Review

Intermolecular Diels-Alder Cycloadditions of Furfural-Based Chemicals from Renewable Resources: A Focus on the Regio- and Diastereoselectivity in the Reaction with Alkenes

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Abstract: A recent strong trend toward green and sustainable chemistry has promoted the intensive use of renewable carbon sources for the production of polymers, biofuels, chemicals, monomers and other valuable products. The Diels-Alder reaction is of great importance in the chemistry of renewable resources and provides an atom-economic pathway for fine chemical synthesis and for the production of materials. The biobased furans furfural and 5-(hydroxymethyl)furfural, which can be easily obtained from the carbohydrate part of plant biomass, were recognized as “platform chemicals” that will help to replace the existing oil-based refining to biorefining. Diels-Alder cycloaddition of furanic dienes with various dienophiles represents the ideal example of a “green” process characterized by a 100% atom economy and a reasonable E-factor. In this review, we first summarize the literature data on the regio- and diastereoselectivity of intermolecular Diels-Alder reactions of furfural derivatives with alkenes with the aim of establishing the current progress in the efficient production of practically important low-molecular-weight products. The information provided here will be useful and relevant to scientists in many fields, including medical and pharmaceutical research, polymer development and materials science.

Keywords: biobased furans; renewable building blocks; plant biomass; Diels-Alder cycloaddition; selectivity; sustainable chemistry; biorefining

1. Introduction

To date, the development of efficient technologies for catalytic or biocatalytic conversion of renewable plant biomass into viable targeted products remains one of the most important and challenging tasks for modern chemical science [1–5]. The primary advantage of biorefining based on renewable carbon sources over traditional refining using exhaustible resources is the realization of a carbon-neutral cycle, leading to zero total carbon emissions into the environment during chemical production and consumption. Biobased furans—furfural (FF) and 5-(hydroxymethyl)furfural (HMF)—can be obtained by acid-catalyzed dehydration of carbohydrates and are recognized as “platform chemicals”. As expected, the key role of biobased technologies is to replace the key existing products of oil-based refinement with renewables [4,6,7]. The tremendous synthetic potential explains the unprecedented scale of research in the fields of synthesis and application of furanic platform chemicals for the production of biofuels, chemicals, polymers and other industrially important products, which was evidenced by the increasing number of relevant publications (partially since 2010, Figure 1) and was highlighted in many recent reviews [7–20].
Figure 1. Number of publications mentioning biobased furans per year. Source: Scopus. Keyword: “furfural”.

One of the focused reactions of furan chemistry is the [4+2]-cycloaddition, well known as the Diels-Alder (DA) reaction, in the classic mechanism based on the interaction of the highest occupied molecular orbital of furanic diene (HOMO$_{\text{diene}}$) and the lowest unoccupied molecular orbital of dienophile (LUMO$_{\text{dienophile}}$). The DA reaction may proceed with high efficiency under solvent-free and/or noncatalytic conditions, representing the ideal example of a “green” process characterized by a 100% atom economy and a low to moderate E-factor [21,22]. Intermolecular furan/alkene DA reactions have a high potential for application in fine organic synthesis, biomedical areas, materials sciences, polymers and bio-organic chemistry (Figure 2) [23–30].

![Diagram of Diels-Alder cycloaddition](image)

**Figure 2.** Diels-Alder cycloaddition with biobased furans as an approach towards practically important products. Summarizing and analyzing scientific data about the regio- and diastereoselectivity of intermolecular Diels-Alder cycloadditions between furfural derivatives and alkenes was a general aim of this review.

The direct Diels-Alder reaction of FF or HMF with common alkenes is thermodynamically unfavorable [31–33], but this type of cycloaddition can be performed after decreasing the HOMO–LUMO gap through reduction of the aldehyde group into more donor functionality. Another approach is redox-neutral chemical activation through modification of aldehyde into acetal or hydrazone with the possibility of aldehyde deprotection. In general, the nature of the substituent at the C2 position in the furan ring strongly affects reactivity in DA cycloadditions; furans with electron-donating groups are well-suited as substrates, while electron-poor furans display low reactivity [34,35].
In the case of highly active dienophiles, DA adducts may be formed under noncatalytic conditions; for other substrates, catalysis by Lewis acids is usually needed. Reactions of furans with alkene dienophiles are often characterized by facile retro-DA (rDA) reactions due to the low reactivity of furan as a diene that leads to low diastereo- and regioselectivity of the cycloaddition (Scheme 1). The orbital $\text{HOMO}_{\text{diene}}$ and $\text{LUMO}_{\text{dienophile}}$ energy difference seems to control the diastereomer distribution [32,36]. Charge interactions between diene and dienophile favor orthoselectivity, while steric hindrance promotes metaselectivity but without strong kinetic or thermodynamic preference for a single regioisomer [32,37].

Scheme 1. Possible regio- and diastereomers in Diels-Alder cycloaddition of C-2-substituted furans with mono-substituted alkenes.

Information about the selectivity of DA reactions is helpful to scientists in many fields, including medical and pharmaceutical research, polymer development and materials science. The regio- and diastereoselectivity of DA cycloaddition are important parameters for the high-yielding synthesis of chemically pure products, especially in the development of drugs, because diastereomers may exhibit different biological activities [38]. The endo- and exo-DA adducts have different steric properties and convert to furan and alkene components at different temperatures, which may be important in the development of various dynamic systems [39,40]. Moreover, the stereo structure of cyclic alkenes may influence the reactivity in ring-opening metathesis polymerization used for the synthesis of stereoregular polymers [41]. This difference for furan-derived oxanorbornanes was clearly demonstrated by Kilbinger and coworkers. They showed in several examples that furan/maleimide DA adducts react quickly and selectively with the G3 catalyst, resulting in the formation of monomolecular carbene complexes that display low reactivity with the second molecule of oxanorbornane (both endo or exo) due to unfavorable steric factors (Scheme 2a). In contrast, exo-oxanorbornane counterparts undergo efficient homopolymerization under the same reaction conditions (Scheme 2b) [41].

