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Perspective

# Biobased $C_6$-Furans in Organic Synthesis and Industry: Cycloaddition Chemistry as a Key Approach to Aromatic Building Blocks

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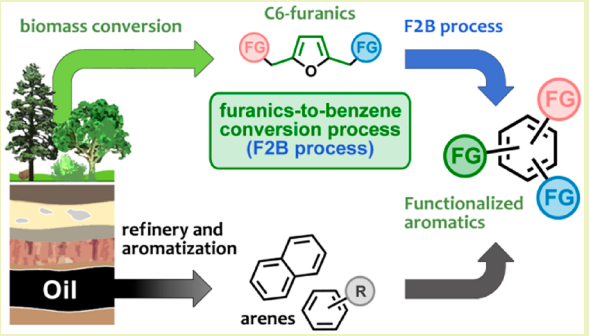
**ABSTRACT:** Rapid development in the area of cellulose biomass conversion to furanic platform chemicals has led to expectations of their valuable practical use. Impressive research progress in this direction has resulted in several achievements but at the same time identified a key challenge—the necessity to produce aromatic compounds. In this perspective, we analyze the current stage of development of the furanics-to-benzene conversion process (F2B process) in connection with a bioderived route to aromatic compounds. Cycloaddition reactions between bioderived $C_6$-furans as diene components and alkene/alkyne units are discussed in detail, followed by considering the subsequent aromatization reaction. Progress in the development of the F2B process and future challenges are outlined in this perspective. The key role of the F2B process in the overall biomass to aromatics transformation is discussed in view of the implementation of carbon neutral sustainable technologies in practice.




**KEYWORDS:** *Biomass, F2B process, Bioderived chemicals, Furan derivatives, Benzene, Aromatic compounds, Sustainable development, Carbon-neutral industry*

## INTRODUCTION

The importance of a number of aromatic compounds for a broad scope of processes in the chemical industry can hardly be overestimated. Since the very beginning of the history of industrial chemistry, aromatic compounds have played a crucial role in the production of chemicals of general demand (Figure 1). From this historical period and until now, fossil carbon sources (oil, coal, gas) have remained the predominant starting materials for the synthesis of aromatic compounds (Figure 1B). Chemical processing of fossil resources produces aromatic compounds, which are subsequently used in a large number of key technologies, for example, to access various solvents, materials, fuels, dyes, explosives, plastics, agrochemicals, and drugs, among many others.[1] To highlight the scale, the annual production of aromatic compounds is approximately 122 million tons (in 2017, which corresponds to a $191.8 billion market with an estimated CAGR of 6.7% for the period 2017−2022).[2] BTX aromatics (benzene, toluene, and xylene isomers) are among the most important industrially produced products, where the particular importance of para-xylene (PX) was mentioned.[3] Indeed, the usage of aromatic compounds is deeply integrated into the manufacturing of vital goods, making these compounds indispensable for modern society.

At the same time, in the new global economy, the implementation of sustainable development has become an essential challenge facing modern science and technology.[4−16] From this point of view, renewable plant biomass appears to be the most promising source of organic carbon for the chemical industry in the future.[17−23] Considering the available sources of renewable aromatics, lignin appears to be a promising choice. Being a complex polymer based on phenolic units, lignin could serve as an alternative source of bioderived aromatics. Indeed, lignin finds its application in the production of materials, adhesives, and fuels.[24−26] However, due to irregularities of the lignin structure, selective transformation into individual products is significantly hampered.[27]

Conversion of carbohydrates into furan derivatives[28−38] is considered a rational approach among existing routes of biomass processing to access $C_6$ chemical building blocks. In the first step of the overall sequence to benzene derivatives (Figure 1A), the biobased approach involves the conversion of cellulose biomass into $C_6$-furanic platform chemicals, such as 5-(hydroxymethyl)furfural

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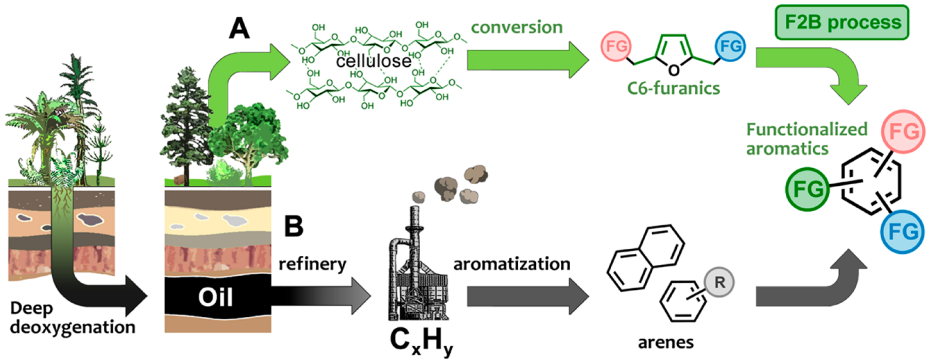
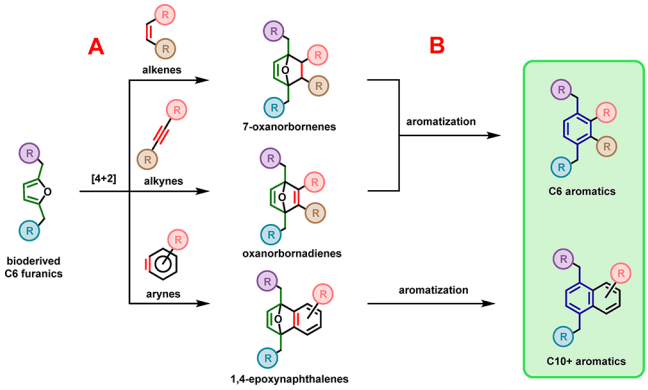



**Figure 1.** Plant biomass-based renewable aromatic compounds (A) and fossil resource-based nonrenewable aromatic compounds (B) and routes to aromatic compounds, with the key F2B process highlighted.

**Scheme 1. Two-Step Pathway from $C_6$-Furanics toward Highly Functionalized Aromatic Derivatives through [4 + 2] Cycloaddition (A) and Subsequent Catalytic Aromatization of Diels–Alder Adducts (B)**




(5-HMF), furan-2,5-dicarboxylic acid (FDCA), 2,5-diformylfuran (DFF), and 5-(chloromethyl)furfural (CMF). This step has been thoroughly studied and is currently a well-developed process with a number of different catalytic systems available from research to industrial scales.[28−49] Sometimes furanic compounds can serve as suitable aromatic units for incorporation into materials (e.g., furan-2,5-dicarboxylic acid vs terephthalic acid in the synthesis of polyesters)[50−55] or biologically active compounds.[56−60] However, in the majority of cases, it is the benzene ring that should be present in the structure of the compound of interest. Indeed, transformation of furanic compounds into benzene derivatives is a cornerstone of sustainable synthesis of functionalized aromatics.[32]

The unquestionable importance of furanics-to-benzene conversion (F2B process) brings a cutting edge emerging trend into the biomass refinery area, which is strongly coupled with organic chemistry studies of cycloaddition/aromatization reactions, as well as with the development of corresponding catalytic implementations. The present perspective is intended to provide a survey of state-of-the-art developments in the field of aromatization of biobased $C_6$-furanics via cycloaddition reactions (Figure 1A). Here, we cover most representative studies published since 1961. It should be noted that the basic cycloaddition chemistry of different five-membered heterocycles, including furans, has been previously reviewed.[61−69] We do not repeat the aforementioned reviewing. Rather, we focus on bioderived $C_6$-furanic building blocks. It has been demonstrated that the reactivity of substituted furans strongly depends on the nature of substituents at the C2 and C5 positions; thus, the reactivity of several

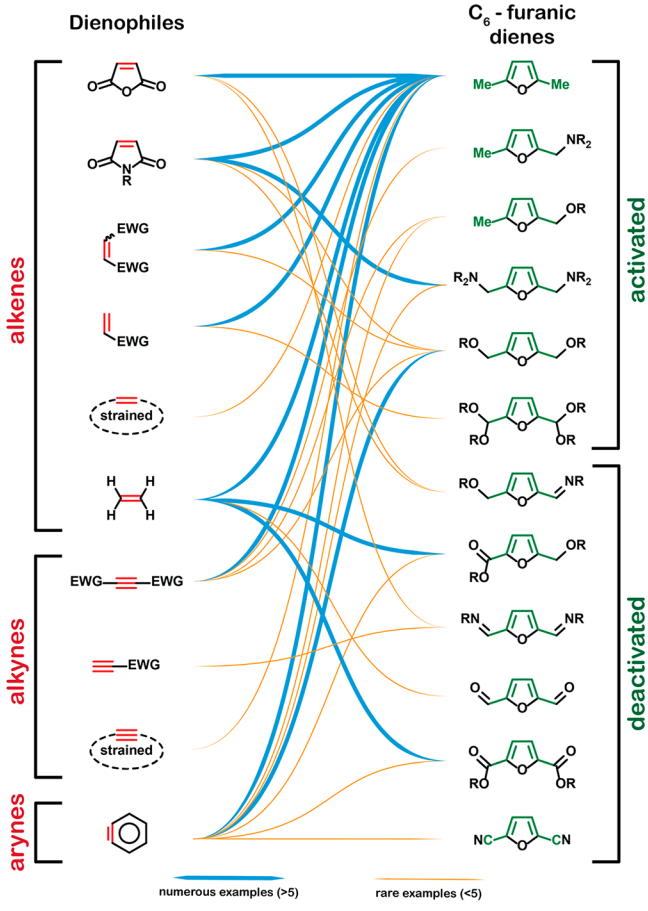



**Figure 2.** Reactivity map for the Diels–Alder reaction with $C_6$-funaric dienes.

bioderivatives with functional groups strongly differs from the commonly accepted behavior of nonfunctionalized furans.[70−73] For example, even the appearance of a single −CHO group at the C2 position completely hampers cycloaddition under regular conditions. Controlling the reactivity and achieving high efficiency in the F2B process are the major challenges with paramount importance for the implementation of carbon neutral sustainable technologies in the chemical industry.

## FURANICS-TO-BENZENE CONVERSION (F2B PROCESS)

The most straightforward way to convert furans into benzenes is the Diels–Alder reaction with subsequent aromatization of the


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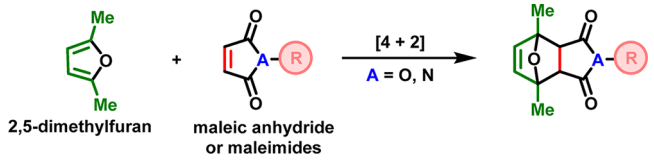
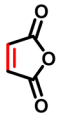
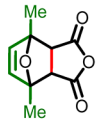
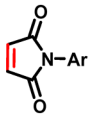
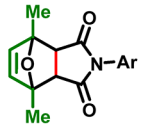
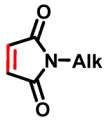
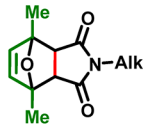
**Table 1. Cycloaddition Reactions of 2,5-Dimethylfuran with Maleic Anhydride and Maleimides**




| Entry | Alkene | Conditions | Diels-Alder adduct | endo / exo | Yield (%) | DA-adduct was used for aromatization[a] | Ref. |
|---|---|---|---|---|---|---|---|
| 1 |  | neat, 22°C, 16 h |  | >1/99 | N/A[b] | ✗ | 74 |
| 2 | | $Et_2O$, 22°C | | N/A[c] | 96 | ✓ | 75 |
| 3 | | $Et_2O$, r.t., 66 h | | N/A[c] | 76 | ✓ | 76 |
| 4 | | neat, 10°C, 3 h | | >1/99 | N/A[b] | ✓ | 77 |
| 5 | | neat, r.t., 3 h | | N/A[c] | 96 | ✓ | 78 |
| 6 | | $Et_2O$, 25°C, 2.5 h | | N/A[c] | 83 | ✓ | 79 |
| 7 | | THF, r.t., 21 h | | >1/99 | N/A[a] | ✗ | 80 |
| 8 |  | neat, 60°C, 3 h |  | >1/99 | 30-94 | ✗ | 81-83 |
| 9 | | 94°C, 1 h or MW, 140°C, 5 min | | 5/95 | 25-60 | ✗ | 84 |
| 10 | | **Ar = Ph** water, 0.6 h, r.t. | | 1.3/1 | quant. | ✗ | 85 |
| 11 | | **Ar = p-Tolyl** PhMe, 60°C, 3 h | | >1/99 | 50 | ✓ | 86 |
| 12 | | **Ar = p-Tolyl** $Et_2O$, r.t., 72 h | | 4/1 | N/A[c] | ✓ | 86 |
| 13 |  | **Alk = -$CH_2CH_2OH$** DCM, 16 h, r.t. |  | 78/22 | quant. | ✗ | 87-88 |
| 14 | | **Alk = -$CH_2CH_2OH$** MeCN, 60°C, 6 h | | 22/78 | quant. | ✗ | 87-88 |
| 15 | | **Alk = -Et** water, r.t., 2.5 h | | 3/2 | quant. | ✗ | 85 |
| 16 | | **Alk = -*t*Bu** water, r.t., 51 h | | 1/8 | 61 | ✗ | 85 |

[a]In this table and in other tables throughout this perspective, the green mark indicates that the corresponding aromatization process was studied; the red mark indicates that the corresponding process was not studied (it does not mean that the reaction does not take place). [b]The crude reaction product was isolated and used in the next step without purification. [c]Data were not provided.

obtained cycloadducts (Scheme 1). This approach allows the preparation of functionalized aromatic compounds with a high degree of atom economy. At first formation of a six-membered ring via Diels–Alder cycloaddition is described. Reactions are classified by the type of dienophile and substitution pattern in the furanic diene. Then, aromatization of the obtained cycloadducts is described. Reactions in this section are classified by the degree of unsaturation of the starting material. Reactions leading to benzene derivatives and condensed polyaromatic systems are discussed separately. Examples of one-pot transformations of furanics into benzene derivatives via cycloaddition/aromatization are summarized in a separate section. A gold-catalyzed alternative to Diels–Alder chemistry for the conversion of furans to benzenes is briefly described in the last section.

The idea of the this perspective was to keep the descriptions concise and brief; thus, we avoid lengthy discussions. In the this perspective, we provide an analytic description of the available data in the form of comparable tables. Tabulated data simplify the comparison and analysis of the synthetic pathways, which are summarized in the Conclusions and Perspectives and mapped in Figure 2.

