Recent Advances on Diels-Alder-Driven Preparation of Bio-Based Aromatics

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The preparation of high value-added chemicals from renewable resources is a crucial approach towards a sustainable economy. One prominent alternative to the production of petroleum-based chemicals from fossil resources is through the sequential Diels-Alder/aromatization reactions of biomass-derived furan platforms. This Concept is focused on the recent boom in bio-based furan DA strategies for aromatization of bio-based platform chemicals, particularly that of furfurals, ranging from indirect use and activation strategies to recent examples of direct DA reaction of these electron-withdrawing biomass-derived furans.

Biomass-derived furans are key building blocks in the current chemical toolbox, bearing both enormous synthetic and market potential. Particularly, the Diels-Alder (DA) reaction of these dienes with electron-withdrawing (EW) alkenes has allowed the sustainable preparation of bioaromatic chemical commodities[1] in agreement with many of the 12 principles of green chemistry.[2] Of particular highlight is its compliance with: i) the principle of atom economy (AE), since the DA reaction occurs with 100% AE, ii) the use of safer solvents, as various reactions are compatible with aqueous conditions, iii) the use of renewable feedstocks, in this case biomass-derived furan platforms that were included in Bozell and Petersen’s list of top 10 + 4 bio-based products from carbohydrates,[3] and iv) the fact that most DA are additive free. Whereas the need for acid/base catalysis in aromatization contradicts the latter aforementioned point, a variety of elegant approaches using homogeneous/heterogeneous catalysts have been reported in an attempt to avoid stoichiometric usage of additives.

According to the frontier molecular orbital theory (FMO), DA [4 + 2]-cycloaddition is governed by the energy gap between the corresponding HOMO of the diene and LUMO the alkene (Scheme 1A). However, post-DA synthetic opportunities are currently hindered by a very limited electron-donating furan platform, mostly comprising furan itself, furfuryl alcohols, and 2-methy/2,5-dimethyl species (Scheme 1B,C). By unfavorably increasing the LUMO_{dienophile}−HOMO_{diene} energy gap, major biorefinery building blocks are currently left out of this chemical toolbox. Notable examples[4] are furfural, 5-hydroxymethylfurfural (HMF) and furan dicarboxylic acid (FDCA), which remain in their “sleeping potential” for the construction of bioaromatics.[5] Concerning the furan/dienophile pair, it poses as an ubiquitously powerful tool in many chemical areas such as material chemistry,[6] bioconjugation,[7] drug discovery[8] and green chemistry.[9] Additionally, its retro-cyclization possesses a clickable character and thermal compatibility with most macromolecular frameworks[9] which have made the furan DA reaction a cornerstone of polymer chemistry (Scheme 1D). In this sense, extensive research has explored the use of this technology for i) co-polymerization,[10] ii) functionalization of biomaterials, namely nanoparticles or surfaces,[11] iii) preparation of cross-linked hydrogels,[12] or even iv) bioconjugation[13] and v) triggerable drug-release.[14]

Additionally, the resulting 7-oxanorbornenes (7-ONB) products offer many options of downstream chemical diversification or application. For once, hydrogenation stabilizes DA adducts, allowing for irreversible ligation and as a source of high-value oxygenated bio-based chemicals. Secondly, the aforementioned aromatization of 7-ONBs generated from biomass-derived furans represents one of the most important routes towards versatile aromatic renewable chemical commodities, allowing easy access to valuable scaffolds such as i) substituted benzenes, ii) phthalic anhydride derivates, iii) maleic anhydrides, and iv) phthalides.[15] Lastly, 7-ONBs themselves can be used as modular linkers for controlled release of cargos by retro-DA,[16] as ligation handles in subsequent DA, as pharmacological scaffolds in drug discovery,[8] or even as a tunable platform to control copolymerization propagation rates.[10]

In line with the unquestionable importance of the furan-to-aromatic sequence, Ananikov and co-workers reported an analytic description of the available data on bio-based C6-furans as pro-aromatic building blocks.[16] Despite all, the direct DA involving furfural, HMF, and FDCA derivatives remains a long-standing key problem in the current mismatch between furan availability and synthetic potential/reactivity towards bioaromatics. However, recent paradigm-shifting efforts in this direction have been reported. In one

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example from 2017, Ananikov and co-workers bypassed this prohibition by performing the reduction of HMF to 2,5-bis(hydroxymethyl)furan (BHMF; Scheme 2). In this form, the furan derivate can readily undergo DA reaction with maleimide to afford mainly the \textit{endo} product in high diastereoselectivity.