Several approaches may be used to increase the regio- and diastereoselectivity of DA reactions: fine-tuning of steric and electronic properties of dienes or dienophiles; variation of reaction conditions such as temperature, time, type of solvent and pressure; and catalysis by Lewis acids. Generally, for furan/alkene cycloadditions, exo isomers are more stable and form under thermodynamic control of the reaction (at high temperature), while endo isomers are kinetically preferred [36,42–44].
2.1. 2-Methylfuran

2-Methylfuran (2-MF) is the simplest 2-substituted furan produced by the reduction of the aldehyde group in FF. The selectivity of IMDA reactions of 2-MF with common cyclic and acyclic alkenes is presented in Tables 1 and 2. Noncatalytic reactions of 2-MF with maleic or citraconic anhydride led to cycloadducts with exo configurations even at room temperature (Table 1, entries 1–3). The current literature provides scarce information about the selectivity of reactions of 2-MF with maleimides under kinetic conditions. In the case of maleimides reacting with 2-MF at room temperature, the formation of >20% endo isomer was observed (entry 4), while at temperatures more than 60 °C, exclusive formation of the exo isomer was found for most maleimides (Table 1). However, in a water medium for some N-substituted maleimides, the content of endo isomers was higher even under high temperature (entries 8, 10). For N-carboxyethyl maleimide reacting with furan, 2-MF or 2,5-dimethylfuran, the best exoselectivity was obtained in the case of furan, while 2,5-dimethylfuran showed the best endoselectivity under kinetic conditions (entries 16–19) [65]. The cycloadduct of 2-MF with N-phenyl maleimide was isolated in a pure, optically active form with 90% ee using dynamic enantioselective crystallization by continuous suspension in heptane or hexane solution with glass beads at 80 °C in the presence of trifluoroacetic acid (TFA) to accelerate the deracemization (entry 13) [44].
Table 1. IMDA cycloadditions of 2-MF with cyclic alkenes.

| №  | Dienophile       | Conditions                  | Selectivity     | Yield of DA Adducts (%) | [Ref.] |
|----|------------------|-----------------------------|-----------------|-------------------------|--------|
| 1  | X = O            | Neat, RT, N₂, 24 h          | Exo             | 91, [66]                |
| 2  | X = O            | Neat, RT, 10–15 °C, 2–3 h   | Exo             | 96 (crude), [67]        |
| 3  | Citraconic anhydride | CH₂Cl₂, RT, 15 kbar        | Exo (ortho/meta 1:1) | 65 ¹, [68] |
| 4  | X = NH           | Et₂O, RT, 3 days            | Endo/exo ²      | 21 (for endo), [69]     |
| 5  | X = NH           | THF, reflux, 4 h            | Exo             | 94, [70]                |
| 6  | X = NMe          | Toluene, 90 °C              | Exo             | 92, [71]                |
| 7  | X = NMe          | Et₂O, 90 °C                 | Exo             | 66, [72]                |
| 8  | X = NEt          | H₂O₂, 65 °C                 | Endo/exo 1:4:1  | 100, [73]               |
| 9  | X = N(Bu)        | H₂O₂, 65 °C                 | Exo             | 100, [73]               |
| 10 | X = NPh          | 4:1 Toluene/benzene, RT, 1.1 GPa | Endo/exo 1.6:1 | 100, [73]               |
| 11 | X = NPh          | 4:1 Toluene/benzene, RT, 1.1 GPa | Endo/exo 1.6:1 | 85, [74]                |
| 12 | X = NPhF₃        | CDCl₃, 60 °C                | Exo with traces of endo | 90, [44] |
| 13 | X = NPhF₃        | Hexane or heptane, TFA, glass beads, 80 °C, 5–8 days ³ | (-)-Exo, 86–90 ee | 80, [44] |
| 14 | X = NPhF₃        | Neat, reflux                | Exo             | 50, [75]                |
| 15 |                 | THF, 65 °C                  | Exo             | 64, [70]                |
| 16 | X = NCH₂CH₂COOH  | CHCl₃, 38 °C, 5 days        | Endo/exo 28:72  | 100, [65]               |
| 17 | X = NCH₂CH₂COOH  | CHCl₃, 38 °C, 5 days        | Exo             | 100, [65]               |
| 18 | X = NCH₂CH₂COOH  | CH₂Cl₂, RT, overnight       | Endo/exo 78:22  | 100, [65]               |
| 19 | X = NCH₂CH₂COOH  | CH₂CN, 60 °C, 6 h           | Endo/exo 22:78  | 100, [65]               |

¹ Yield of DA adduct after hydrogenation. ² Ratio of diastereomers was not provided. ³ The reaction was conducted under dynamic enantiomeric crystallization conditions. ⁴ Furan as a substrate. ⁵ 2,5-Dimethylfuran as a substrate.

An important possible application of 2-MF is the protection of double bonds in functionalized alkenes against nucleophiles using the DA reaction. For example, modification of the 2-MF/maleimide DA adduct by alkylation or a Mitsunobu reaction, followed by thermal deprotection, was used for the synthesis of N-alkylated maleimides (Scheme 3) [69,70].