## DIELS–ALDER REACTION WITH $C_6$-FURANICS

Five-membered aromatic heterocycles are known 4$\pi$ diene components for the Diels–Alder reaction despite their aromaticity, while furans are most reactive among them. Since furan is an electron-rich diene, only normal electron demand [4 + 2] cycloadditions can be performed utilizing such substrates. There are distinct differences with respect to yields, reaction times, experimental conditions, and stereoselectivities, depending on the substitution pattern on the furan ring and the nature of the dienophile.[73] Substituents in positions 2 and 5 of the furan ring are mandatory for hexose-derived furanics, and therefore, only this type of furans is discussed. It is important to note that these substituents create steric hindrance for the approach of dienophiles, making the described furans less reactive than their 2,5-unsubstituted analogues. However, the presence of substituents allows excellent stereoselectivity in the course of cycloaddition.

## [4 + 2] REACTIONS OF $C_6$-FURANICS WITH ALKENES

Activated alkenes bearing electron-withdrawing groups are well-known dienophiles in the classical Diels–Alder reaction. The reactivity of dienophiles can be increased by the addition of Lewis acids, which decrease the energy of dienophile LUMO. In addition, alkenes with strained double bonds are reactive enough to undergo cycloaddition with 2,5-disubstituted furans. Nonactivated double bonds can act as dienophiles only in an intramolecular fashion.

## REACTIONS OF 2,5-DIMETHYLFURAN WITH ALKENES

Among the bioderived $C_6$-furanics, 2,5-dimethylfuran (2,5-DMF) proved to be the most attractive diene. The electron-donating


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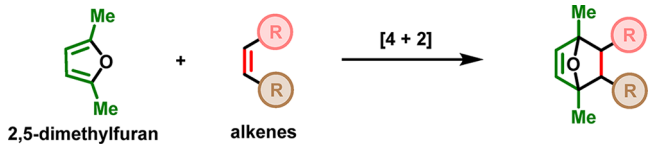
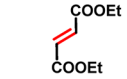
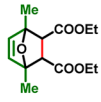
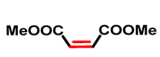
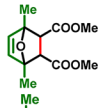
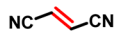
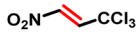
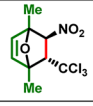
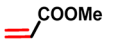
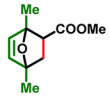
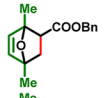
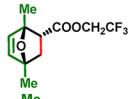
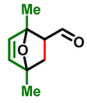
**Table 2. Cycloaddition Reactions of 2,5-Dimethylfuran with Acyclic Alkenes**




| Entry | Alkene | Conditions | Diels-Alder adduct | endo / exo | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|---|
| 1 |  | $HfCl_4$, DCM, -20°C, 10 h |  | — | N/A[a] | × | 74 |
| 2 | | 1.1eq $HfCl_4$, DCM, -20°C, 11 h | | — | 81 | × | 89 |
| 3 | | DCM, -40°C, 24 h, oxazaborolidine-$AlBr_3$ cat. | | — | 72 | × | 90 |
| 4 | | F-oxazaborolidine cat., -40°C, 16 h | | ee 90% | 68 | × | 99 |
| 5 |  | 0.2 eq $HfCl_4$, DCM, -30°C, 11 h |  | >98/2 | 97 | × | 89 |
| 6 |  | MW, 120°C, 45 min, Ti(Si) catalyst | | — | 60 | × | 92 |
| 7 |  | neat, r.t., 21 day |  | 100/0 | 70 | × | 93 |
| 8 |  | neat, r.t., 24 h, Al(Si) catalyst |  | 75/25 | 32[b] | × | 92 |
| 9 | | neat, $ZnI_2$, r.t., 48 h | | — | 45 | × | 78 |
| 10 | | 0.2 eq $HfCl_4$, DCM, -20°C, 16 h |  | 80/20 | 98 | × | 89 |
| 11 | | DCM, -78°C, 12 h, oxazaborolidine-$AlBr_3$ catalyst |  | 90/10 ee 94% | 99 | × | 90-91 |
| 12 | | 0.1mol% $Sc(OTf)_3$ MS 4Å, -60°C, 68.5 h, $CDCl_3$ |  | 6/5 | 84 | ✓ | 94 |
| 13 | | MW, 40°C, 7 min Zn(Si) catalyst, 3 bar Ar | | 48/52 | 80 | × | 92 |

[a]The crude reaction product was isolated and used in the next step without purification. [b]Yield of major isomer.

effect of methyl groups increases the diene HOMO energy, and a relatively small size does not create steric hindrances for cycloaddition. Indeed, numerous examples of Diels−Alder reactions of 2,5-DMF with various dienophiles have been reported.

Maleic anhydride and N-substituted maleimides occupy the leading position in this series as the most convenient substrates for cycloaddition (Table 1). These reactions are characterized by high yield and diastereoselectivity and have no need for a catalyst. The obtained tricyclic adducts serve not only as starting compounds for branched structure synthesis but also as sources for 3,6-dimethyl phthalic acid derivatives (Table 1, entries 2−6, 11, 12).

In the reactions of 2,5-DMF with acyclic alkenes, dienophiles are represented by derivatives of fumaric and acrylic acids (Table 2). In that case, Lewis acid catalysts are essential, and hafnium(IV) chloride has shown the best performance. Moreover, higher endo/exo selectivity could be obtained when a catalytic amount of $HfCl_4$ was employed (Table 2, entries 5, 10).

Particular attention should be given to bulky polycyclic alkenes such as 1,5-dehydroquadricyclane and pentacyclo[4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$]-non-4-ene (Table 3, entries 1, 2). These strained structures could be generated *in situ* from corresponding dihalogen derivatives by reaction with butyllithium. In that case, 2,5-DMF serves as a trap for the forming alkene, resulting in polycyclic adducts.

Photolysis of the 1,2,3-thiadiazole system with a low-pressure mercury lamp produced fused thiirene, which could be trapped by 2,5-DMF, giving a framed thiirane derivative with low yield and high diastereoselectivity (Table 3, entry 3). Considering the extreme reactivity of the generated alkene, 2,5-DMF was used as the reactive medium.



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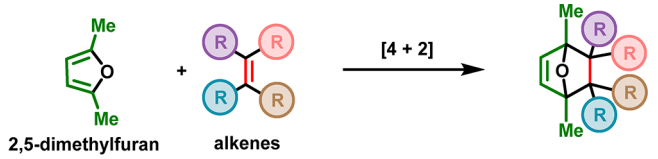
**Table 3. Cycloaddition Reactions of 2,5-Dimethylfuran with *In Situ* Generated Cyclic Alkenes**



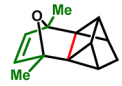
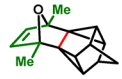
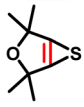
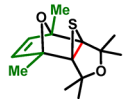
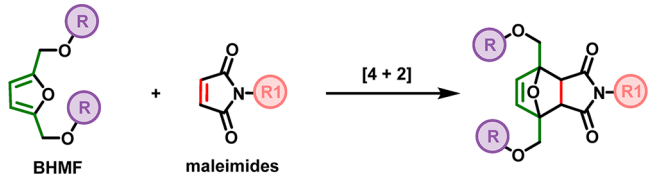
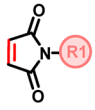
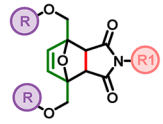

| Entry | Alkene | Conditions | Diels-Alder adduct | endo / exo | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | | THF/pentane, -78°C → r.t. |  | 1/3 | 23 | × | 95 |
| 2 | | $Et_2O$/pentane, -78°C → 0°C |  | — | 22 | × | 96 |
| 3 |  | neat 2,5-DMF, hν |  | >1/99 | 12 | × | 97 |

**Table 4. Cycloaddition Reactions of 2,5-Bishydroxymethylfuran (BHMF) Derivatives with Maleimides**




| Ent. | Alkene | Conditions | Diels-Alder adduct | endo / exo | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | | **R = H, R1 = H** EtOAc, 24°C, 16 h | | >99/1 | 83 | × | 70 |
| 2 | | **R = Et, R1 = H** EtOAc, 24°C, 24 h | | >99/1 | N/A[a] | × | 70 |
| 3 |  | **R = Ac, R1 = H** EtOAc, 24°C, 24 h |  | >99/1 | N/A[a] | × | 70 |
| 4 | | **R = oxiran-2-ylmethyl, R1 = Hex** $CHCl_3$, 30°C, 12 h | | N/A[b] | 96 | × | 101 |
| 5 | | **R = H, R1 = Me** DMSO-$d_6$, 40°C, 20 h | | N/A[b] | 76[c] | × | 98 |
| 6 | | **R = H, R1 = $CH(CH_2OH)_2$** DMSO-$d_6$, 40°C, 20 h | | N/A[b] | 83[c] | × | 98 |

[a]The crude reaction product was used in the next step without purification. [b]Data were not provided. [c]Conversion value adapted from graphical data was provided.

## REACTIONS OF FUNCTIONALIZED 2,5-DISUBSTITUTEDFURANS WITH ALKENES

Preservation of reactive groups in the side chains of $C_6$-furans boosts synthetic diversity. At the same time, electron-withdrawing moieties could notably decrease the reactivity of furanic diene in the Diels–Alder cycloaddition. Among bioderived bis-functional $C_6$-furans, 2,5-bishydroxymethylfuran (BHMF) carries the greatest synthetic potential since its structure contains two hydroxyl groups combined with preservation of the reactivity of the diene.

Indeed, BHMF and its ethers and esters freely enter cycloaddition with maleimides (Table 4). High yields in these chemical transformations clearly indicate that the BHMF core exhibits sufficient reactivity for the [4 + 2] reaction. It is all the more surprising to observe the small number of research papers on this matter, where still the scope of alkenes remains limited to maleimides.

Nevertheless, among the maleimides, there are interesting examples where all functional groups were exploited. Specifically, utilization of bifunctional alkenes makes it possible to obtain dimeric compounds, opening up interesting opportunities in structure design (Scheme 2).[98] The reversibility of the Diels–Alder reaction was also used for controlled cross-linking of polymer chains in BHMF-based polymers and the creation of healable thermoreversible polyurethane.[99]

Polyamides based on furan-2,5-dicarboxylic acid (FDCA) can be thermally cross-linked via a reaction with bismaleimides.[100]

Bis(N,N-dialkylmethylamine) furanic derivatives demonstrate behavior similar to BHMF and its ethers in the interaction with maleimide (Scheme 3).[70] However, due to the reversible nature of cycloaddition, oxanorbornene intermediates were not isolated in their individual form. Following the reduction of double bond leads to corresponding oxanorbonanes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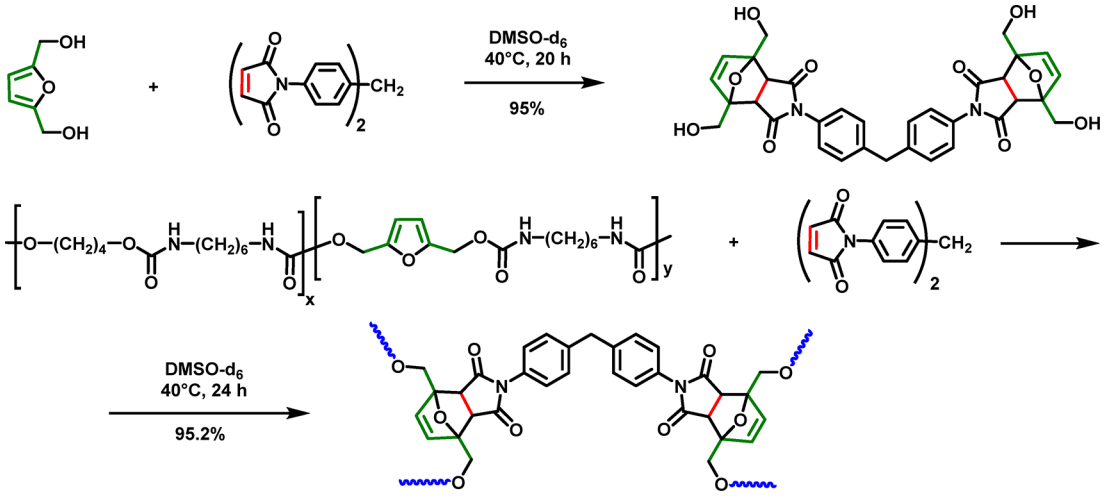
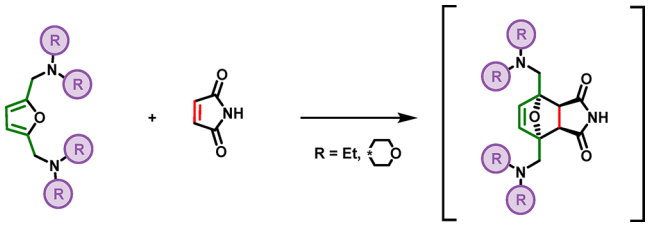
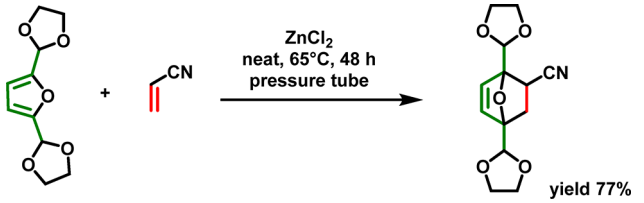
**Scheme 2. Usage of Diels–Alder Reaction for Cross-Linking in BHMF-Based Polymer**[a]




**Scheme 3. Reactions of Tertiary Amine Furanic Derivatives with Maleimide**




**Scheme 4. Reaction of 2,5-Di(1,3-ioxolan-2-yl)furan with Acrylonitrile**




which indicates that the Diels–Alder reaction has taken place.