Tandem/one-pot hydrogenation affords norcantharimide derivative \textit{1} in good overall yield.\[16\] Interestingly, the use of aqueous media is possible, but less efficient, as both the high solubility of BHMF-7-ONB and concomitant promotion of the retro-DA complicate the isolation of pure product. Additionally, transformation of BHMF or HMF to the corresponding diamines by reductive amination with the dialdehyde, allowed production of derivates with two dialkylaminomethyl groups with increased anticancer activity.\[17\]

Since then, a recent burst on the development of novel strategies to render these “sleeping scaffolds” suitable partners for DA has been observed. Nonetheless, most comprise indirect chemical activation strategies to produce a more electron-rich diene, adding synthetic steps and limiting post-modification. For instance, modification of the EW-aldehyde in furfural to dimethylhydrazone has allowed DA-dehydration cascade with maleic anhydride or \textit{N}-ethyl maleimide in chloroform to afford bioaromatic products (including phthalimides) in 65\%–94\% yield.\[18\] More re-
cently, Hailes and co-workers reported the \textit{in situ} preparation of furfuryl hydrazones and cyclization with maleimides to yield polysubstituted aromatics \(^2\) (Scheme 3).\(^{[19]}\)

Preparation of cyclic acetals from furfurals were also reported to undergo DA with highly electrophilic dienophiles such as maleimides (50 °C, 72 h)\(^{[14a]}\) and acrylonitrile (60 °C, 120 h; Scheme 4A,B).\(^{[19,20]}\) Interestingly, when subjected to an acidic trigger (pH < 3) the resulting acetal hydrolysis triggers a molecular orbital mismatch in the HMF-7-ONB product and induces the retro-DA reaction to readily release the furfuryl aldehyde and the corresponding dienophile (Scheme 4B). Six-membered cyclic acetals present higher stability, and consequently afford higher DA yield and decreased retro-DA chemical release rate. Attempts to use oxazolidine-derived as furfurals mostly resulted in the release of the amino alcohols and consequent aza-Michael with the strong EW-dienophile. Furfural acetals can also react with other EWG dienophiles such as acrolein, methyl vinyl ketone, and methacrylate, albeit in lower yields. When using these non-meso dienophiles instead of typical maleimide, selectivity between \textit{ortho}/\textit{meta} 7-ONB can be addressed and tuned in a multivariate stereoelectronic manner. In such regard: i) \textit{ortho} product is the kinetic product; ii) \textit{meta} product is the thermodynamic product, governed by a lower HOMO-LUMO gap; iii) substituents on the dienes and dienophiles impact \textit{ortho}/\textit{meta} selectivity, with a high steric repulsion favoring the \textit{meta} product, and electronic interactions favoring the \textit{ortho}. Aromatization of these 7-ONB to aryl acetals \(^4\) can be performed either in DMSO or in toluene/DMSO (97.5:2.5) under basic conditions with continuous removal of water (Scheme 4A).