![Scheme 3. Synthesis of N-substituted maleimides from 2-MF and maleimide using the DA approach.](image-url)

Representative reactions of 2-MF with acyclic alkenes containing one or two electron-withdrawing groups (EWGs) are covered in Table 2. High endoselectivity was obtained for the HfCl₄-catalyzed reaction of 2-MF with dimethyl maleate at low temperatures (Table 2,
entries 1, 2). However, under the same conditions, benzyl acrylate showed exoselectivity for cycloaddition (entries 7, 8). An adduct of 2-MF and trans-4,4,4-trifluorocrotonic acid formed with high regio- and diastereoselectivity (entry 3). An enantioselective version of DA reactions with some fluorinated alkene dienophiles was implemented using chiral oxazaborolidine organocatalysts, which affords corresponding chiral oxabicyclic products with high yields and selectivity (entries 4–6). In the case of acrylonitrile reacting with 2-MF, regio- and diastereoselectivity was poor even in the presence of Lewis acid catalysts (entries 9, 10). Orthoadducts of 2-MF with 1-cyanovinyl acetate or 2-chloroacrylonitrile that are favored over meta-isomers due to electronic reasons were obtained under kinetic conditions with high regioselectivity (entries 11–15). A shift towards endo-products was found for reactions of 2-MF with allenic esters in the presence of Eu(fod) as the catalyst (entries 16–19).

Table 2. IMDA cycloadditions of 2-MF with acyclic alkenes.

| №  | Dienophile | Conditions           | Selectivity                        | Yield of Adducts (%) |
|----|------------|----------------------|------------------------------------|----------------------|
| 1  | Dimethyl maleate | HfCl₄, CH₂Cl₂, −30 °C | Endo/exo 84:16                     | 94, [76]             |
| 2  | Dimethyl maleate | HfCl₄, CH₂Cl₂, −50 °C | Endo/exo > 98:2                    | 82, [76]             |
| 3  |            |                      |                                    | 90, [77]             |
| 4  |            |                      |                                    | 99 [78]              |
| 5  |            |                      |                                    | 74, [78]             |
| 6  |            |                      | Ortho (Endo/exo 94:6), 98 ee (for endo isomer) | 74, [79]             |
| 7  | Benzyl acrylate | HfCl₄, CH₂Cl₂, −78 °C | Endo/exo 28:72 (mixture of regio isomers) | 84, [76]             |
| 8  | Benzyl acrylate | HfCl₄, CH₂Cl₂, −50 °C | Endo/exo 31:69 (mixture of regio isomers) | 85, [76]             |
Table 2. Cont.

| № | Dienophile          | Conditions           | Selectivity                        | Yield of Adducts (%) | [Ref.] |
|---|---------------------|----------------------|------------------------------------|----------------------|--------|
| 9 | Acrylonitrile       | ZnI₂, neat, 50 °C    | N.d.                               | 69 [80]             |
| 10| Acrylonitrile       | Neat, 60 °C          |                                    | 69 [31,32]           |
| 11| 1-Cyanovinyl acetate| ZnI₂, neat, 0 °C, 8 days | Ortho (endo/exo 1:1)² | 52 [81] |
| 12| 1-Cyanovinyl acetate| ZnI₂, neat, 20 °C, 26 h | Ortho endo²                        | 17 [81] |
| 13| 1-Cyanovinyl acetate| ZnI₂, neat, RT, 24 h | Ortho (endo/exo 3:1)² | 30 [82] |
| 14| 1-Cyanovinyl acetate| MgI₂, neat, RT, 24 h | Ortho (endo/exo 4:1)² | 57 [82] |
| 15| 2-Chloroacrylonitrile| ZnI₂, neat, 0 °C     | Ortho/meta 10:1 (mixture of endo/exo) | 91 [3,83] |

1 Yield of DA adduct after hydrogenation. ² Endo- and exoconformation with regard to the position of the OAc group. ³ Structure of regio- and diastereomers in DA cycloaddition of C-2-substituted furans with itaconic anhydride are provided in Scheme 5. ⁴ Was detected by NMR. N.d.—not determined.

2.2. Furanic Acetals

With rare exceptions, furfural does not react with dienophiles, but the introduction of aldehyde groups by DA reaction may be performed using an acetalization strategy that reduces the electron-withdrawing character of the carbonyl group. Table 3 highlights the results of reactions of furanic acetals with cyclic and linear alkenes. Literature data about the stereoselectivity of reactions of furanic acetals with cyclic alkenes are scarce. Predominant formation of endoadducts under kinetic conditions was detected by NMR when N-methyl maleimide was used as a dienophile (entry 1). For reactions of furfural acetals with mono-substituted acrylic alkenes, regioselectivity significantly depended on the type of substrates and reaction conditions. For dioxolane acetal reacting with methyl vinyl ketone, methyl acrylate or acrolein at 60 °C, a mixture of regio- and stereoisomers was obtained with predominant meta- and endoselectivity. In the case of acrylonitrile reacting with furanic acetals, the selectivity of cycloadditions was poor even in the presence of Lewis acid catalysts (entries 5–9). For the ZnCl₂-catalyzed reaction of ethylthioacetal with acrylonitrile at 30 °C, 91% ortho selectivity and moderate endoselectivity were observed (entry 10). According to DFT calculations, the regioselectivity of reactions of furanic acetals with alkenes is a result of two opposite factors: charge interactions between the furan and alkene favor orthoselectivity, while steric factors promote metaselectivity [32].
Table 3. IMDA cycloadditions of furfural acetals with alkenes.