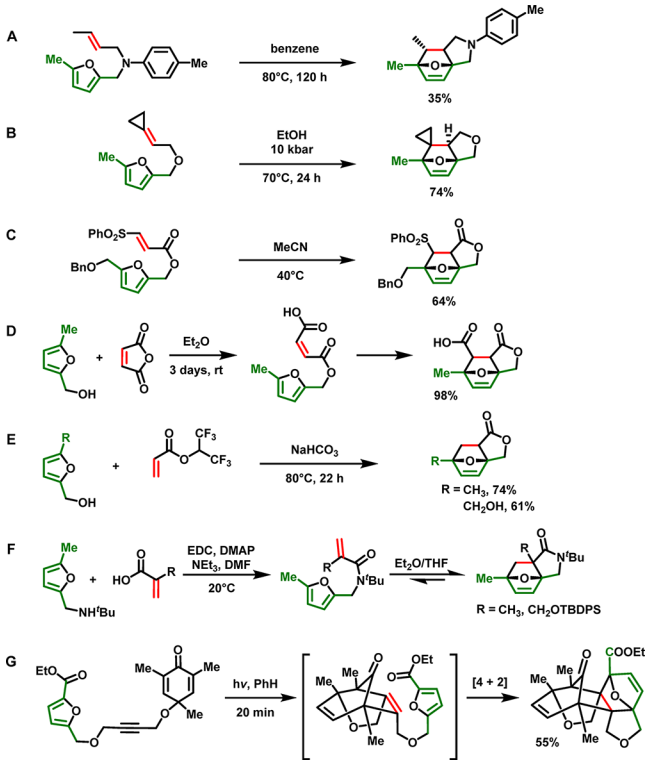
The approach to the benzene derivatives was patented starting from furanic diacetal and utilizing acrylonitrile as dienophile (Scheme 4). The Diels–Alder product was obtained as a mixture of endo/exo isomers with good yield and was further was used for aromatization.[102]

## INTRAMOLECULAR CYCLOADDITION OF $C_6$-FURANICS WITH ALKENES

In the presence of an alkene moiety in the side chain and a sufficient spacer length, the furanic core could undergo intramolecular [4 + 2] cycloaddition. This approach leads to polycyclic compounds with controlled stereochemistry.

During reflux in benzene over 5 days, the 2-aminomethyl-5-methylfuran derivative with the but-2-ene fragment undergoes intramolecular cyclization with a moderate yield of 35% of the corresponding epoxyisoindoline (Scheme 5A).[103] In the case of a more sterically loaded terminal cyclopropane fragment, a similar reaction proceeds with greater difficulty and requires increased pressure (Scheme 5B).[104] Introduction of the (phenylsulfonyl)-acrylate moiety to the side chain of the monobenzylated BHMF

**Scheme 5. Intramolecular [4 + 2] Cycloaddition Reactions Involving the $C_6$-Furanic Core**




derivative results in intramolecular cycloaddition with good yield (Scheme 5C).[105] It was shown that during the interaction of 2-(hydroxymethyl)-5-methylfuran with maleic anhydride, ester formation occurs before [4 + 2] cycloaddition (Scheme 5D).[106] Hexafluoroisopropyl acrylate as a dienophile reacts with 5-methylfurfuryl alcohol and 2,5-bishydroxymethylfuran in a similar manner (Scheme 5E).[107,108]

The N-acryloyl derivative of aminomethylfurans reversibly undergoes an intramolecular Diels–Alder reaction (Scheme 5F). The obtained mixture of stereoisomeric cycloadducts was introduced in a parallel kinetic resolution via asymmetric hydroboration.[109]

The $C_6$-furanic core can serve as a trap for the *in situ*-formed reactive double bonds. Specifically, alkynol ether substrates tethered with furanyl ether undergo photoinduced cyclization,


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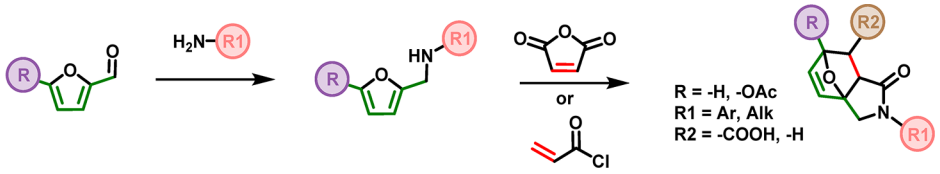
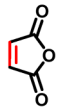
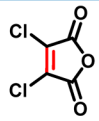
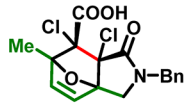
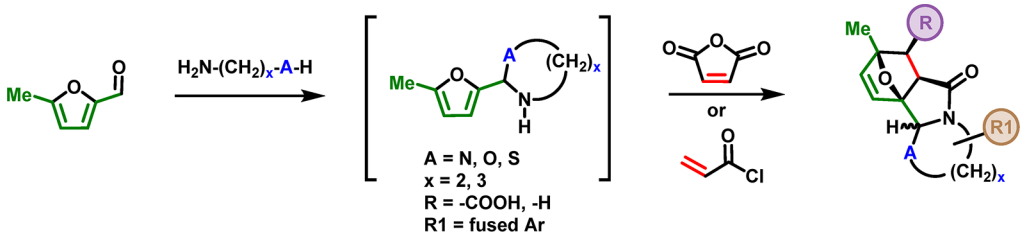
**Table 5. Tricyclic Compounds Derived from 5-Methylfurfural and HMF**

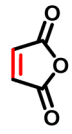
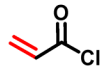



| Entry | Alkene | Conditions | Diels-Alder adduct | endo / exo | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | | PhH, r.t., 48 h | R = Me, R1 = Ph, R2 = -COOH | >1/99 | 85 | ✗ | 111 |
| 2 | | PhH, r.t., 48 h | R = Me, R1 = Bn, R2 = -COOH | >1/99 | 89 | ✗ | 111 |
| 3 |  | Py/DMF, r.t., 24 h | R = $CH_2H_2NC(O)(CH_2)_2COO$- R1 = Cy, R2 = -COOH | N/A[a] | 45 | ✗ | 112 |
| 4 | | Py/DMF, r.t., 24 h | R = $CH_2H_2NC(O)(CH_2)_2COO$- R1 = Bn, R2 = -COOH | N/A[a] | 40 | ✗ | 112 |
| 5 | | PhH, r.t. | **A:** R = Me, R1 = furfuryl, R2 = COOH **B:** R = H, R1 = 5-Me-furfuryl R2 = COOH | N/A[a] | 79 A/B 3/7 | ✗ | 113 |
| 6 |  | PhH, 72 h, r.t. |  | N/A[a] | 55 | ✓ | 113 |
| 7 | | PhMe, reflux, 10 h | R = Me, R1 = Ph, R2 = H | >1/99 | 45 | ✓ | 111, 114 |

[a]Data were not provided.

**Table 6. Polycyclic Compounds Derived from 5-Methylfurfural through Sequential Diels–Alder Cycloaddition and Intramolecular Cyclization**




| Ent. | Alkene | Conditions | Diels-Alder adduct | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 |  | DCM, 24 h, 48 h | A = O, x = 3, R = -COOH **3 examples** | 19-58 | 115-116 |
| 2 | | $CHCl_3$, 22°C, 16 h | A = S, x = 2-3, R = -COOH **3 examples** | 33-48 | 115-116 |
| 3 | | PhMe, Δ, 2 h | A = N, x = 3, R = -COOH **5 examples** | 39-95 | 116-117 |
| 4 |  | PhMe, TEA, Δ, 2 h | A = O, x = 3, R = H | 20 | 115-116 |
| 5 | | PhMe, TEA, Δ, 30 h | A = S, x = 2, R = H | 57 | 115-116 |
| 6 | | PhMe, TEA, Δ, 2-4 h | A = N, x = 3, R = H **2 examples** | 38-48 | 117 |

producing framed structures with reactive alkene moieties that further engage in [4 + 2] reactions (Scheme 5G).[110]

A much more appealing synthetic protocol was composed of two successive steps performed under one-pot conditions: [4 + 2] cycloaddition and amidation of the secondary amine moiety. The 2-methyl-5-(aminomethyl) derivative obtained from 5-methylfurfural reacts with acryloyl chloride through sequential acylation followed by intramolecular Diels–Alder cycloaddition (Table 5, entry 7). In the case of the reaction of the 2-(hydroxymethyl)-5-(aminomethyl)furan scaffold with maleic anhydride, the tricyclic structure assembled in the reverse order (Table 5, entries 1–5).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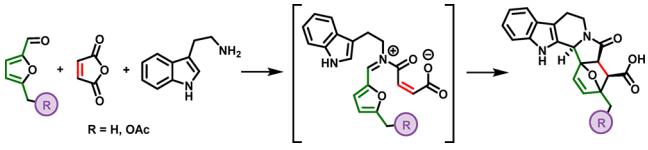
**Scheme 6. N-Acyliminium/Pictet−Spengler/Diels−Alder Sequential Reaction**




**Scheme 7. Four-Component Tandem Ugi/Intramolecular Diels−Alder Reactions**

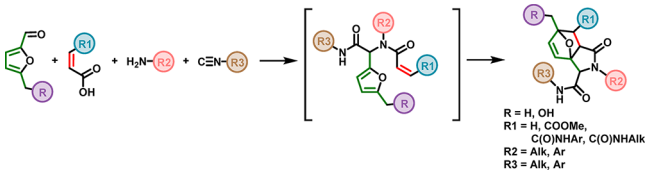
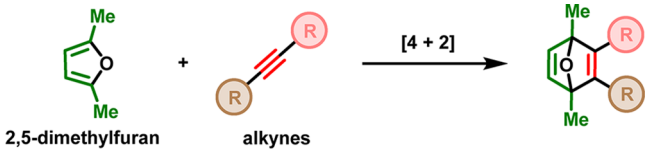
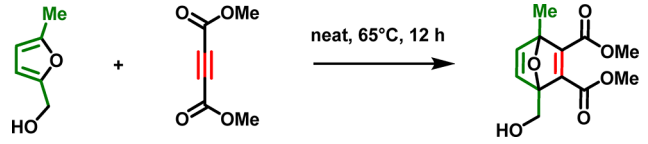



**Table 7. Cycloaddition Reactions of 2,5-Dimethylfuran with Alkynes**




**Scheme 8. Reaction of 2-Hydroxymethyl-5-Methylfuran with Dimethyl Acetylenedicarboxylate**




Employing this strategy, even more complex structures can be acquired starting from 2-furyl-1,3-oxazinanes, 1,3-oxazolidine, and 1,3-thiazolidines (Table 6). Performing the condensation−acylation−cycloaddition sequence in a one-pot procedure yields 8,10a-epoxy[1,3]oxazino[2,3-*a*]isoindole-7-carboxylic acids, while epoxy[1,3]thiazolo[2,3-*a*]isoindoles form as individual diastereomers.

Overall, tandem reactions with functionalized $C_6$-furans are powerful tools for the rapid construction of molecules where Diels−Alder cycloaddition could take different places in the general sequence of transformations. A triple N-acyliminium/Pictet−Spengler/Diels−Alder reaction was reported, starting from 5-methylfurfural or 5-acetoxymethyl-2-furaldehyde and resulted in an extremely complex polycyclic structure (Scheme 6, R = H, OAc, two examples, yields 76%−80%).[118]

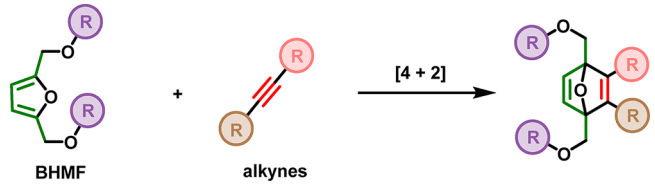
In tandem reactions, [4 + 2] cycloaddition could occur at the final stage of a multistep process. The Ugi reaction followed by intramolecular Diels−Alder addition could serve as an example of such a transformation (Scheme 7). Usage of 5-methylfurfural, alkylamine, benzyl isocyanide, and activated dienophile acid led to a number of corresponding cycloaddition products as a mixture of diastereoisomers. Furthermore, the method was improved by introduction of resin-bound amine (Scheme 6, R = H, six examples, yields 72%−95%).[119]

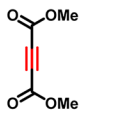
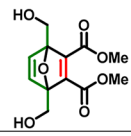
This approach was successfully implemented in another work also using 5-methylfurfural, alkyl/aryl amines, an isonitrile, and maleic acid monoamides. All products were obtained in a diastereomerically pure exo form after recrystallization (Scheme 7, R = H, seven examples, yields 68%−92%).[120] Utilization of acrylic acid as dienophile and 5-methylfurfural as diene produced a corresponding tricycle (Scheme 7, R1 = H, R2 = 4-(MeO)-$C_6H_4CH_2$, R3 = *t*-Bu, yield 44%).[121]

The presence of a hydroxyl group in the side chain does not affect the tandem Ugi/Diels−Alder reaction. That way usage of 5-HMF as the starting aldehyde gives rise to corresponding tricyclic compounds with the hydroxymethyl moiety at the bridgehead atom (Scheme 7, R = OH, 23 examples, yields 35%−55%).[122]

Moreover, the hydroxymethyl group in 5-HMF can be utilized as a link with polymers in solid phase synthesis. Thus, a series of parallel UDA reactions were carried out using 5-HMF immobilized with a poly(ethylene glycol) monomethyl ether (MW 5000) as the soluble polymer support. Final cleavage of the products from the platform gave a synthetic library of nearly 100 compounds (Scheme 7, R = OH, 96 examples, yields 41%−99%).[123]

**Table 8. Cycloaddition Reactions of 2,5-Bishydroxymethylfuran (BHMF) and Its Ethers with Alkynes**




| Entry | Alkyne | Conditions | Diels-Alder adduct | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|
| 1 |  | **R = H** Toluene, reflux, 8 h |  | 35 | × | 140 |
| 2 | | **R = Bn** Toluene, reflux, 10 h | | 83 | × | 141 |
| 3 | | **R = H** THF, 100°C, 24 h | | 87 | × | 142 |



https://dx.doi.org/10.1021/acssuschemeng.0c09229
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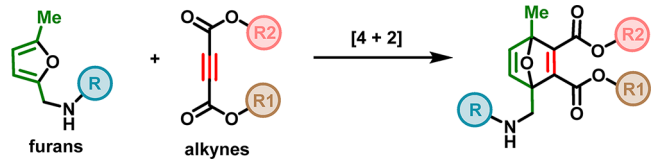
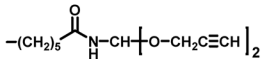
**Table 9. Cycloaddition Reactions of Single Aminomethyl $C_6$-Furanics with Acetylenedicarboxylate Diesters**




| Entry | Substituents | Conditions | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|
| 1 | **R = dansyl; R1 = R2 = $CH_2C{\equiv}CH$** | neat, 80°C, 5h | 40 | × | 143-144 |
| 2 | **R = p-$NO_2$-benzoyl; R1 = R2 = Me** | toluene, 70 °C, 10 h | N/A[a] | × | 143-144 |
| 3 | **R = -C(O)$(CH_2)_3$C(O)-; R1 = R2 = Me** | toluene, argon, 60°C, 36 h | 45 | × | 145 |
| 4 | **R = C(O)$(CH_2)_2$-mifepristone; R1 = Me, R2 =**  | toluene, 60°C, 48 h | 44 | × | 146 |

[a]Data were not provided.

## [4 + 2] REACTIONS OF $C_6$-FURANICS WITH ALKYNES

Alkynes are less reactive dienophiles than the corresponding alkenes due to the higher energy of the $\pi$-bond.[124] Therefore, reactions of $C_6$-furanics only with alkynes bearing two activating electron-withdrawing groups (e.g., COOR, $CF_3$) or alkynes with strained triple bonds were reported.