For the synthesis of \(p\)-xylene, dimethylfuran (DMeF) has been an attractive platform in the furan-to-aromatic DA-dehydration strategy\(^{[1a]}\) not only by its increased HOMO energy, but also by the small steric repulsion generated by its donating 2,5-methyl substitution. Extensive work has been reported exploring the direct cycloaddition of this furan as starting point for high yielding and diastereoselective 4+2 cycloadditions with cyclic alkenes (e.g., maleic anhydride and maleimide),\(^{[21]}\) linear alkenes (e.g., acrylic acid, acrolein, ethylene),\(^{[21d,22]}\) linear alkynes,\(^{[23]}\) and arynes,\(^{[24]}\) followed by acid/base promoted aromatization (Scheme 5A). Whereas extensively exploring this ED-furan is not within the main focus of this concept work, this platform has recently and concisely analyzed.\(^{[1c]}\) However, recent significant efforts focusing on this technology towards commercially valuable \(p\)-xylene should be briefly highlighted. Wu and co-workers described the use of heterogeneous Bi-BTC catalysts under relatively mild conditions to afford \(p\)-xylene in promising 92% from DMeF and ethylene (160 °C, 10 bar).\(^{[25]}\) Additionally, Toste, and more recently Al-Naji and co-workers have rendered acrolein and acrylic acid as viable dienophiles for DA+ decarboxylation-dehydration with DMeF.\(^{[22,26]}\) Continuous flow synthesis of DMeF from HMF using Ni on \(N\)-doped carbon\(^{[27]}\) followed by reaction with acrylic acid over a \(\beta\)-zeolite system have also been used to produce \(p\)-xylene in good yields (up to 83%).\(^{[26a]}\) However, even these novel methods fail to utilize furfurals as the core platform for DA-aromatization. An interesting tackle on this limitation was reported by Cao and co-workers in 2018.\(^{[28]}\) Capitalizing on the well-established procedure for the preparation of \(p\)-xylene from the DA reaction of DMeF and ethylene,\(^{[14a,b,29]}\) the authors showed that \(p\)-xylene can be

![Scheme 3. One pot tandem Diels-alder/aromatization reaction of furfurals promoted by the formation of furfuryl hydrazone.](image)

![Scheme 4. Furfuryl acetals as dienes for the furan Diels-Alder reaction.](image)

![A. Furfural acetal Diels-Alder reaction (Jérôme and co-workers)](image)

![B. HMF acetal Diels-Alder reaction (Jérôme and co-workers)](image)
obtained in one pot directly from HMF through a noble metal catalyzed deoxygenation of HMF to DMeF to undergo tandem DA-aromatization reaction with ethylene (Scheme 5B).

Regarding terephthalic acid platforms – a cornerstone in polymer chemistry – these scaffolds can be classically accessed by DA of electron-rich methyl or dimethyl furans followed by either dehydration or oxidation of oxabicyclic compounds, despite notable problems regarding DA adduct instability. More recently, partially oxidized HMF (5-(hydroxymethyl)furoic acid (HMFA)) and its ether- and ester-derivatives were shown to undergo one-pot DA-dehydration with high pressure ethylene over heterogeneous catalysts (e.g., a pure-silica molecular sieve containing Sn-framework, Zr-β zeolites, and zincosilicates; Scheme 6). However, the direct reaction of HMF and its oxidized derivates is still in high demand as it should both enhance the efficiency and elegance of the processes towards bio-based terephthalic acid platform. In fact, Clark and co-workers directly oxidized HMF to its dicarboxylate analogues followed by furan-to-aromatic reaction, reducing the number of operation steps and improving green metrics.

Notably, heterogeneous catalysts (e.g., aluminum pillared montmorillonite clay [Al-P–MC]), heteropolyacid catalysts have also been recently used for the preparation of bio-based diethyl/dimethyl terephthalates from the corresponding 2,5-furandicarboxylic diethyl/dimethyl (Scheme 6).

A successful alternative use of the aforementioned EW-furans was explored by Sibi and co-workers through the direct reaction with highly reactive benzene. Recently, the Sibi Group reported the reaction of 2,5-furandimethyl ester with this reactive dienophile followed by reductive aromatization to afford naphthalene dicarboxylic acid derivatives (Scheme 6). Yet, the latter aromatization step remains problematic, resulting in poor yields and highlighting the need for alternative approaches. In this sense, stepwise hydrogenation of 7-ONB followed by acid-promoted dehydroaromatization has emerged as a viable option. Whereas Amberlyst 15 afforded the aromatic product in poor yields, HCl promoted the aromatization in 91% yield. However, the diester is not compatible with the latter conditions, resulting in the diacid product. The LUMO of aryne lies much lower comparing to unstrained alkynes, contributing to a more favorable LUMO dienophile-HOMO diene with ED-furans which correlates with the diversity of examples in the literature. Interestingly, albeit only few examples of DA oxidized EW-furans are reported, benzene reacts effectively with these species despite bearing only a slight increase of the HOMO comparing to unstrained alkynes. Such reactivity may be justified by distortion/interaction models, given the strain release in the transition state.