| №  | Furfural Acetal | Dienophile | Conditions | Selectivity | Yield of Adducts (%) | Ref. |
|----|----------------|------------|-------------|-------------|----------------------|------|
| 1  | ![Furfural Acetal](image1) | N-Methylmaleimide | CH\_2Cl\_2, 23 °C | Endo/exo 87:13 | N.d., [86] |
| 2  | ![Furfural Acetal](image2) | Methyl vinyl ketone | Neat, 60 °C | Ortho 13 (endo/exo 74:26), meta 87 (endo/exo 65:35) | 36, [32] |
| 3  | ![Furfural Acetal](image3) | Methyl acrylate | Neat, 60 °C | Ortho 33 (endo/exo 87:13), meta 67 (endo/exo 77:23) | 40, [32] |
| 4  | ![Furfural Acetal](image4) | Acrolein | Neat, 60 °C | Ortho 38 (endo/exo 71:29), meta 62 (endo/exo 43:57) | 28, [32] |
| 5  | ![Furfural Acetal](image5) | Acrylonitrile | Neat, 60 °C, 120 h | Ortho 48 (endo/exo 72:28), meta 52 (endo/exo 42:56) | 76, [32] |
| 6  | ![Furfural Acetal](image6) | Acrylonitrile | ZnCl\_2, neat, 60 °C | Ortho 50 (endo/exo 70:30), meta 50 (endo/exo 56:44) | 75, [32] |
| 7  | ![Furfural Acetal](image7) | Acrylonitrile | ZnI\_2, neat, 60 °C | Ortho 53 (endo/exo 70:30), meta 67 (endo/exo 60:40) | 75, [31] |
| 8  | ![Furfural Acetal](image8) | Acrylonitrile | ZnCl\_2, neat, 60 °C | Ortho 43 (endo/exo 85:15), meta 57 (endo/exo 56:44) | 68, [32] |
| 9  | ![Furfural Acetal](image9) | Acrylonitrile | ZnCl\_2, neat, 60 °C | Ortho 39 (endo/exo 67:33), meta 61 (endo/exo 54:46) | 67, [32] |
| 10 | ![Furfural Acetal](image10) | Acrylonitrile | ZnCl\_2, neat, 30 °C | Ortho 91 (endo/exo 66:33), meta 9 (endo/exo 53:47) | 73, [32] |
| 11 | ![Furfural Acetal](image11) | Acrylonitrile | ZnCl\_2, neat, 60 °C | Ortho 53 (endo/exo 60:40), meta 47 (endo/exo 54:46) | 81, [32] |
| 12 | ![Furfural Acetal](image12) | Acrylonitrile | ZnCl\_2, neat, 60 °C | Ortho 52 (endo/exo 62:38), meta 48 (endo/exo 56:44) | 85, [32] |

N.d.—not determined.
2.3. Functionalyzed Furfural Derivatives

Mild reduction of the aldehyde group in FF is a path to important furanic building blocks furfuryl alcohol (FA) and furfuryl amine (FAM), which are widely used for the development of functional or dynamic molecular and biomolecular systems. Examples of possible areas of applications include but are not limited to the synthesis of biologically active compounds [87–90], oxanorbornane-based amphiphiles [91–94], supramolecular systems [95], self-assemblies [96], self-healing polymers and other dynamic systems [28].

The diastereoselectivity of DA reactions of FA, FAM and some common derivatives with cyclic and acyclic alkenes is shown in Tables 4–6. Preferable formation of exo-adducts was observed for reactions of maleic and citraconic anhydrides with selected furanic substrates even at low temperatures (Tables 5 and 6), except for the vinylated derivative of FA, which showed preferable endo-selectivity (Table 5, entries 5–10).

Table 4. IMDA cycloadditions of FA with alkenes.

| №  | Dienophile                  | Conditions                  | Selectivity   | Yield of Adducts (%) | [Ref.] |
|----|-----------------------------|-----------------------------|---------------|----------------------|--------|
| 1  | Maleimide                   | Ethyl acetate, 24 °C        | Endo/exo 96:4 | 87, [33]             |        |
| 2  | Maleimide                   | Ethyl acetate, 24 °C        | Endo/exo 97:3 | 42, [32]             |        |
| 3  | N-Me-maleimide              | Et₂O, 90 °C                 | Endo/exo 21:79| 43, [72]             |        |
| 4  | N-Bn-maleimide              | CH₃CN, 35 °C                | Endo/exo 70:30| 75, [96]             |        |
| 5  | N-Propargylmaleimide        | CH₃CN, 35 °C                | Endo/exo 80:20| 72, [96]             |        |
| 6  | N-(2-Hydroxyethyl)maleimide | Ethyl acetate, 80 °C        | Endo/exo 76:30| 76, [97]             |        |
| 7  | N-(3-Hydroxypropyl)maleimide | Benzene, reflux             | Endo/exo 86:14| 86, [98]             |        |
| 8  | N-(4-Hydroxyphenyl)maleimide| Toluene, 80 °C              | Endo/exo 77:23| 77, [99]             |        |
| 9  | N-(4-Hydroxyphenyl)maleimide| Acetone, 55 °C              | Endo/exo 71:29| 71, [40]             |        |
| 10 | N-(4-Hydroxyphenyl)maleimide| Acetone, 35 °C              | Endo/exo 80:20| N.d., [40]           |        |
| 11 | N-(p-Methoxyphenyl)maleimide| CH₃CN, 40 °C, 18 h          | Mostly endo   | 89, [100]            |        |
| 12 | N-(p-Nitrophenyl)maleimide  | CH₃CN, 60 °C                | Endo/exo 70:23| 52, [100]            |        |
| 13 | BMI ⁴                       | Toluene, 75–80 °C, 2 days   | Mostly endo   | 92, [101]            |        |
| 14 | Acrylonitrile               | Neat, 60 °C                 | Ortho 56 (endo/exo | 69:31), meta 44  | 81, [32] |
|    |                             |                             | (endo/exo 56:44)|                    |        |
| 15 | CO₂CH(CF₃)₂                 | Neat, RT, 96 h              | N.d.          | 66, [37]             |        |

1 2,5-bis(Hydroxymethyl)furan (BHMF) as a substrate. 2 2,5-bis(Acetoxymethyl)furan (BAMF) as a substrate. 3 Slowly transformed to the exo isomer over a period of several months. ⁴ 4,4′-bis(Maleimido)diphenylmethane. N.d.—not determined.