## REACTIONS OF 2,5-DIMETHYLFURAN WITH ALKYNES

As in the case of alkenic dienophiles, examples of reactions of alkynes with 2,5-dimethylfuran as a diene are the most numerous (Table 7). While [4 + 2] cycloaddition with alkynes generally requires harsh conditions, reactions with strained cyclooctyne derivatives proceed smoothly at room temperature (Table 7, entries 17−19).

## REACTIONS OF HYDROXYMETHYLFURANS WITH ALKYNES

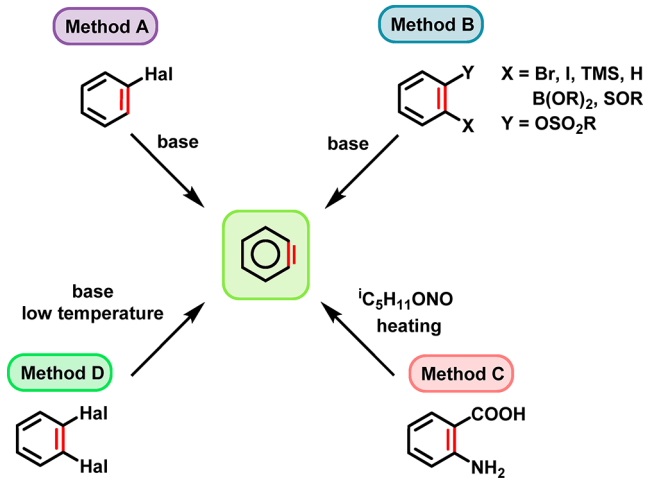
2-(Hydroxymethyl)-5-methylfuran in terms of reactivity can be considered a transition compound between the completely clear functional groups 2,5-dimethylfuran and 2,5-bis(hydroxymethyl)-furan. Reaction with acetylenedicarboxylate proceeds smoothly in high yield (Scheme 8, yield 91%).[139]

2,5-Bis(hydroxymethyl)furan and its dibenzyl ether interact with activated alkynes, leading to corresponding cycloadducts (Table 8).

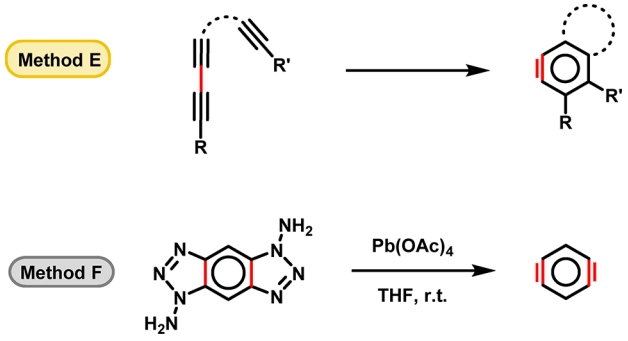
## REACTIONS OF OTHER BIODERIVED $C_6$-FURANICS WITH ALKYNES

The $C_6$-furanic fragment could take part in the construction of extremely complex conjugates and carry bulk substituents linked to amino-methyl moieties. For example, the steroidal glucocorticoid antagonist RU-486 was attached through a spacer to the 2-aminomethyl-5-methylfuran core (Table 9, entry 4). The alkyne part also features a polyfunctional linker at the acetylenedicarboxylate ester. The resulting oxanorbornadiene serves as the centerpiece of the cleavable linker utilizing the retro-Diels−Alder reaction for programmed drug release.

**Scheme 9. Typical Aryne Generation Methods for Subsequent Diels−Alder Reaction**




**Scheme 10. Particular Cases of Aryne Generation Methods for Subsequent Diels−Alder Reaction**




## [4 + 2] REACTIONS WITH ARYNES

Arynes are some of the most reactive dienophiles for the Diels−Alder reaction.[147−150] Moreover, the Diels−Alder reaction often serves as a trapping method for the detection of arynes. Due to their high reactivity, cycloadditions of arynes often proceed under very mild conditions. Typical methods of aryne generation



https://dx.doi.org/10.1021/acssuschemeng.0c09229
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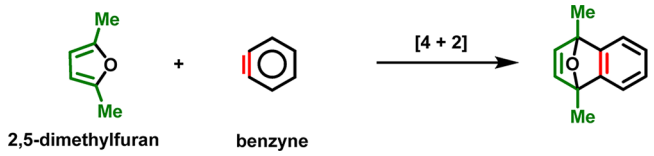
**Table 10. Cycloaddition Reactions of 2,5-Dimethylfuran with Monocyclic Arynes**




| Ent. | Aryne generation method [a] | Aryne | Conditions | Diels-Alder adduct | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | D | | $Et_2O$, -70°C, 90 min | | 45 | ✓ | 151 |
| 2 | C | | 60°C, 1 h | | 65 | ✗ | 152 |
| 3 | D | | toluene, THF, -20°C → r.t., 0.5 h | | 68 | ✓ | 153 |
| 4 | B | | MeCN, r.t., 16 h | | 97 | ✓ | 154 |
| 5 | C | | DCM, reflux, 1.5 h | | 85 | ✓ | 155 |
| 7 | B | | PhCN, 80°C, 24 h | | 77 | ✗ | 156 |
| 8 | B | | MeCN, 120°C, MW, 2 h | | 84 | ✗ | 157 |
| 9 | B | | THF, -78°C, 10 min | | 79 | ✗ | 158 |
| 10 | B | | THF, 60°C, 24 h | | 82 | ✗ | 159 |
| 11 | B | | MeCN, 60°C | | 99 | ✗ | 160 |
| 12 | B | | THF, 25°C, 24 h | | 87 | ✗ | 161 |
| 13 | B | | $Et_2O$, -78 → r.t., 0.5 h | | 95 | ✗ | 162 |
| 14 | B | | THF, MW, 80°C, 0.5 h | | 89 | ✗ | 163 |
| 15 | D | | Toluene, -78 → r.t., 1.5 h | | N/A [b] | ✓ | 164 |
| 16 | C [c] | | DCM, 0°C → r.t., 1 h | | 52 | ✗ | 165 |

[a]Methods overview provided in Scheme 9. [b]Data were not provided. [c]Aryne was generated from N-(2-boronylaryl)-N′-tosyldiazene via Rh-catalyzed cascade process.

are summarized in Scheme 9. Methods for the generation of polycyclic arynes and diarynes are shown in Scheme 10. Here, we mentioned only specific aryne reactions directly related to the discussed transformations. Other details about aryne generation and reactions can be found elsewhere.[147−150]

## [4 + 2] REACTIONS OF 2,5-DIMETHYLFURAN WITH ARYNES

As it was stated above, 2,5-dimethylfuran is the most active diene among bioderived $C_6$-furanics. Therefore, the major examples of [4 + 2]-cycloadditions with arynes and $C_6$-furanics are reactions with 2,5-dimethylfuran (Tables 10−13). A broad scope of benzoannulated 7-oxanorbornenes can be obtained via this approach. The utilization of diarynes (Table 12) and polycyclic arynes (Table 13) leads to the formation of condensed polycyclic systems.

## [4 + 2] REACTIONS OF FUNCTIONALIZED $C_6$-FURANICS WITH ARYNES

A series of O-substituted 1-hydroxymethyl-1,4-epoxy-1,4-dihydronaphthalenes was obtained by the interaction of the corresponding (2-hydroxymethyl)-5-methylfurans with benzyne (Scheme 11, eight examples, yield data were not provided[187]). A variety of protecting groups were used. A hydroxymethyl derivative was also mentioned (R1 = H), although it remains unclear whether this compound was obtained by direct reaction of unprotected (2-hydroxymethyl)-5-methylfuran with benzyne or by deprotection of the O-silyl Diels−Alder adduct. Part of this work also concerned the reactions of silylated BHMF (Table 14, entries 3−4, 7).

Several methods for generating benzyne for transformations were described (Scheme 9, methods A, D, C). The resulting substances served as starting compounds for aromatic derivatives.

The high reactivity of benzyne as a dienophile makes the Diels−Alder reaction possible with less attractive dienes such as methyl 5-(hydroxymethyl)furan-2-carboxylate (Table 15), dimethyl furan-2,5-dicarboxylate (Table 16), and furan-2,5-dicarbonitrile (Scheme 12).[154] Even the presence of two electron-withdrawing groups does not prevent the formation of the corresponding 1,4-epoxynaphthalenes in good yield.

$C_6$-Furanics could be utilized as building blocks for the construction of complex compounds, for example, as spacers in alicyclophanes (Scheme 13). Moreover, it was shown that such polynorbornane macrocycles with rack-mounted furan rings could easily undergo cycloaddition with arynes.[194]

## AROMATIZATION OF DIELS−ALDER ADDUCTS

The transformation of furan Diels−Alder cycloadducts into aromatic compounds is a key step in the formation of aromatic compounds from biomass. Cycloadducts with varying degrees of unsaturation can be aromatized, leading to highly substituted aromatic compounds. Reactions resulting in benzene derivatives and polycyclic aromatic compounds are discussed separately.

## AROMATIZATION OF CYCLOADDUCTS LEADING TO BENZENE DERIVATIVES

The aromatization procedures for the products of the Diels−Alder reaction between $C_6$-furanics and alkenes or


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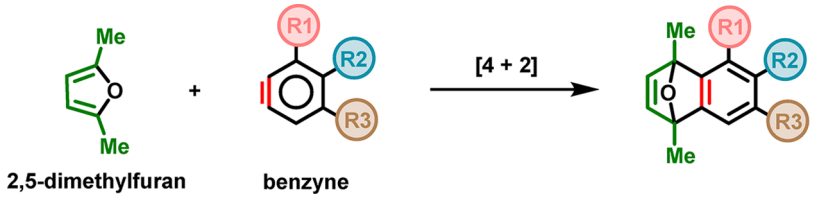
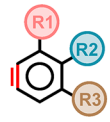
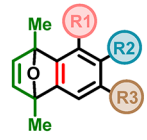
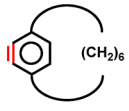
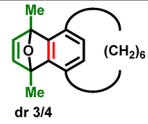
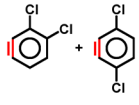
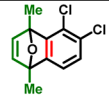
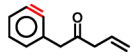
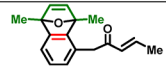
**Table 11. Cycloaddition Reactions of 2,5-Dimethylfuran with Functionalized Benzynes**




2,5-dimethylfuran benzyne

| Ent. | Aryne generation method [a] | Aryne | Conditions | Diels-Alder adduct | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | D |  | R1 = **H,** R2 = R3 = **Me**<br>$Et_20$, -70°C, 1.5 h |  | 25 | ✓ | 151 |
| 2 | D | | R1 = **H,** R2 = R3 = **Br**<br>N/A [b] | | 56 | ✓ | 166 |
| 3 | C | | R1 = R2 = **H,** R3 = **OMe**<br>THF, -78°C | | 58 | ✓ | 167 |
| 4 | B | | R1 = R2 = **H,** R3 = **OMe**<br>THF, -78°C | | 100 | ✗ | 168 |
| 5 | C | | R1 = R2 = **H,** R3 = **Br**<br>THF, 95°C, 1-2 h | | 44 | ✓ | 167 |
| 6 | B | | R1 = R2 = **H,** R3 = **Br**<br>MeCN, 120°C, MW, 2 h | | 82 | ✗ | 157 |
| 7 | C | | R1 = R2 = **H,** R3 = **$CF_3$**<br>THF, -78°C | | 25 | ✓ | 167 |
| 8 | C | | R1 = R3 = **OMe,** R2 = **H**<br>THF, -78°C | | 20 | ✓ | 167 |
| 9 | C | | R1 = **Me,** R2 = R3= **H**<br>THF, 95°C, 1-2 h | | 50 | ✓ | 167 |
| 10 | B | | R1=R2= **H,** R3 = **Ac**<br>MeCN, 120°C, MW, 2 h | | 77 | ✗ | 157 |
| 11 | B | | R1 = R2 = **H,** R3 = **CN**<br>MeCN, 120°C, MW, 2 h | | 70 | ✗ | 157 |
| 12 | B | | R1 = R2 = **H,** R3 = **$NH_2$**<br>MeCN, 120°C, MW, 2 h | | 65 | ✗ | 157 |
| 13 | B | | R1 = **OMe,** R2 = R3 = **H**<br>$Et_2O$, -78→25°C, 30 min | | 81 | ✗ | 162 |
| 14 | B | | R1 = **TMS,** R2 = **H,** R3 = **Me**<br>$Et_2O$, -78→25°C, 30 min | | 81 | ✗ | 162 |
| 15 | B | | R1 = **OTf,** R2 = **H,** R3 = **Br**<br>n-hexane, -30°C, 1 h | | 65 | ✓ | 169 |
| 16 | D | | R1 = **H** R2 = R3 = **F**<br>$Et_2O$, -78°C → 25°C | | 40 | ✓ | 170 |
| 17 | A |  | THF |  dr 3/4 | 28 | ✓ | 171 |
| 18 [c] | A |  | THF, -78°C, overnight |  | 29<br>38 | ✗<br>✗ | 172 |
| 19 | B [d] |  | MeCN, r.t., 12 h |  | 89 | ✗ | 173 |

[a]Methods overview provided in Scheme 9. [b]Data were not provided. [c]Mixture of arynes was generated from 1,2,4-trichlorobenzene. [d]Aryne was generated from corresponding benzocyclobutanol.

alkynes are summarized in Scheme 14. Depending on the degree of unsaturation of the substrate and the structure of the product, four methods (A−D) of aromatization can be distinguished.