Multicomponent reactions have also been used as a strategy to bypass the electrophilic character of furfurals, despite few and limited recent advances. For instance, the reaction mixture of 2-methyl furfural or O-acetylated HMF...
with maleic anhydride and tryptamine can undergo tandem N-acyliminium/Pictet-Spengler/Diels-Alder reaction to afford polycyclic adducts in good stereoselectivity and yield.\(^{[39]}\) Ugi reaction of aldehyde-containing furans, including HMF, can also undergo DA reaction via the transiently activated furans.\(^{[40]}\) Whereas such synthetic approaches may be useful to produce more complex polycyclic systems, they are of narrow applicability in a furan-to-bioaromatic rationale towards high-volume aromatic commodities.

Despite the important advances of the aforementioned transformations, the direct DA reaction of biomass-derived furfurals (as is) to provide access to functionalized benzoaldehydes/benzoic acids remains a challenging task. The first direct DA cycloaddition of formyl-substituted furans was reported recently by Bruijnincx and co-workers by reacting the desired furfurals in a concentrated aqueous solution with maleimide at 60 °C for 16 h, to afford the corresponding 7-ONBs in yields up to 58% (Scheme 7).\(^{[41]}\) Two possible mechanistic explanations to this elegant simplistic approach are suggested. For once, the in situ hydration of the aldehyde promotes a dampening effect on electron-withdrawing character of the aldehyde, lowering the LUMO\(_{\text{dienophile}}\)-HOMO\(_{\text{diamine}}\) energy gap. Alternatively, a post-DA hydration can occur to afford a more thermodynamically favored DA adduct, hence shifting the equilibrium towards the desired product. The latter is supported both by density functional theory (DFT) calculations and the authors observation that <1% of furfural is hydrated at equilibrium. Interestingly, the presence of a second electron withdrawing substituent (namely an aldehyde or a carboxylic acid) still did not completely prohibit the DA, despite significant decrease in the yield (5–7%). However, tolerance to even small structural changes of the dienophile was shown to be low, as the LUMO\(_{\text{dienophile}}\)-HOMO\(_{\text{diamine}}\) again increases upon use of less EW alkenes.

The corresponding DA adducts were readily transformed into novel value-added chemicals, expanding the scope to aldehyde and hydrazone-containing bioaromatics and high-value oxygenated bio-based chemicals. The masked aldehyde in the 7-ONB was successfully modified to afford the tosylhydrazone, oxime, acid (by Pinnick oxidation), and to undergo hydrogenation, which has been shown to stabilize the DA adduct, and aromatization by reaction with \(N,N\)-dimethylhydrazine (Scheme 7).

In conclusion, the DA reaction of biomass-derived furans is an unquestionable cornerstone towards valuable bioaromatics and is now undergoing its first steps regarding the direct use of EW-furans. This provides privileged access to high-volume commodity chemicals, in particular functionalized bioaromatics, from easily accessible biomass furfurals.

Despite this, challenges remain to further reduce our dependence on petroleum-based bulk chemicals, such as i) extending the scope of the furan DA to various dienophiles, ii) extending the scope of the furanic platform (e.g., HMF, oxidized HMF derivatives, polyethylene furanoate (PEF)), iii) isolation of nonhydrated DA adducts, and iv) increasing the efficiency of such reactions so that they become economically competitive with petroleum-based commodities. Finally, efficient HMF- and FDCA-based access to bioaromatics is still in demand.

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**Conflict of Interest**

The authors declare no conflict of interest.

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\[\text{Scheme 7. Preparation of DA adducts from electron-poor biomass-derived furfurals and further derivatizations.}\]
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