The adduct of FA with maleic anhydride (1-exo) is unstable and undergoes irreversible intramolecular cyclization during storage or warming, yielding the corresponding thermodynamically stable lactone 2-exo (Scheme 4) [102].

![Diagram of IMDA cycloadditions of FA with alkenes.](image-url)
The diastereoselectivity of the reactions with N-alkyl- and N-benzyl-substituted maleimides was in accordance with typical kinetic profiles demonstrating a shift towards endo- and exo-products under kinetic or thermodynamic conditions, respectively (Tables 4–6). However, this relationship was disrupted for some N-aryl maleimides reacting with various furanic substrates under both kinetic and thermodynamic conditions. For example, the diastereoselectivity of the cycloaddition of vinyl-substituted FA and N-Ph-maleimide shifted from a 1:2.8 endo/exo ratio under kinetic conditions to Et₂O to a 4:1 endo/exo ratio in toluene at 80 °C (Table 5, entries 11, 12).

Table 5. IMDA cycloadditions of FA derivatives with cyclic alkenes.

| №  | R         | Dienophile      | Conditions         | Selectivity | Yield of Adducts (%) | Ref. |
|----|-----------|-----------------|--------------------|-------------|----------------------|------|
| 1  | Allyl     | N-Me-maleimide  | Toluene, 50 °C, 24 h | Endo        | 65 (endo), [103]     |      |
| 2  | Allyl     | N-Ph-maleimide  | Toluene, 50 °C, 24 h | Endo        | 26 (exo), [103]      |      |
| 3  | Bn        | Maleic anhydride| Toluene, RT, 3 days | Exo         | 43, [91]             |      |
| 4  | Bn        | Maleic anhydride| 15 kbar, CH₂Cl₂, 60 h | Exo (ortho/meta 5:7) | 31, [68]             |      |
| 5  | Vinyl     | Maleic anhydride| Et₂O, 22-24 °C, 48 h | Endo        | 72, [104]            |      |
| 6  | Vinyl     | Maleic anhydride| Et₂O, 35 °C, 48 h | Endo/exo 8:1 | 66, [104]            |      |
| 7  | Vinyl     | Maleic anhydride| THF, 22-24 °C, 90 h | Endo/exo 8:1 | 66, [104]            |      |
| 8  | Vinyl     | Maleic anhydride| MeCN, 22-24 °C, 48 h | Endo/exo 4:1 | 68, [104]            |      |
| 9  | Vinyl     | Maleic anhydride| Toluene, 22-24 °C | Endo/exo 12:1 | 64, [104]            |      |
| 10 | Vinyl     | Maleic anhydride| Toluene, 80 °C  | Endo/exo 4:1 | 66, [104]            |      |
| 11 | Vinyl     | N-Ph-maleimide  | Et₂O, 22-24 °C | Endo/exo 1:2:8 | 47, [104]            |      |
| 12 | Vinyl     | N-Ph-maleimide  | Toluene, 80 °C  | Endo/exo 4:1 | 66, [104]            |      |
| 13 | Ac        | Maleic anhydride| Et₂O, 25 °C, 7 days | Exo         | 34, [105]            |      |
| 14 | Ac        | Maleic anhydride| Toluene, RT, 97 h | Exo         | 74, [88]             |      |
| 15 | Ac        | Maleic anhydride| 15 kbar, CH₂Cl₂, 60 h | Exo (ortho/meta 6:5) | 59, [68]             |      |
| 16 | Ac        | N-Me-maleimide  | CH₂Cl₂, 23 °C  | Endo/exo 77:23 | N.d., [86]            |      |
| 17 | Ac        | N-Dodecylmaleimide| THF, 23 °C | Endo/exo 64:36 | N.d., [86]            |      |
| 18 | Ac        | N-Ph-maleimide  | CH₂Cl₂, 23 °C  | Endo/exo 65:35 | N.d., [86]            |      |
| 19 | Ac        | N-(p-Nitrophenyl)maleimide| CH₂Cl₂, 23 °C | Endo/exo 55:45 | N.d., [86]            |      |
| 20 | Ac        | N-(p-Methoxyphenyl)maleimide| CH₂Cl₂, 23 °C | Endo/exo 67:33 | N.d., [86]            |      |
| 21 | Ac        | N-(p-Methoxy-2-propyl)maleimide| CH₂Cl₂, 23 °C | Endo/exo 76:24 | N.d., [86]            |      |
| 22 | Ac        | N-(2-Methoxyethyl)maleimide| CH₂Cl₂, 23 °C | Endo/exo 75:25 | N.d., [86]            |      |
| 23 | Bz        | Maleic anhydride| Toluene, 80 °C, 456 h | Exo     | 46, [88]             |      |
### Table 5. Cont.