## AROMATIZATION OF 7-OXANORBORNENES TO BENZENES (METHOD A)

Aromatization of cycloadducts of 2,5-dimethylfuran with maleic anhydride (Table 17, entries 1−5) and acrylic acid (Table 17,



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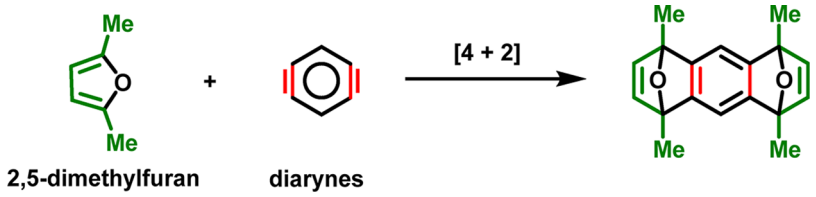
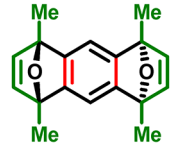
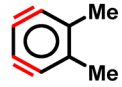
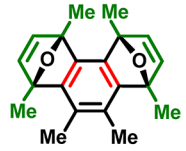
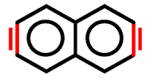
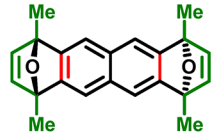
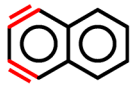
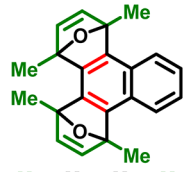
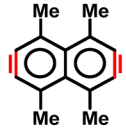
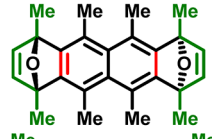
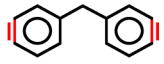
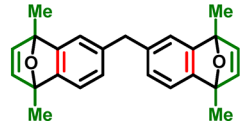
**Table 12. Cycloaddition Reactions of 2,5-Dimethylfuran with Diarynes**




| Ent. | Aryne generation method [a] | Aryne | Conditions | Diels-Alder adduct | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | F | | THF, r.t., 40 min |  | 81 dr 81:19 | ✓ | 174 |
| 2 | D |  | toluene, -78°C → r.t. 4 h |  | 34 dr 10:7 | ✓ | 175 |
| 3 | B |  | THF, r.t., 20 h |  | 72[b] | ✓ | 176 |
| 4 | B |  | THF, r.t., overnight |  | 47 | ✓ | 177 |
| 5 | D |  | toluene, -23°C → r.t., 16 h |  | 52 dr 49:3 | ✗ | 178 |
| 6 | C |  | DCE, dioxane, reflux, 1 h |  | 61 | ✓ | 179 |

[a]Methods overview provided in Schemes 9 and 10. [b]A mixture of sin/anti isomers was obtained, and the ratio was not provided.

entry 6) can be accomplished using concentrated sulfuric acid with moderate yield. The cycloadduct of 2,5-dimethylfuran with N-tolylmaleimide (Table 17, entry 7) undergoes aromatization in the presence of TsOH in quantitative yield. A rare example of aromatization under basic conditions was reported for the cycloadduct of DFF diacetal and acrylonitrile (Table 17, entry 9).

## TRANSFORMATION OF 7-OXANORBORNANES TO BENZENES (METHOD B)

7-Oxanorbornanes can be obtained by the reduction of cycloadducts of furanics with alkenes (Scheme 14). The transformation of 7-oxonorbornanes to benzenes requires both dehydration and dehydrogenation processes to proceed. For this purpose, acid zeolite HY was utilized as the dehydration catalyst, and Pd/C was utilized as the dehydrogenation catalyst (Table 18). Interestingly, it was reported that dehydrogenation can proceed without the addition of Pd/C (Table 18, entry 2).

## TRANSFORMATION OF 7-OXANORBORNADIENES TO BENZENES (METHOD C)

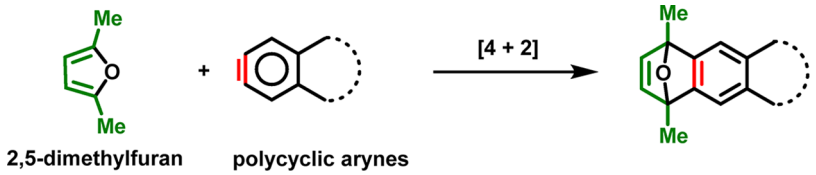
Cycloadducts of 2,5-dimethylfuran and alkynes can be aromatized by means of the $TiCl_4/LiAlH_4$ system with moderate to excellent yields (Table 19, entries 2−4). Recently, the $NH_4ReO_4/P(OPh)_3$ system was suggested for this transformation (Table 19, entry 1).

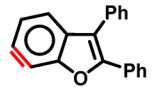
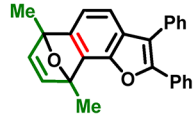
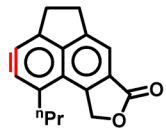
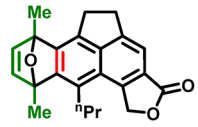
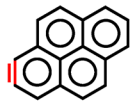
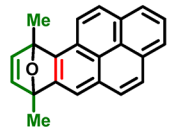
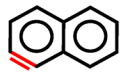
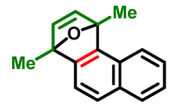
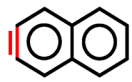
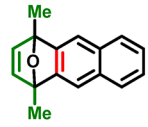
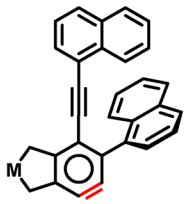
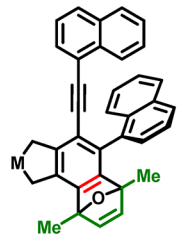
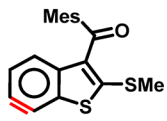
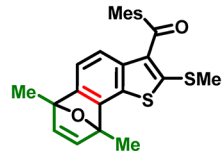
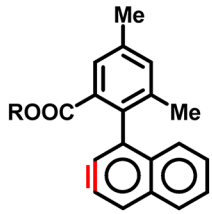
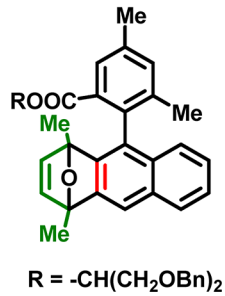
## TRANSFORMATION OF 7-OXANORBORNADIENES TO PHENOLS (METHOD D)

Transformation of 7-oxanorbornadienes to phenols was shown on the only example with the product of cycloaddition between 2,5-dimethylfuran and dimethyl acetylenedicarboxylate (Scheme 15).[130] This reaction proceeds in acidic media with microwave assistance and leads to the formation of two isomeric substituted phenols. It is important to note that skeletal rearrangement of a carbon backbone is observed in this example.


https://dx.doi.org/10.1021/acssuschemeng.0c09229
ACS Sustainable Chem. Eng. XXXX, XXX, XXX−XXX

**Table 13. Cycloaddition Reactions of 2,5-Dimethylfuran with Polycyclic Arynes**




| Ent. | Aryne generation method [a] | Aryne | Conditions | Diels-Alder adduct | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | B |  | THF, r.t., 1 h |  | 87 | ✗ | 180 |
| 2 | E |  | $CHCl_3$, $N_2$, 130°C, 40 h |  | 85 | ✗ | 181 |
| 3 | A |  | THF, reflux, overnight |  | 33 | ✓ | 182 |
| 4 | B |  | THF, -78°C → r.t., 6h |  | 75 | ✓ | 183 |
| 5 | B |  | $Et_2O$, -78°C → 25°C, 30 min |  | 76 | ✗ | 162 |
| 6 | E |  | M = **$C(COOMe)_2$** $CDCl_3$, r.t., 9 h |  | 77 | ✗ | 184 |
| 7 | B |  | $TMSCH_2MgCl$ THF, –78 °C |  | 76 | ✓ | 185 |
| 8 | B |  R = -$CH(CH_2OBn)_2$ | $TMSCH_2MgCl$ $Et_2O$, 0 °C |  R = -$CH(CH_2OBn)_2$ | 81 | ✗ | 186 |

[a]Methods overview provided in Schemes 9 and 10.

## AROMATIZATION OF CYCLOADDUCTS LEADING TO POLYAROMATIC DERIVATIVES

Since arynes are the most reactive dienophiles, their cycloadducts with $C_6$-furanics are highly diverse. Aromatization can be performed for cycloadducts themselves (Methods E, G, H, Scheme 16), as well as for their reduced derivatives (Method F, Scheme 16).



https://dx.doi.org/10.1021/acssuschemeng.0c09229
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**Scheme 11. Cycloaddition Reactions of O-Substituted (2-Hydroxymethyl)-5-methylfurans with Arynes**

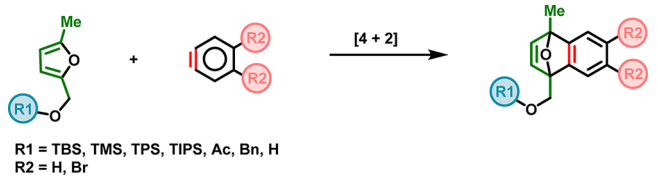
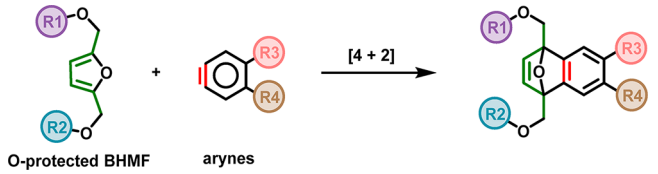
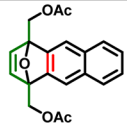
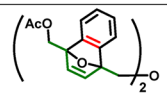
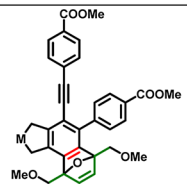



**Table 14. Cycloaddition Reactions of BHMF Derivatives with Arynes**




| Ent. | Aryne generation method [a] | Conditions | Diels-Alder adduct | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|
| 1 | C | R1=R2=R3=R4= **H**<br>DCE, -20 → 60°C | | 48 | ✗ | 188 |
| 2 | C | R1=R2=R3=R4= **H**<br>DCE, 60°C, 0.5 h | | 74 | ✗ | 189 |
| 3 | D | R = **TPS**, R1 = R2 = **Br**<br>THF, -78°C | | N/A [b] | ✓ | 187 |
| 4 | D | R = **TPS**, R1 = **H**, R2 = **OMe**<br>THF, -78°C | | N/A [b] | ✓ | 187 |
| 5 | B | R = **Bz**, R1 = R2 = **H**<br>MeCN, 70°C, 16 h | | 91 | ✓ | 154 |
| 6 | C | R = **Ac**, R1 = R2 = **H**<br>DCM, reflux, 90 min | | 92 | ✓ | 190 |
| 7 | C | R = **TBS**, R1 = R2 = **H**<br>THF, r.t., 1 h | | 88 | ✗ | 152 |
| 8 | C | R1=R2= **Ac**, R3=R4= **H** [c]<br>DCE, -20 → 60°C | | 80 | ✗ | 188 |
| 9 | C | R1=R2= **Ac**, R3,R4= **(CH)$_4$**<br>DCE, reflux, 16 h |  | 65 | ✗ | 188 |
| 10 | C | R1 = **Ac**, R2 = **CH$_2$FurCH$_2$OAc**<br>R3=R4= **H**<br>THF, 60°C |  | 80 | ✗ | 191 |
| 11 | E | R1=R2= **OMe**, M = **C(COOMe)$_2$**<br>$CDCl_3$, r.t., 9 h |  | 71 | ✗ | 184 |

[a]Methods overview provided in Schemes 9 and 10. [b]Data were not provided. [c]2,5-Bis-[hydroxy(dideuteromethyl)]-furan was used as the starting compound.

## TRANSFORMATION OF 1,4-DIHYDRO-1,4-EPOXYNAPHTHALENES TO POLYAROMATICS (METHOD E)

1,4-Dihydro-1,4-epoxynaphthalenes obtained by the Diels–Alder reaction between $C_6$-furanics and arynes can be transformed into corresponding polyaromatic compounds (Scheme 16, Method E) in good yield using a combination of a Lewis acid and reductant (Table 20). $Me_3SiCl$/NaI and $TiCl_4$/$LiAlH_4$ systems are most common for this transformation. There are two unusual methods: aromatization with excess Grignard reagent (Table 20, entry 3) and reaction with $Fe_2(CO)_9$ followed by interaction with cerium-ammonium nitrate (Table 20, entry 7).

## TRANSFORMATION OF ANNELATED 7-OXANORBORNANES TO POLYAROMATICS (METHOD F)

Annelated 7-oxanorbornanes obtained by the reduction of cycloadducts of $C_6$-furanics and arynes can be transformed into polyaromatic compounds (Scheme 16, Method F) using Brønsted acids (Table 21). Notably, this method was utilized for the synthesis of polynuclear aromatic compounds via


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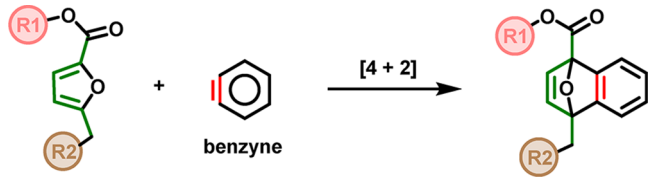
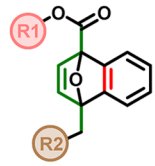
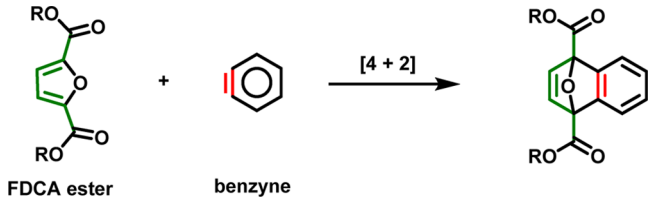
**Table 15. Cycloaddition Reactions of 5-(Hydroxymethyl)furan-2-Carboxylic Acid Derivatives with Benzyne**




| Ent. | Aryne generation method [a] | Furan Conditions | Diels-Alder adduct | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|---|
| 1 | C | R1 = **Me**, R2 = **OAc** DCM, reflux, 90 min |  | 89 | ✓ | 190 |
| 2 | C | R1 = **Et**, R2 = **OAc** DCM, reflux, 90 min | | 78 | ✓ | 190 |
| 3 | C | R1 = **Me**, R2 = **OTBS** DCM, reflux, 90 min | | 85 | ✓ | 190 |
| 4 | C | R1 = **Me**, R2 = **OTHP** DCM, reflux, 90 min | | 85 | ✓ | 190 |
| 5 | C | R1 = **Me**, R2 = **H** DME, 100°C | | 54 | ✗ | 192 |

[a]Methods overview provided in Scheme 9.

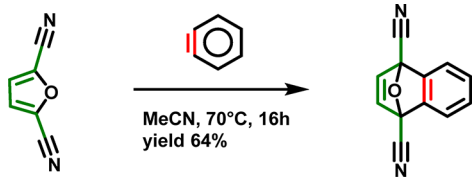
**Table 16. Cycloaddition Reactions of 2,5-Furandicarboxylic Acid Derivatives with Benzyne**



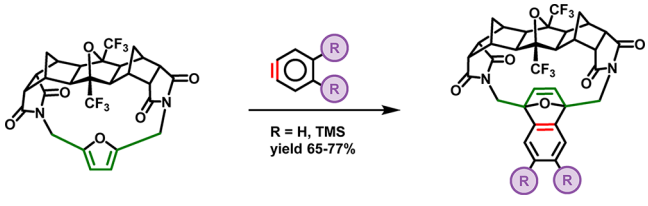

| Entry | Aryne generation method [a] | Furan Conditions | Yield (%) | DA-adduct was used for aromatization | Ref. |
|---|---|---|---|---|---|
| 1 | B, C | R = **Me**, DCM, reflux, 90 min | 91 | ✓ | 155 |
| 2 | B | R = **Me**, MeCN, 70°C, 16 h | 87 | ✓ | 154 |
| 3 | C | R = **Me**, DCM, reflux, 90 min | 86 | ✓ | 190 |
| 4 | C | R = **tBu**, DCE, 70°C,18 h | N/A[b] | ✗ | 193 |

[a]Methods overview provided in Scheme 9. [b]Data were not provided.

