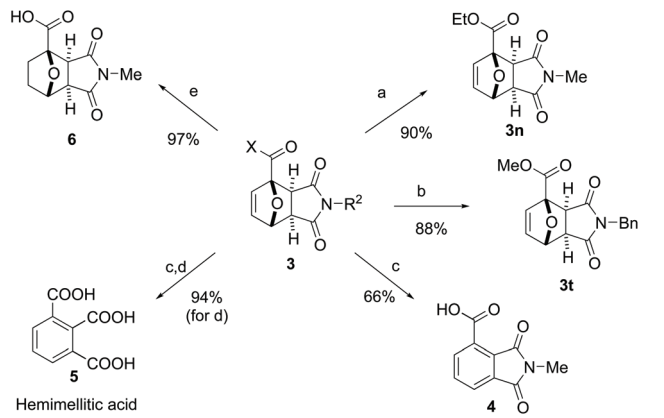
In addition to their facile preparation, Diels–Alder adducts **3** represent valuable synthons for further synthetic elaboration (Scheme 2). To complement the broad synthetic scope of our methodology, diversification at the X- and R^2-positions in **3** (Scheme 2) can also be readily achieved by straightforward transformations of title adducts **3a** and **3l**: ethyl ester **3n** can be obtained by esterification of **3a** in the presence of $SOCl_2$ (90% yield), whereas alkylation of **3l** with benzyl bromide afforded **3t** in 88% yield. Aromatization of the 7-oxanorbornene core by dehydration is a particularly interesting (and extensively studied) transformation,[45] as it provides access to renewable aromatics based on the carbohydrate fraction of lignocellulosic biomass. For the substrates studied here, the presence of an electron-withdrawing substituent at the bridgehead position in **3** is anticipated to hinder (typically) acid-mediated dehydration. Nonetheless, preliminary experimentation indicated that 33 wt% HBr in AcOH[46] is a suitable acid for the conversion of **3a** to phthalimide derivative **4** (66% iso-

Table 4 Scope of DA reaction between 2-furoic acid derivatives (esters, amides) and maleimides under aqueous conditions



Entry	X	R^2	3	Conv. **1**[a]	*exo*-**3**, %	*endo*-**3**, %	Isolated[b], %
1	OMe	Me	**3k**	70	65	5	52(74)
2	OMe	H	**3l**	67	65	2	43(64)/82[c]
3	OMe	Et	**3m**	65	61	4	47(72)
4	OEt	Me	**3n**	63	59	4	29(46)
5	O^{i}Pr	Me	**3o**	54	50	4	26(49)
6	O^{t}Bu	Me	**3p**	54	51	3	25(46)
7	NH_2	Me	**3q**	94	91	3	77(83)
8	NMe_2	Me	**3r**	81	77	4	41(51)
9	NHOH	Me	**3s**	92	76	16	69(75)

General procedure: 2-Furoic acid derivative and maleimide (1.5 equiv.) stirred in/on water (1 M) at 50 °C for 16 h. [a] Conversion determined from the ^{1}H-NMR ratios of product isomers and starting material. [b] Isolated yield after (chromatographic) workup (in brackets, yield corrected on reacted starting material). [c] 2 M initial concentration.



Scheme 2 Follow-up chemistry starting with adduct **3**. Reagents and conditions: a. $SOCl_2$, EtOH, rt (from **3a**); b. BnBr, K_2CO_3, DMF, rt (from **3l**); c. 33 wt% HBr in AcOH, rt to 60 °C (from **3a**); d. 35% HCl, 100 °C (from **4**); e. H_2, Pd/C, rt (from **3a**).

lated yield). Acidic hydrolysis of **4** produces in high yield hemimellitic acid **5**, an aromatic tricarboxylic acid with potential application in the polymer and lubricant industry.[47,48] Finally, catalytic hydrogenation towards oxanorbornane derivative **6** was also facile.

Mechanistic understanding

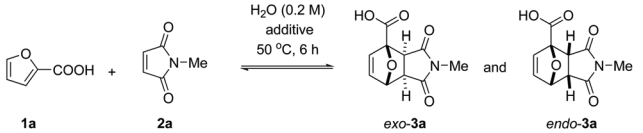
The above shows that furan carboxylic acid derivatives undergo surprisingly efficient Diels–Alder couplings to maleimides in aqueous solution. This result challenges the widely accepted idea that the diene scope in furan Diels–Alder chemistry is limited to electron-rich derivatives. While the nature of the furan substituent impacts the cycloaddition kinetics in a relatively predictable manner (the stronger the electron-withdrawing effect, the slower the DA reaction), we would like to note that moderate thermal activation can provide sufficient acceleration for seemingly unreactive inputs such as the 2-furoic acid derivatives used here; this is particularly true when water is used as solvent. The effect water has on the reaction can have multiple causes and may differ for the furoic acids on the one hand and the esters and amides on the other, depending on their physical characteristics. The hydrophobic effect[49] is evidently relevant for the biphasic reactions, but may not play a decisive role for the highly water-soluble 2-furoic acid substrates. To probe the operation of the hydrophobic effect in this case, we studied the title reaction between **1a** and maleimide **2a** in the presence of salting-in and salting-out reagents (Table 5). The effect of salt additives on the rate of aqueous Diels–Alder reactions has been extensively studied.[50] In general, salting-out reagents (*e.g.* simple inorganic salts like NaCl and $CaCl_2$) lead to rate enhancements, whereas additives that disturb hydrophobic interactions like guanidinium (Gn) salts characteristically retard conversion.[51] In addition, enhanced hydrophobic interactions are typically associated with an increased preference for the *endo* configuration of the adduct (the more compact geometry). Both of these hallmarks of the hydrophobic effect are consistently augmented with increasing additive concentration. Data in Table 5 summarizes the effect of additives on the rate of the cycloaddition between **1a** and **2a** (0.2 M). The observed yield and stereochemistry are generally consistent with the expected trends, illustrating that hydrophobic effect is a relevant influence in this system.