| № | R       | Dienophile                        | Conditions         | Selectivity | Yield of Adducts (%) | Ref. |
|---|---------|-----------------------------------|--------------------|-------------|----------------------|------|
| 24 | Bz      | Maleic anhydride                  | Et₂O, 24 °C, 24 h  | Endo        | N.d., [106]          |      |
| 25 | Bz      | N-Me-maleimide                    | CH₂Cl₂, 23 °C      | Endo/exo    | 70:30                |      |
| 26 | Bz      | N-Dodecylmaleimide                | THF, 23 °C         | Endo/exo    | 63:37                |      |
| 27 | CO'Bu   | N-iPr-maleimide                   | CHCl₃, 55 °C       | Endo/exo    | 60:40                |      |
| 28 | CO'Bu   | N,N'-Bu-maleimide                 | CHCl₃, 55 °C       | Endo/exo    | 45:55                |      |
| 29 | CO'Bu   | N,N'-Bu-maleimide                 | CHCl₃, 55 °C       | Endo/exo    | 51:49                |      |
| 30 | CO'Bu   | N-Bn-maleimide                    | CHCl₃, 55 °C       | Endo/exo    | 44:56                |      |
| 31 | CO'Bu   | 2-Methylphenyl-maleimide          | CHCl₃, 55 °C       | Endo/exo    | 26:74                |      |
| 32 | CO'Bu   | N-(2-Methylphenyl)-maleimide      | CHCl₃, 55 °C       | Endo/exo    | 67:33                |      |
| 33 | CO'Bu   | BMI                               | CHCl₃, 55 °C       | Endo/exo    | 19:81                |      |
| 34 | CO'Bu   | N-Me-maleimide                    | CH₂Cl₂, 23 °C      | Endo/exo    | 71:29                |      |
| 35 | CO'Bu   | N-Dodecylmaleimide                | THF, 23 °C         | Endo/exo    | 62:38                |      |

1 Yield of DA adduct after hydrogenation. 2 BHMF dibenzoate as a substrate. N.d.—not determined.

Information about the regio- and diastereoselectivity of functional FF derivatives with acyclic alkenes is scarce. A mixture of regio- and diastereoisomers with approximately equal distribution was detected after the noncatalytic reaction of FA with acrylonitrile (Table 4, entry 14). A mixture of regio- and diastereomers with ortho (endo/exo)/meta (endo/exo) 2:1/8:6 ratio was formed from itaconic anhydride reacting with FA acetate (Scheme 5) [85]. However, unfavorable thermodynamic parameters of cycloaddition with this dienophile were overcome using FA as a substrate, where proximal (ortho) DA adducts undergo further intramolecular cyclization, shifting the reaction equilibrium towards metastable lactone 5, which was isolated in 94% yield (Scheme 5) [85].

![Scheme 5](image)

**Scheme 5.** Diels—Alder reactions of FA and FA acetate with itaconic anhydride.

Overall, the diastereoselectivity of DA reactions of alkenes with FF derivatives containing donor substituents at the C2 position is not always predictable, because it strongly depends on the structure of both the diene and dienophile. More predictable diastereoselective construction of functionalized oxabicyclic structures may be performed using HMF-derived 2,5-disubstituted furans that predominantly react with cyclic alkenes with high endoselectivity (Table 4, entries 1–2; Table 5, entry 24) [33,43,106,108].
Examples of DA reactions of furfural derivatives containing acceptor-type substituents with alkenes are rare. After the reaction of 2-furoic acid with β-alanine-substituted maleimide, only a small amount of one isomer was detected at 40 °C after 128 h [26]. Interestingly, a very low equilibrium constant for this reaction was observed in DMF media, while the equilibrium constant in water was at least two orders of magnitude greater. This difference was explained by the statement that water has a significant effect on the entropy of the reaction. The model reaction of methyl furoate with 1,6-bis(N-maleimido)hexane was investigated by NMR. Only approximately 20% conversion was detected after 4 days at 70 °C in a DMSO-d6 medium [35]. However, despite the low reactivity of furans with acceptor substituents, dynamic materials containing furanic ester-[35] or oxime-[114] functionalized polymers and maleimide functionalities showed moderate self-healing efficiency based on the DA reaction.

Bruijnincx and coworkers reported a new strategy for the direct introduction of furans containing aldehyde groups into DA cycloaddition [34]. Reactions of furanic aldehydes with water-soluble maleimides at 60 °C in a water medium led to the formation of DA adducts with good selectivity (Table 7). In the case of furfural, good exoselectivity of cycloaddition was achieved, while for some HMF derivatives, endoselectivity was preferable. In-water formation of the DA adduct was also detected for 2-acetylfuran, which reacts with N-methylmaleimide with the formation of only the exoadduct (entry 9). DFT calculations showed that the formation of furan/maleimide DA adducts through hydration of the aldehyde group is thermodynamically possible if hydration occurs both prior to (which increases the rate of the forward DA reaction) or after the cyclization step (which decreases the rate of the retro-DA reaction) [34].
Table 7. Direct DA reaction of furanic aldehydes with maleimides in water medium.

| №  | Furanic Substrate | R¹  | Products, Selectivity ¹ |
|----|------------------|-----|------------------------|
| 1  | R = H            | Me  | 6a (endo/exo 18:40), 7a (endo/exo 1:3) |
| 2  | R = H            | H   | 6b (endo/exo 8:30), 7b (endo/exo 0:6) |
| 3  | R = H            | Et  | 6c (endo/exo 8:28), 7c (endo/exo 1:6) |
| 4  | R = H            | ³Pr | 6d (endo/exo 1:7), 7d (endo/exo 1:11) |
| 5  | R = H            | Ph  | 6e (endo/exo 0:1), 7e (endo/exo 1:5)  |
| 6  | R = Me           | Me  | 6f (endo/exo 3:8), 7f (endo/exo 0:3)  |
| 7  | R = CH₂OH        | Me  | 6g (endo/exo 37:13), 7g (endo/exo 0:0) |
| 8  | R = CH₂OMe       | Me  | 6h (endo/exo 7:5), 7h (endo/exo 3:3)  |
| 9  | 2-Acetylfuran    | Me  | 7i (endo/exo traces:32)              |

Reaction conditions: H₂O, 60 °C, 16 h. ¹ Determined by ¹H NMR (data were obtained from reference [34]).