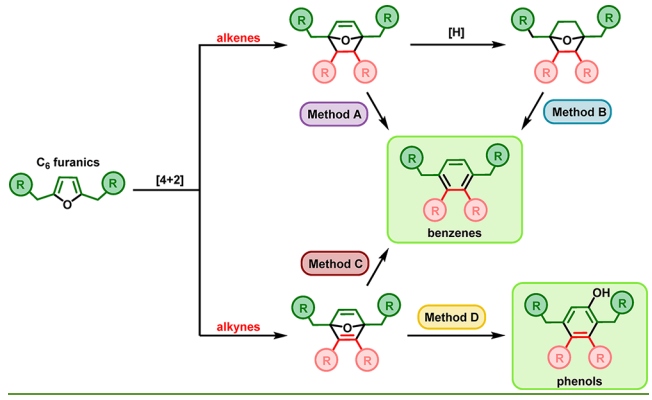
**Scheme 12. Diels−Alder Reaction of Dehydrobenzene with Furan-2,5-dicarbonitrile**




**Scheme 13. Reaction of Rack-Furan with Benzynes**




**Scheme 14. Possible Pathways for Transitions from $C_6$-Furanics through Diels−Alder Adducts toward Aromatic Derivatives**




aromatization of reduced cycloadducts of 2,5-dimethylfuran and various diarynes (Table 21, entries 7−12).



https://dx.doi.org/10.1021/acssuschemeng.0c09229
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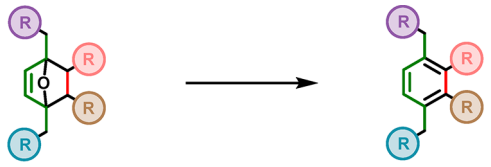
**Table 17. Aromatization of 7-Oxanorbornenes to Benzenes**



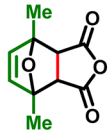
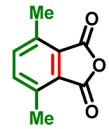
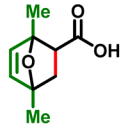
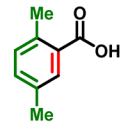
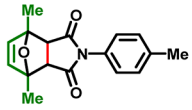
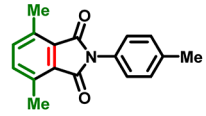
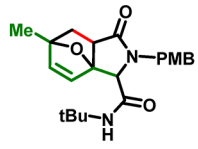
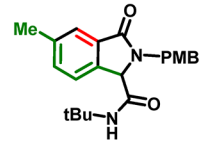
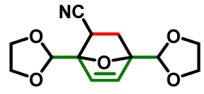
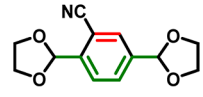
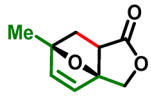
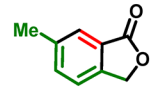
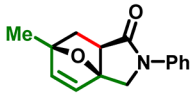
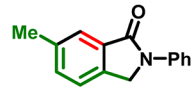
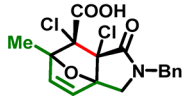
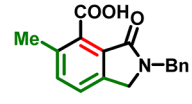
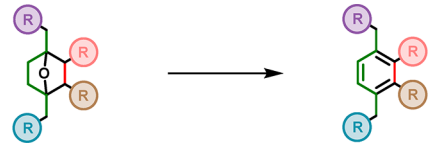
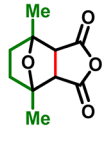
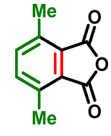
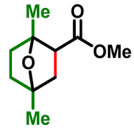
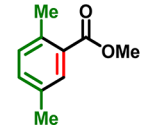
| Entry | Diels-Alder adduct | Conditions | Benzene | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 | | conc. $H_2SO_4$ | | 56 | 75 |
| 2 |  | $H_2SO_4$ (90%), -10 - 0°C, 2.5 h |  | 52 | 76 |
| 3 | | conc. $H_2SO_4$, -6 - 0°C | | 48 | 195 |
| 4 | | conc. $H_2SO_4$, -6 - 0°C | | 58 | 79 |
| 5 | | conc. $H_2SO_4$ | | 52 | 196 |
| 6 |  | conc. $H_2SO_4$, 0°C, 15 min |  | 48 | 94 |
| 7 |  | p-TsOH, toluene, 80°C, 16 h |  | 100 | 86 |
| 8 |  | p-TsOH, toluene, reflux, 0.5 h |  | 51 | 121 |
| 9 |  | KOH, DMSO, r.t., 1h |  | 93 | 102 |
| 10 |  | $Ac_2O$, $H_2SO_4$, 0 → 60°C, 2 h |  | 99 | 107 |
| 11 |  | $BF_3$•$Et_2O$-$Ac_2O$, 25°C, 24 h |  | 41 | 114 |
| 12 |  | Zn, AcOH, 70°C, 2 h |  | 40 | 113 |

**Table 18. Aromatization 7-Oxanorbornanes to Benzenes**



| Entry | Diels-Alder adduct | Conditions | Benzene | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 |  | acid zeolite HY, Pd/C, toluene, 200°C, 24 h |  | 67 | 77 |
| 2 | | acid zeolite HY, $N_2$, 200°C, 2-3 h | | 72 | 78 |
| 3 |  | acid zeolite HY, Pd/C, toluene, $N_2$, 200°C, 2 h |  | 20 | 78 |



https://dx.doi.org/10.1021/acssuschemeng.0c09229
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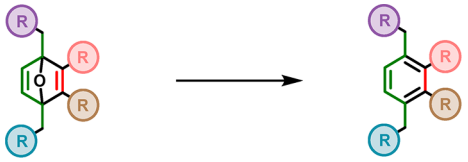
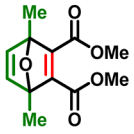
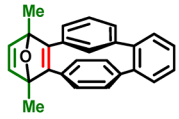
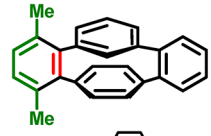
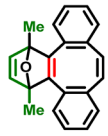
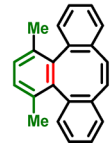
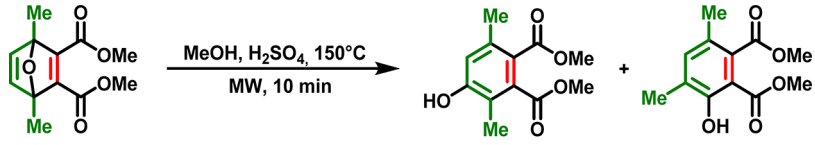
**Table 19. Aromatization of 7-Oxanorbornadienes to Benzenes**



| Ent. | Diels-Alder adduct | Conditions | Benzene | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 |  | $NH_4ReO_4$, $P(OPh)_3$, toluene, 110°C, 18 h | | 79 | 197 |
| 2 | | $TiCl_4$, $LiAlH_4$, $Et_3N$, THF, rt, 24h | | 54 | 127 |
| 3 |  | $TiCl_4$, $LiAlH_4$, $Et_3N$, THF |  | 90 | 198 |
| 4 |  | $TiCl_4$, $LiAlH_4$, $Et_3N$, THF, reflux, 24 h |  | 78 | 137-138 |

**Scheme 15. Aromatization of Dimethyl 1,4-Dimethyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[130]**




## TRANSFORMATION OF 1,4-DIHYDRO-1,4-EPOXYNAPHTHALENES TO NAPHTHOLS (METHOD G)

1,4-Dihydro-1,4-epoxynaphthalenes can be transformed into naphthols (Scheme 16, Method G) using diverse catalytic systems with good to excellent yields (Table 22). It is important to note that this transformation can result in $\alpha$- and $\beta$-naphthols; therefore, aromatization can be accompanied by structural rearrangement (Table 22, entries 1, 5, 6).

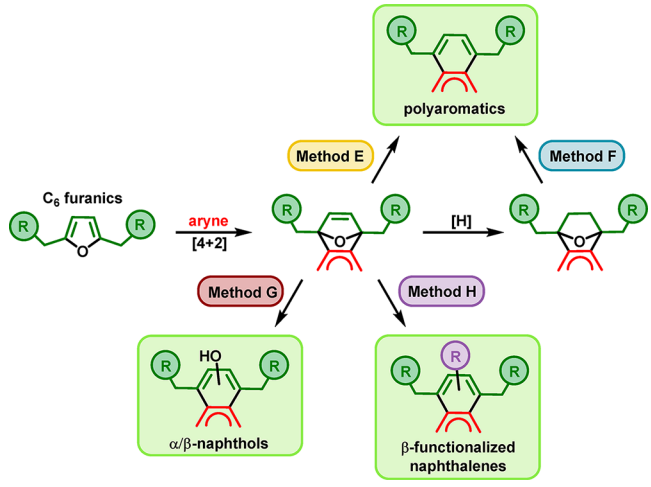
## TRANSFORMATION OF 1,4-DIHYDRO-1,4-EPOXYNAPHTHALENES TO $\beta$-FUNCTIONALIZED NAPHTHALENES (METHOD H)

Aromatization of 1,4-dihydro-1,4-epoxynaphthalenes can be accompanied by introduction of an additional substituent in the $\beta$-position of the naphthalene ring (Scheme 16, Method H). Examples of this type of aromatization are summarized in Table 23. Aryl, heteroaryl, and allyl substituents can be introduced using this approach with moderate to excellent yields.

## ONE-POT TWO-STEP TRANSFORMATIONS OF $C_6$-FURANICS INTO AROMATICS

The most straightforward approach for the transformation of $C_6$-furanics into benzene derivatives is one-pot cycloaddition/aromatization. In this section, the methods are classified by the type of starting material and target product.

**Scheme 16. Possible Pathways for Transitions from $C_6$-Furanics through Aryne Diels–Alder Adducts toward Polyaromatic Derivatives**




## SYNTHESIS OF *P*-XYLENE FROM 2,5-DIMETHYLFURAN

The interaction between 2,5-dimethyfuran and ethylene is the most thoroughly studied. These reactions proceeded under high temperature and pressure, leading to *p*-xylene in good to excellent yields (Table 24). The process consists of two steps: [4 + 2] cycloaddition and dehydration. Zeolites and modified zeolites are the most common type of catalysts for this transformation.



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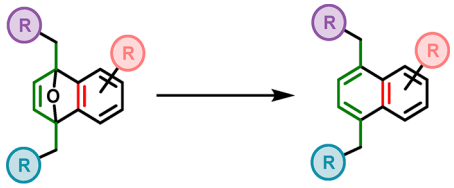
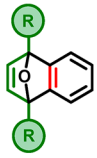
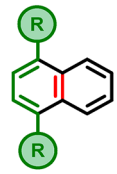
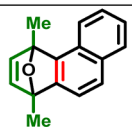
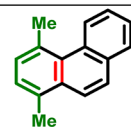
**Table 20. Aromatization of 1,4-Dihydro-1,4-epoxynaphthalenes to Benzenes**



| Entry | Diels-Alder adduct | Conditions | Benzene | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 |  | **R = Me;** MeCN, NaI, $Me_3SiCl$, 20°C, 16 h |  | 92 | 155 |
| 2 | | **R = Me;** MeCN, NaI, $Me_3SiCl$, r.t., 24 h | | 92 | 154 |
| 3 | | **R = Me;** $^{i}$PrMgBr, THF, reflux, 2 h | | 73 | 199 |
| 4 | | **R = COOMe;** MeCN, NaI, $Me_3SiCl$, 70°C, 16 h | | 25 | 155 |
| 5 | | **R = COOMe;** $TiCl_4$, $LiAlH_4$, $Et_3N$, THF, r.t., 24 h | | 33 | 154 |
| 6 | | **R = $CH_2OBz$;** MeCN, NaI, $Me_3SiCl$, r.t., 24 h | | 94 | 154 |
| 7 | | **R1 = OTf, R2 = R4 = H, R3 = Br** 1)$Fe_2(CO)_9$, toluene, 80°C, 1 h 2) $(NH_4)_2Ce(NO_3)_6$, MeCN, r.t., 2 h | | 70 | 169 |
| 8 | | **R1 = R4 = Me, R2=R3= Br** $Me_3SiCl$, NaI, MeCN, Ar, r.t., 3 h | | 67 | 200 |
| 9 | | **R1 = R4 = H, R2 = R3 = Br** Zn/$TiCl_4$ | | 90 | 166 |
| 10 | | **R1,R4 = -$(CH_2)_6$-, R2 = R3 = H** $TiCl_4$, $LiAlH_4$, $Et_3N$, THF, 0°C - r.t., 2h | | 60 | 171 |
| 11 |  | $Me_3SiCl$, NaI, MeCN, r.t., 3 h |  | 78 | 183 |

The mechanism of this process was thoroughly studied both theoretically and experimentally.[211−221] Despite harsh reaction conditions, this transformation is a real breakthrough in the field of biomass aromatization since *p*-xylene is a compound of general importance for the chemical industry.

The transformation of 2,5-dimethylfuran to *p*-xylene can be accomplished using an alternative $C_2$ source (Table 25). Ethanol and diethyl ether can serve as ethylene precursors (Table 25, entries 1−4). Utilization of acrylic acid as a $C_2$ source allows the synthesis of xylene under ambient conditions if an ionic liquid is used as the reaction medium (Table 25, entries 5−7). In this case, an additional step of decarboxylation is required, and 2,5-dimethylbenzoic acid is the main byproduct. Additional $Cu_2O$-promoted decarboxylation increases the yield of *p*-xylene to 57%.[250] A theoretical study unveiled important mechanistic features of this process.[251] The zeolite-catalyzed reaction with acrylic acid performed in continuous flow mode allows an 83% yield of *p*-xylene to be achieved (Table 25, entry 6). While the effectiveness of systems based on alternative $C_2$ sources is currently lower than that of ethylene-based systems, utilization of biobased building blocks (bioethanol and glycerol-derived acrylic acid) allows the production of completely bioderived *p*-xylene.