In addition, hydrogen bonding is likely to also play an important role in our system, for instance by preferentially stabilizing the transition state (and product) over the addends.[37] For example, the electron density around the oxygen atom in the furan ring expectedly changes significantly during the reaction since aromaticity is lost as the reaction proceeds; moreover, in the product (and transition state), both oxygen lone pairs can serve as hydrogen bond acceptors. In addition, the engagement of the COOH group as H-bond donor in interactions with surrounding water molecules increases the electron density around the furan ring and thus the rate of the DA coupling. Indeed, the addition of base is the extreme case of this, *i.e.* leading to complete proton transfer, as illustrated by the observations that 2-furoate salts already react with maleimides at ambient temperatures and that the bis-Na salt of FDCA is, counter to expectation, a reactive diene. It is important to also note that in base-mediated reactions the thermodynamics is favourably impacted as well: adduct **3a** is roughly 4 times more acidic than the starting 2-furoic acid **1a** (ΔpK_a approx. 0.6, see ESI†), which supplies an additional −3.6 kJ mol^{-1} to the $\Delta G^{\circ}_{323\,K}$, sufficient to render the reaction essentially irreversible (>95% equilibrium conversion, see Table 2, entry 4 *vs.* entry 2).

When 2-furoic acid esters are used as dienes, the system is no longer homogeneous and the reactions proceed 'on-water'. Hydrophobic interactions and hydrogen bonding with water molecules at the interface play an activating role here, together with the high local concentration effect (in neat conditions for example, the reaction also proceeds readily, but conversion is hampered by the poor solubility of **2a** in methyl furoate). In addition, the yield of adduct formed, *i.e.* the ultimate efficiency of the reaction, is definitely impacted by the crystallization of the product; this improves kinetics by reducing the rate of the back reaction and pushes the conversion beyond the solution equilibrium. Indeed, in all examples where product crystallization occurred, increased conversions were obtained (*e.g.* Table 4, entries 1, 7 and 9).

Finally, furamides show comparable behaviour to the parent furoic acids, as the aqueous reactions commence homogeneously at 50 °C. In terms of kinetics, furamides are likely somewhat more reactive than furoic acids, while the tendency of the corresponding adducts to crystallize out of aqueous solution is more pronounced. For instance, with unsubstituted 2-furamide precipitation was observed within minutes (at 50 °C), benefiting conversion. In the absence of product crystallization (entry 8, Table 4, adduct **3r**) the efficiency of the reaction is lower and quite comparable to the case of parent furoic acid **1a** under similar conditions (entry 2, Table 2).

Table 5 DA reaction between 2-furoic acid **1a** and maleimide **2a** in aqueous solution: effect of additives



Entry	Additive	Amount	*exo*-**3a**, %	*endo*-**3a**, %	Total, %	*endo* selectivity, %
1	None	n/a	39	5	44	13
2	NaCl	1 M	42	5	47	12
3	NaCl	2 M	43	7	50	16
4	NaCl	4 M	43	9	52	22
5	$CaCl_2$	2 M	50	9	59	18
6	GnCl[a]	2 M	37	4	41	11

General procedure: 2-Furoic acid **1a** (0.5 mmol), (additive) and *N*-methyl maleimide **2a** (1.5 equiv.) stirred in H_2O (0.2 M) at 50 °C for 6 h; yields determined from the ^{1}H-NMR ratios of product isomers and starting material. [a] GnCl = guanidinium chloride.

Conclusions

Herein we showcase the successful use of biomass-derived 2-furoic acids, esters and amides as dienes in Diels–Alder cycloadditions. Thus, a variety of novel DA adducts could be selectively obtained following a green synthetic protocol involving the use of renewable feedstock, aqueous solvent, mild conditions, and non-chromatographic purification. The DA couplings proceed surprisingly efficiently with these readily available dienes, which represents an important expansion of the current scope of furan DA reactions to include underrepresented electron-poor derivatives. Some opportunities for downstream diversification of the adducts into valuable chemical products, including substituted bio-based aromatics, is also demonstrated. Expansion of the dienophile scope beyond maleimides[52] is currently underway in our laboratories.

Conflicts of interest

There are no conflicts to declare.

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52 We observed that the imide motif in **2a** (and **4**) is much more prone to ring opening that in the product **3a**. For instance, imide **3a** is fully stable in 35% HCl at 100 °C. This suggests that the fused succinimide ring in **3a** has less strain than the flat structures (all sp^2 atoms in the ring) **2a** and **4**. Thus, upon DA cycloaddition with **2a**, strain energy is presumably released, which would be an important contributor to the reaction overall thermodynamics. This might explain (in part) why maleimides are such efficient dienophiles.