3. Regioselectivity in the Synthesis of Aromatics Using the IMDA Reaction of Furfural Derivatives with Alkenes

The dehydration of furan/alkene adducts is an important sustainable approach to accessing renewable aromatic chemicals (Scheme 6) [7,30,37,115–117]. Utilization of HMF-derived C6 renewable furans (especially 2,5-dimethylfuran or 2,5-furandicarboxylic acid) provides access to para-substituted aromatics (as a route towards “green” polymers) and various polysubstituted aromatic products (Scheme 6) [116]. The presence of only one substituent in furfural increases the diversity of possible aromatic products to ortho- and meta-xylene derivatives as well as various 1,2,3-trisubstituted compounds (Scheme 6).
following the DA reaction stage. The tandem Diels-Alder cycloaddition/dehydration reaction of 2-MF with ethylene is an important approach to renewable toluene (Table 8). This type of DA cycloaddition is thermodynamically difficult and therefore requires the use of a catalyst, high temperature and pressure. Heterogeneous Brønsted-acidic catalysts, mainly zeolites or MOFs, are beneficial for these reactions [118]. Significant problems include side reactions such as the formation of furanic dimers (benzofurans), larger oligomers, products of furan hydrolysis and other reactions [115,118–120]. The introduction of acrylic acid instead of ethylene in reactions with 2-MF over zeolites or using ionic liquid catalysts showed good efficiency in the formation of aromatics [121]. Fast pyrolysis of a mixture of 2-MF and propylene using various zeolites under continuous flow conditions gives a mixture of monocyclic and polycyclic aromatic hydrocarbons with low selectivity [122].

Table 8. Synthesis of toluene by DA reaction of 2-MF with alkenes.

| №  | R      | Conditions                      | Products Yield (%) | [Ref.] |
|----|--------|---------------------------------|--------------------|--------|
| 1  | H      | H-BEA zeolite, heptane, 62 bar, 250 °C | Toluene (46%), [119] |
| 2  | H      | H-Beta-22 zeolite, 300 °C, 20 h  | Toluene (50%), [123] |
| 3  | COOH   | Bi-BTC, 160 °C, 24 h             | Toluene (65%), 2-methyl benzoic acid (23%), [121] |
| 4  | COOH   | [Emim]NTf2, Sc(OTf)3, 15 °C, 0.5 h | Toluene (12%), 2-methyl benzoic acid (2%), 3-methyl benzoic acid (9%), [124] |
| 5  | COOH   | [BSO3HIm]HSO4, 100 °C, 2h       | Toluene (12%), 2-methyl benzoic acid (30%), 3-methyl benzoic acid (3%), [125] |

Furfural dimethyl hydrazone reacts with active dienophiles such as maleic anhydride or maleimides, yielding corresponding arene derivatives through noncatalytic in situ DA cycloaddition followed by spontaneous dehydration (Table 9) [126–128]. One-pot synthesis of arenes starting from furfural using a hydrazine strategy was carried out with good yields in water (entries 7–11) [129].

Table 9. Preparation of phthalimides from furfural using a hydrazine strategy.

| №  | Substrates                                      | Conditions             | Yield of Aromatic Product, [%] | [Ref.] |
|----|-------------------------------------------------|------------------------|--------------------------------|--------|
| 5  | 2-Furaldehyde dimethylhydrazone, maleic anhydride | CHCl3, RT              | 94, [126]                      |
| 6  | 2-Furaldehyde dimethylhydrazone, N-Et-maleimide | CHCl3, RT              | 90, [126]                      |
| 7  | 2-Furaldehyde, N,N-dimethylhydrazone, N-Et-maleimide | H2O2, 50 °C            | 97, [129]                      |
| 8  | 2-Furaldehyde, N,N-dimethylhydrazone, maleimide  | H2O2, 50 °C            | 86, [129]                      |
| 9  | 2-Furaldehyde, N,N-dimethylhydrazone, N-cyclopropylmaleimide | H2O2, 50 °C | 80, [129]                      |
| 10 | 2-Furaldehyde, N,N-dimethylhydrazone, N-Ph-maleimide | H2O2, 50 °C            | 73, [129]                      |
| 11 | 2-Furaldehyde, N,N-dimethylhydrazone, N-(4-Methylbenzyl)maleimide | H2O2, 50 °C | 68, [129]                      |

Acid-catalyzed dehydration of furan-derived oxanorbornenes to aromatic products requires strong reaction conditions and therefore may be used only for a narrow range...
of substrates. Renewable 3-methylphthalic anhydride (MPA) was obtained using acid-catalyzed dehydration of the corresponding 2-MF-derived DA adduct 8 with only 48% maximum yield (Scheme 7) [130]. An important problem in this synthetic approach is the facile retro-DA reaction, which is forced to carry out these transformations at industrially non-practical temperatures (−30 °C and lower) [124,125]. A novel approach to MPA synthesis that overcomes the problem of the rDA reaction is the introduction of oxanorbornane 9 (which is unable to recycle) instead of 8 into the aromatization stage (Scheme 7) [67,131,132]. Aromatization of 9 by solid acid catalysts led to MPA with 67% maximum yield. Some important byproducts, such as 2-methyl benzoic acid and 3-methyl benzoic acid, were also formed during this reaction, and their ratio depended on the catalyst used [67,131]. Higher selectivity of aromatization was achieved by oxidative dehydrogenation of 9 into phthalate 10 using a silicomolybdic acid catalyst in diethyl carbonate (Scheme 7) [132].