## ONE-POT SYNTHESIS OF 1,4-DISUBSTITUTED BENZENES

As the most basic reagent in the series of alkene dienophiles, ethylene facilitates 1,4-functionalized benzene formation via the F2B route. Specifically, this approach leads to terephthalate derivatives, which is a critical step for bioderived polyethylene terephthalate (bio-PET) creation. Currently, a scope of substituted 2-carboxyfurans have been subjected to [4 + 2] aromatization sequential reactions with ethylene (Table 26). All these transformations require high ethylene pressure, extreme temperatures, and complex catalytic systems.

In the course of systematic research, a series of C-6 furans were converted into corresponding benzenes using solid silica-based Lewis acid catalysts (Table 26, entries 1, 3, 6−10, 13). Unfortunately, the majority of the described transformations were characterized by low yields. A maximum yield of 24% was achieved only in the case of methyl 4-(methoxymethyl)benzoate starting from methyl-5-methoxymethyl-2-furancarboxylate (Table 26, entry 6). Interestingly, in the reaction of HMF with ethylene, significant carbon deposition or coking of the catalyst was only observed.

Derivatives of funancarboxylic acid were introduced into a one-pot cycloaddition/aromatization process with ethylene catalyzed by microporous and mesoporous zincosilicates (Table 26, entries 4, 11). Only poor yields of the corresponding benzene derivatives were achieved. An alternative approach to these transformations utilizing silica molecular sieves that have zeolite beta topology and contain framework Lewis acid centers as catalysts led to a significant yield increase (Table 26, entries 2, 5). Phosphotungstic acid supported on silica proved to be an effective catalyst for sustainable terephthalic acid ester production (Table 26, entry 12).


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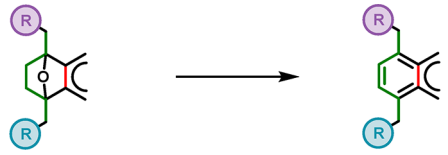
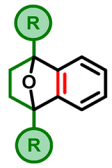
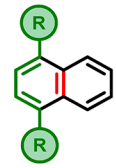
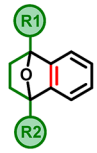
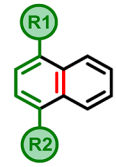
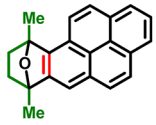
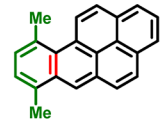
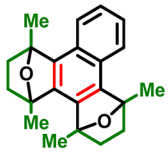
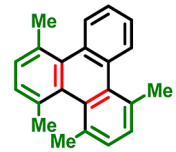
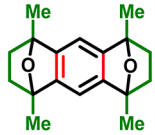
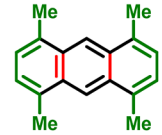
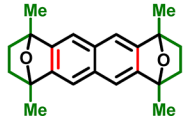
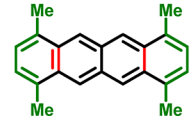
**Table 21. Aromatization of Annelated 7-Oxanorbornanes to Polyaromatics**



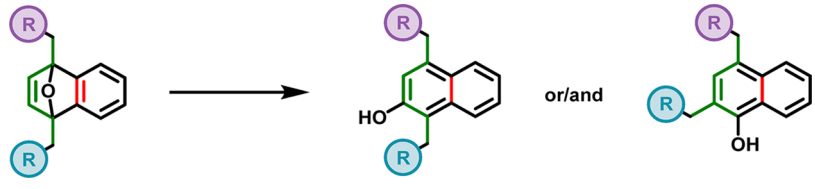
| Ent. | Diels-Alder adduct | Conditions | Benzene | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 |  | **R = Me;** DCE, Amberlyst 15, reflux, 1.5 h |  | 97 | 155 |
| 2 | | **R = COOMe;** DCE, Amberlyst 15, reflux, 1.5 h | | 17 | 155 |
| 3 | | **R = COOMe;** Amberlyst 15, DCE, 1.5 h | | 22 | 190 |
| 4 | | **R = $CH_2OAc$;** Amberlyst 15, DCE, 1.5 h | | 75 | 190 |
| 5 |  | **R1 = COOMe; R2 = $CH_2OAc$** Amberlyst 15, DCE, 1.5 h |  | 55 | 190 |
| 6 | | **R1 = COOEt; R2 = $CH_2OAc$** $Ac_2O$, $MeSO_3H$, 100°C, 90 min | | 82 | 190 |
| 7 |  | HCl, MeOH, reflux, 2.5 h |  | 87 | 182 |
| 8 | | EtOH, HCl, reflux, 2 h | | 22 | 175 |
| 9 |  | TFA, $CHCl_3$, reflux, 2.5 h |  | 27 | 177 |
| 10 |  | HCl, EtOH |  | N/A[a] | 174 |
| 11 |  | HCl, $Ac_2O$, r.t., 1 h |  | 27 | 176 |
| 12 | | HCl, $H_2O$ | | 56 | 177 |

[a]Data were not provided.

A highly efficient and 100% biobased procedure for diethyl terephthalate synthesis via a one-pot heterogeneous Lewis acid-catalyzed tandem Diels–Alder addition/dehydration reaction of ethylene with 2,5-furandicarboxylic acid was developed recently (Table 26, entry 14). Aluminum-pillared montmorillonite clay served as the catalyst.

Another method for the transformation of 2,5-furandicarboxylic acid dimethyl ester into terephthalates was patented (Table 26, entry 15). The starting diester subjected to the reaction with ethylene under harsh conditions gives rise to a mixture of corresponding ethyl and methylterephthalate esters, as well as ethyl-methyl diesters of 2,5-furandicarboxylic acid.

**Table 22. Aromatization of Diels–Alder Adducts to Phenols**





https://dx.doi.org/10.1021/acssuschemeng.0c09229
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**Table 22. continued**

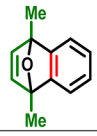
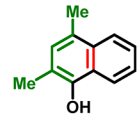
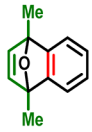
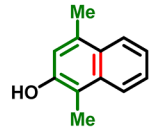
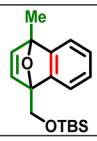
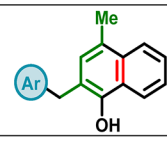
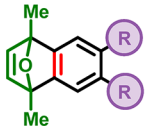
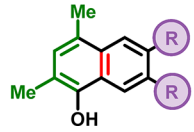
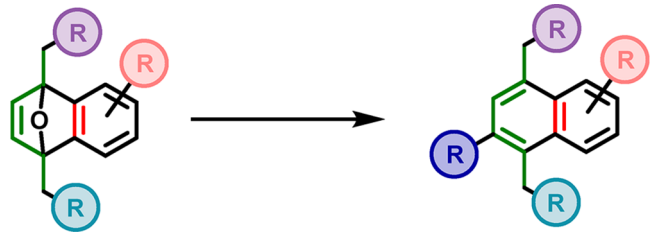
| Entry | Diels-Alder adduct | Conditions | Phenol | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 |  | $In(OTf)_3$, allylTMS, DCM, -40 – 0°C |  | 30 | 201 |
| 2 |  | HCl, $H_2O$, 90 – 100°C, 5 min |  | 69 | 202 |
| 3 | | $[RhCl(COD)]_2$, $AgBF_4$, BINAP, DCE, 60°C, 1 h | | 86 | 203 |
| 4 | | $[RuCl_2(CO)_3]_2$, DCE, 60°C, 18 h | | 85 | 204 |
| 5 |  | $ArH$, $FeCl_3$, DCE, r.t., 30 min |  | 34-90 | 205 |
| 6 |  | **R = H, Me, Br** $Cu(OTf)_2$, DCE, r.t., 15 – 60 min |  | 87-90 | 206 |

**Table 23. Aromatization of 1,4-Dihydro-1,4-epoxynaphthalenes Accompanied by Additional Functionalization**



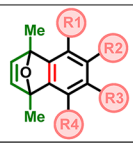
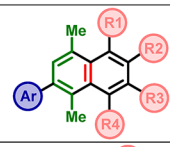
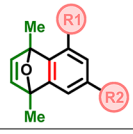
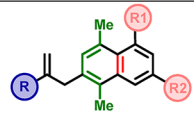
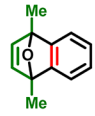
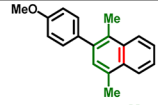
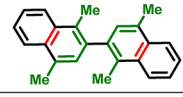
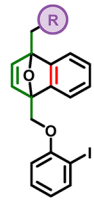
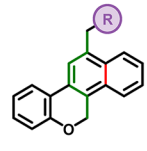
| Entry | Diels-Alder adduct | Conditions | Benzene | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 |  | **R1, R2, R3, R4 = H, Br, OMe; Ar = Aryl, HetAryl** ArH, $FeCl_3$, $CH_2Cl_2$, r.t. |  | 24-97 | 207 |
| 2 |  | **R1, R2 = H, OMe, Br, COOMe, F; R = H, Me, Ph, Br** $AuCl_3$, $AgSbF_6$, allylsilane, DCM, -40 — 0°C |  | 55-98 | 201 |
| 3 |  | $(4\text{-}MeOC_6H_4)_3P$, $Pd(OTf)_2$, $Cu(OAc)_2$, p-xylene, 120°C, 12 h |  | 73 | 153 |
| 4 | | Zn powder, $Pd(dba)_2$, $HSiCl_3$, toluene, $N_2$, 0°C - r.t., 6 h |  | 30 | 208 |
| 5 |  | **R = H** $PdCl_2(PPh_3)_2$, Zn, $Et_3N$, MeCN, 60°C |  | 86 | 209 |
| 6 | | **R = OTIPS** $PdCl_2(PPh_3)_2$, Zn, $Et_3N$, MeCN, 60°C | | 75 | 209 |
| 7 | | **R = H** $NiCl_2(PPh_3)_2$, Zn, $Et_3N$, MeCN, 40°C | | 82 | 210 |
| 8 | | **R = OTIPS** $NiCl_2(PPh_3)_2$, Zn, $Et_3N$, MeCN, 40°C | | 80 | 210 |



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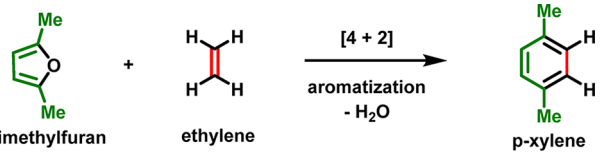
**Table 24. Production of *p*-Xylene via Cycloaddition of 2,5-Dimethylfuran and Ethylene and Subsequent Aromatization**




| Entry | Conditions | Yield (%) [a,b] | Ref. |
|---|---|---|---|
| 1 | Ethylene(57 bar), H−Y zeolite, n-heptane, 300°C | 71 | 222 |
| 2 | Ethylene(54 bar), $WO_3$/SBA-15, n-heptane, 250°C | 59 | 223 |
| 3 | Ethylene(30 bar), HSiW/$SiO_2$, n-heptane, 250°C | 80 | 224 |
| 4 | Ethylene(55 bar), H-ZSM-5, n-octane, 250°C | 63 | 225 |
| 5 | Ethylene(40 bar), Au-Pd/t-$ZrO_2$, n-heptane, 275°C | 90 | 226 |
| 6 | Ethylene(20 bar), $WO_x$-$ZrO_2$, hexadecane, 250°C | 46 | 227 |
| 7 | Ethylene(62 bar), Zr-BEA, n-heptane, 250°C | 82 | 228 |
| 8 | Ethylene(156 bar), $Cu(OTf)_2$, 1,4-dioxane, 250°C | 98 | 229-231 |
| 9 | Ethylene(14 bar), H−Beta zeolite, n-heptane, 250°C | 89 | 232 |
| 10 | Ethylene(33-40 bar), activated carbon, n-heptane, 200-335°C | N/A[c] | 233 |
| 11 | Ethylene(34 bar), $Cu(OTf)_2$, 4Å sieves, 1,4-dioxane, 220°C | 95 | 234 |
| 12 | Ethylene(40 bar), AcOH, BzOBz, 150°C | 92 | 235 |
| 13 | Ethylene(38 bar), P-BEA, n-heptane, 250°C | 96 | 236 |
| 14 | Ethylene(40 bar), $Al_2O_3$/H-Beta, 300°C | 97 | 237 |
| 15 | Ethylene(50 bar), MFI zeolite, n-hexane, 250°C | 76 | 238 |
| 16 | Ethylene(35 bar), $Sc(OTf)_3$, 1,4-dioxane, 200°C | 70 | 239 |
| 17 | Ethylene(20 bar), ZrP-SBA/KIT, n-heptane, 250°C | 87 | 240 |
| 18 | Ethylene(60 bar), K- faujasite, n-heptane, 230°C | N/A[c] | 212 |
| 19 | Ethylene(55 bar), H/Zr/Sn-BEA, 427°C | 26 | 241 |
| 20 | Ethylene, $Cp_2TiCl_2$/$SiO_2$/$Al_2O_3$, 180°C | 92 | 242 |
| 21 | Ethylene(40 bar), H-BEA, n-heptane, 300°C | 99 | 243 |
| 22 | Ethylene(54 bar), $WO_3$/SBA-15, n-heptane, 300°C | 46 | 218 |
| 23 | Ethylene(50 bar), $WO_x$-$ZrO_2$, n-heptane, 250°C | 85 | 244 |
| 24 | Ethylene(20 bar), H-SAPO, n-hexane, 250°C | 50 | 245 |
| 25 | Ethylene(20 bar), BEA, n-hexane, 230°C | 69 | 219 |
| 26 | Ethylene(30 bar), H-Beta, n-heptane, 300°C | 97 | 246 |
| 27 | Ethylene(20 bar), Sn-P/H-Beta, n-heptane, 250°C | 93 | 220 |
| 28 | Ethylene(30 bar), $SiO_2$-$Al_2O_3$ aerogel, 1,4-dioxane, 250°C | 60 | 247 |
| 29 | Ethylene(54 bar), $NbO_x$, n-heptane, 250°C | 81 | 248 |
| 30 | Ethylene(15 bar), $SiO_2$-$SO_3H$, n-heptane, 250°C | 84 | 249 |
| 31 | Ethylene(46.9 bar), HY-zeolite, 255°C | 89 | 221 |

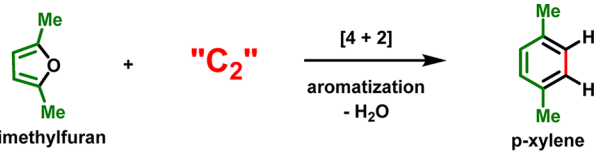
[a]If not provided in the article, the yield was calculated by multiplying the conversion to selectivity (as an estimation only, see the corresponding articles for complete details). [b]Data corresponding to the best results are provided if a series of experiments was performed. [c]Data were not provided.