Scheme 7. Synthesis of arenes by aromatization of 2-MF-derived tricycles.

The deprotonation of DA adducts formed from 2-(furan-2-yl)-1,3-dioxolane and acrylonitrile by CH₃ONa/DMSO superbase affords aromatic products at 30 °C with high total yield and a good ortho/meta ratio (Table 10, entries 1, 2) [31]. The study of kinetic features of the aromatization stage showed that the meta-adduct is more reactive than the ortho-isomer, which made it possible to isolate pure meta-adducts from the reaction mixture at 50% conversion, with subsequent regeneration of the ortho-isomer. Aromatization of DA adducts by tBuONa/DMSO superbase was also efficient for 2-MF and methyl group-protected FA but showed a low yield of aromatics in the case of unprotected FA (Table 10, entries 3–5) [31].

Table 10. Preparation of aromatics by base-catalyzed dehydration of acrylonitrile-derived oxanorbornenes.

| No | Oxanorbornene       | Yield of DA Adducts | Yield of Aromatic Products |
|----|---------------------|---------------------|---------------------------|
| 1  | R = dioxolane acetal | 76 (ortho/meta ~1:1) | 84 (ortho/meta ~1:1.5)  |
| 2  | R = dioxolane acetal | 76 (ortho/meta ~1:1) | 86 (ortho/meta ~1:1.8)  |
| 3  | R = Me              | 53 (ortho), 13 (meta) | 97 (ortho), 62 (meta)   |
| 4  | R = CH₂OEt          | 36 (ortho), 18 (meta) | 94 (ortho), 100 (meta) |
| 5  | R = CH₂OH           | 47 (ortho), 26 (meta) | 21 (ortho), 42 (meta)  |

1 Data were obtained from reference [31]. 2 After 120 h of the reaction. 3 CH₃ONa as a base. 4 Relative to the corresponding ortho- or meta-DA cycloadduct.

Recently, a new dynamic kinetic trapping strategy was developed for the construction of “drop-in” phthalide systems using tandem IMDA/lactonization and then aromatization reactions (Scheme 8) [37]. The first stage of this process is the reversible formation of
unstable adducts (mixture of regio- and stereoisomers) of FA (11a–c) or BAMF (14) with acrylates substituted by EWGs (HFIP, TFE or 4NP) at an oxygen atom. The role of EWG in the dienophile was the activation of both double bonds for the IMDA reaction and the carbonyl group towards diastereoselective intramolecular cyclization and into a more thermodynamically stable exo-lactone (the next step). The last aromatization stage was performed using an Ac₂O/strong acid mixture yielding phthalides 13 or 16 with maximum 98% and 60% yields, respectively.

Scheme 8. Synthesis of phthalides from furanic alcohols using a dynamic kinetic trapping strategy. HFIP = 1,1,1,3,3,3-hexafluoroisopropyl. TFE = 2,2,2-trifluoroethyl. 4NP = 4-nitrophenyl.

4. Conclusions

The IMDA reactions of biobased furans with alkene dienophiles are an important strategy for accessing practically important products, such as fundamental building blocks, fine chemicals, biologically active compounds or various organic and hybrid dynamic systems. Based on the literature highlighted in this review, we can assume that the problem of low regio- and stereoselectivity, which significantly reduces the synthetic potential of furan/alkene DA cycloaddition in fine organic synthesis and materials development, is still not solved for many functional furfural derivatives and alkene substrates. The reactivity of furfural-derived acceptor furans towards common alkenes, as well as the synthesis and aromatization of DA adducts of functional furfural derivatives with acyclic alkenes, are very poorly represented in the current literature. However, these types of reactions are important sustainable approaches towards functional aliphatic or aromatic products and therefore require further scientific investigations.

Rapid progress in this area can be anticipated, taking into account emerging trends in sustainable development towards the incorporation of bioderived chemicals and materials into the chemical industry. The focus of this review clearly shows that selectivity issues are far from solved and do not match current requirements. More studies are needed to develop practical and easy-to-use procedures to achieve high selectivity in reactions involving simple bioderived furanic starting materials.

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Abbreviations

2-MF  2-methylfuran
Ac    acetate
BAMF 2,5-bis(acetoxymethyl)furan
BHMF 2,5-bis(hydroxymethyl)furan
BMI   4,4′-bis(maleimido)diphenylmethane
BOC   tert-butyloxycarbonyl
Bn    benzyl
Bz    benzoyl
DA    Diels–Alder
DFT   density functional theory
DMF   dimethylformamide
DMSO  dimethyl sulfoxide
Emim  1-ethyl-3-methylimidazolium
EWG   electron-withdrawing group
FAM   furfuryl amine
FF    furfural
HMF   5-(hydroxymethyl)furfural
HOMO  highest occupied molecular orbital
IMDA  intermolecular Diels–Alder
LUMO  lowest unoccupied molecular orbital
MOF   metal organic framework
MPA   3-methylphthalic anhydride
N.d.  not determined
NMR   nuclear magnetic resonance
PEG   polyethylene glycol
rDA   retro-Diels–Alder
RT    room temperature
Tf    triflate
TFA   trifluoroacetic acid
THF   tetrahydrofuran

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