## ONE-POT SYNTHESIS OF POLYFUNCTIONALIZED BENZENES

An interesting example of conversion of the substituted 2,5-bis(alkoxymethyl)furans into the corresponding phthalonitriles without isolation of the intermediate Diels−Alder adducts was described (Scheme 17). Transformations proceeded in a one-pot manner with poor yields (10 examples, yield 4%−23%).[265]

As was shown previously, the presence of electron-withdrawing groups, such as aldehydes, at the alpha-position of the furanic core significantly reduces the reactivity of diene in cycloaddition. To tackle this problem, aldehydes could be transformed into hydrazone moieties by changing the electronic properties to facilitate the Diels−Alder reaction. Indeed,

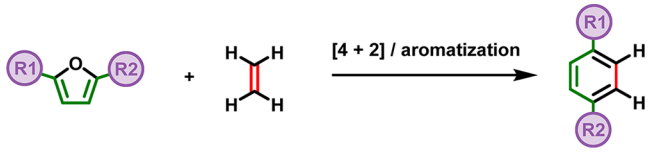
**Table 25. Production of *p*-Xylene via Reaction of 2,5-Dimethylfuran with Alternative $C_2$ Source**



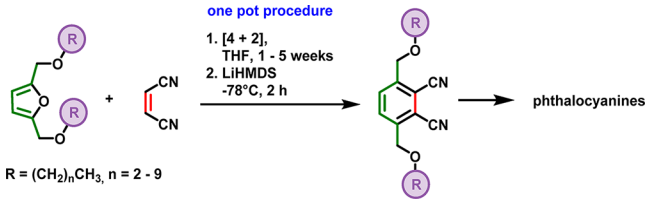

| Entry | $C_2$ - source | Conditions | Yield (%) [a,b] | Ref. |
|---|---|---|---|---|
| 1 | EtOH | H−USY zeolite, 300°C | 64 | 252 |
| 2 | EtOH | ZSM-5, 350°C | 82 | 253 |
| 3 | EtOH | $Al_2O_3$/$SiO_2$, 60 bar, n-heptane, 245°C | 5 | 254 |
| 4 | $Et_2O$ | $Al_2O_3$/$SiO_2$, 70 bar, n-heptane, 245°C | 5 | 254 |
| 5 | Acrylic acid | [bmim]$HSO_4$, 25°C | 45 | 255 |
| 6 | Acrylic acid | H-Beta, n-heptane, 30 bar, 200°C, microflow | 83 | 256 |
| 7 | Acrylic acid | $Sc(OTf)_3$, $H_3PO_4$, [emim]$NTf_2$, 15°C | 48 | 250 |

[a]If not provided in the article, the yield was calculated by multiplying the conversion to selectivity (as an estimation only, see the corresponding articles for complete details). [b]The data corresponding to the best results are provided if a series of experiments were performed.

**Table 26. Cycloaddition−Dehydration Reactions of Ethylene with Functionalized Furans**




**Scheme 17. One-Pot Synthesis of Substituted Phthalonitriles from 2,5-Bis(alkoxymethyl)furans**




5-HMF and its derivatives were engaged in cycloaddition with maleic anhydride and N-substituted maleimides after conversion of the formyl group into hydrazone by N,N-dimethylhydrazine. A hydrazone formation/Diels−Alder/dehydration three-step cascade process proceeds smoothly in one-pot conditions yielding corresponding phthalimides (Table 27).

The developed approach allows one to obtain even phthalic acid derivatives baring two 2,2-(dimethylhydrazono)methyl groups starting from low-reactive 2,5-diformylfuran (Table 28, entry 5). Analogous O-benzyloxime exhibits much lower activity than diene; in that case, the cascade reaction results in a poor yield of 20% (Table 28, entry 4).

There are several examples of multicomponent reactions when one-pot cycloaddition/aromatization is accompanied by complex functionalization. For example, a tandem process involving Ugi four-component condensation, intramolecular Diels−Alder cycloaddition, and subsequent deselenization−aromatization promoted by $BF_3$-$OEt_2$ leads to isoindolinones (Scheme 18). Similar tandem processes excluding the aromatization step were described above.


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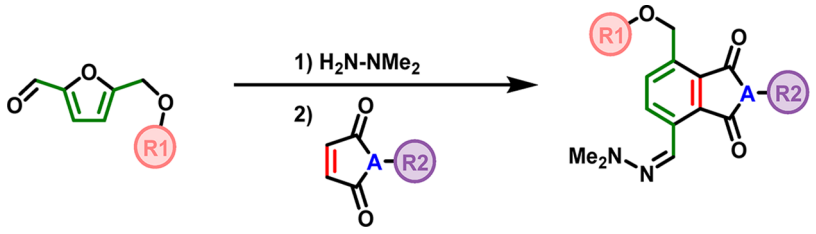
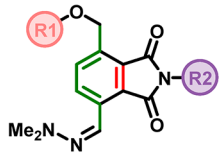
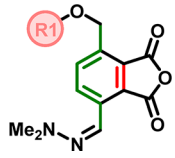
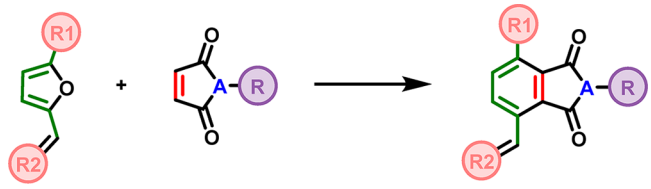
**Table 27. One-Pot Three-Step Transformations of O-Functionalized 5-HMF to Phthalic Acid Derivatives**

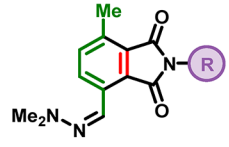
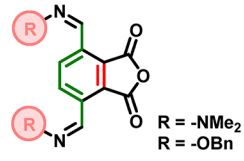



| Entry | Conditions | Benzene | Yield (%) | Ref. |
|---|---|---|---|---|
| 1 | R1=R2= **H**, A = **N**<br>$H_2O$ (pH = 6), 60°C |  | 87 | 266 |
| 2 | R1=R2= **Et**, A = **N**<br>$H_2O$ (pH = 6), 60°C | | 72 | 266 |
| 3 | R1 = **H**, R2 = **Et**, A = **N**<br>$H_2O$ (pH = 6), 60°C | | 95 | 266 |
| 4 | R1 = **H**, R2 = **Et**, A = **N**<br>2-*sec*-butylphenol<br>20°C, 1h | | — [a] | 267 |
| 5 | R1 = **H**, A = **O**<br>EtOAc, TFA, 1 h |  | 13 [b] | 264 |
| 6 | R1 = **Me**, A = **O**<br>EtOAc, 60°C, 150 min<br>then 20°C 40 h | | 41 | 264 |

[a]Data were not provided. [b]Over two steps starting from 5-(hydroxymethyl)furfural.

**Table 28. Furan-to-Benzene Synthetic Route Utilizing One-Pot Two-Step Conditions**




| Entry | Conditions | Benzene | Yield (%) | Ref. |
|---|---|---|---|---|
| 1 | **R1 = Me, R2 = $NNMe_2$**<br>**A = N, R = Et, Ph, Hex**<br>[bmim][Cl], MW<br>100°C, 2 h |  | 46-65 | 268 |
| 2 | **R1 = Me, R2 = $NNMe_2$**<br>**A = O**<br>$CHCl_3$, r.t., 16 h | | 74 | 269-270 |
| 3 | **R1 = Me, R2 = $NNMe_2$**<br>**A = N, R = Et**<br>$CHCl_3$, r.t., 16 h | | 65 | 269-270 |
| 4 | **R1 = CHNOBn, R2 = NOBn**<br>**A = O**<br>TFA, EtOAc, r.t., 40 h |  | 20 | 264 |
| 5 | **R1 = $CHNNMe_2$, R2 = $NNMe_2$**<br>**A = O**<br>TFA, EtOAc, r.t., 40 h | | 98 | 264 |

[a]Data were not provided. [b]Over two steps starting from 5-(hydroxymethyl)furfural.

## GOLD-CATALYZED CYCLIZATIONS OF $C_6$-FURANS WITH ALKYNES LEADING TO PHENOLS

Discussing the synthesis of aromatics on the basis of the interaction of furans with alkynes, a number of specific examples immediately are noticed. In that kind of transformation, furans react with monosubstituted alkynes, producing phenols. However, what seems like a two-step Diels–Alder/aromatization process is actually catalytic cycloisomerization (Scheme 19).[272−274]

The reaction proceeds by a mechanism that differs from the above-discussed cycloaddition/aromatization pathway and requires mandatory use of gold-complex catalysts. The topic was reviewed in detail in the literature.[274−279] Although such



https://dx.doi.org/10.1021/acssuschemeng.0c09229
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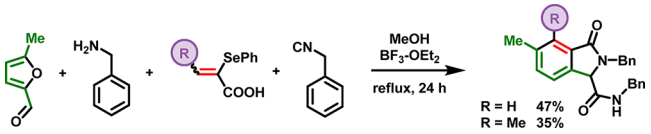
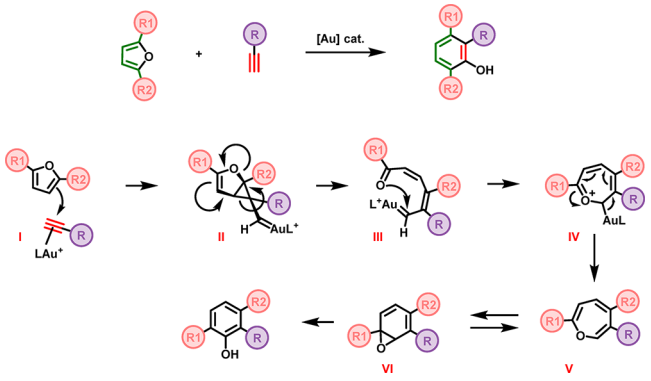
**Scheme 18. Furan-to-Benzene Route Utilizing One-Pot Conditions**[a]




[a]One-pot synthesis of substituted isoindolinones via an Ugi four-component condensation/Diels–Alder cycloaddition–deselenization–aromatization sequence.[271]

**Scheme 19. Gold(I)-Catalyzed Cycloisomerization Reaction of Furans with Alkynes Producing Phenols**




processes are currently not optimized in view of biomass-scale conversion, the great practical potential of such transformations may be explored in the future.

## CONCLUSIONS AND PERSPECTIVES

Analysis of the experimental data summarized in the present perspective has shown that, despite the importance of the topic, the transformation of bioderived $C_6$-furanics into benzene derivatives remains challenging. Diels–Alder cycloaddition of $C_6$-furanics was most thoroughly studied for symmetrical activated furans: 2,5-dimethylfuran, derivatives of 2,5-bis(hydroxymethyl)-furan, and 2,5-bis(aminomethyl)furan (Figure 2). Reactions with these dienes usually lead to corresponding cycloadducts in good yield. At the same time, furans bearing electron-withdrawing substituents are less reactive and can undergo cycloaddition only with highly reactive dienophiles. Otherwise, these cycloadditions can proceed with ethylene under harsh conditions. Unfortunately, there are no successful examples of Diels–Alder reactions with unmodified 5-(hydroxymethyl)furfural, which is a parent compound for furan-based platform chemicals. Side group reduction or hydrazone formation can be used to activate 5-HMF as a diene.

Among aliphatic dienophile derivatives of maleic acid (maleic anhydride and maleimide), acrylic acid derivatives and derivatives of acetylenedicarboxylic acid are the most studied in the discussed transformation (Figure 2). Examples of cycloadditions with nonactivated alkenes and alkynes are extremely rare. Even activated dienophile reactions can be successfully accomplished in good yield only with reduced $C_6$-furanics. Such limitations significantly narrow the application area of aromatized products due to the presence of excessive mandatory structural fragments in the final compound. A high yield in reaction with ethylene as dienophile was achieved for 2,5-dimethylfuran, although such transformation requires severe conditions. The practical importance of 1,4-disubstituted benzenes has stimulated intensive investigations in the field of cycloaddition/aromatization processes with ethylene as the dienophile.

Arynes are the most active dienophiles; therefore, the broadest scope of furanic dienes undergoes Diels–Alder reaction with them. Even deactivated furans bearing electron-withdrawing groups interact with arynes in good yield. Aromatization of cycloadducts obtained from furans and arynes can often be accomplished with excellent yield. Barely available polycyclic compounds can be obtained by means of these transformations, but the complex structure of cycloadducts makes their practical application very specific.

Special attention should be paid to one-pot transformations that convert $C_6$-furanics to *p*-xylene. There are more than 30 zeolite-based catalytic systems that allow *p*-xylene to be obtained from 2,5-dimethylfuran and ethylene. Nearly quantitative yield can be achieved for this transformation. Unfortunately, harsh cycloaddition/aromatization conditions make this process uncompetitive compared to existing oil-based *p*-xylene production from an industrial point of view.

Terephthalic acid derivatives can also be obtained by the reaction of ethylene with functionalized furans under harsh conditions, but only low to moderate yields were achieved for such transformations.

In conclusion, development of the F2B process is a rapidly evolving research field with great potential. The utilization of biobased dienophiles and furanic dienes opens the opportunity for atom-economic production of totally biomass-derived aromatic compounds. Despite significant success in this area already achieved, important problems have to be solved to introduce F2B to the chemical industry. Undoubtedly, the transition from fossil-carbon-based production to F2B-based production of aromatics will make all of industrial organic chemistry substantially more green and sustainable. Among the nearest goals, developing reliable F2B processes for practically demanding raw materials and increasing the cost efficiency of procedures are the cutting edge challenges. An efficient F2B process is the key to integrating biomass processing into a sustainable chemical industry.

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### Notes

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## Biographies

Fedor A. Kucherov received his doctoral degree from Zelinsky Institute of Organic Chemistry (Moscow) in 2004. In 2006 he joined the Chemical Diversity Institute as senior researcher in the medicinal chemistry lab. In 2015, he moved back to his *alma mater* to continue research work. His scientific interests include organic chemistry, selective drug delivery, green chemistry, and biomass conversion.

Leonid V. Romashov received his B.Sc. in chemistry from the Higher Chemical College of Russian Academy of Sciences in 2012 and joined Prof. Ananikov's research group at the Zelinsky Institute of Organic Chemistry as a graduate student where he investigated biomass conversion and the chemistry of biomass-derived compounds, receiving his Ph.D. in 2017. His current studies are focused on chemical transformations of HMF and organic synthesis.

Gleb M. Averochkin received his M.Sc degree in chemistry from Lomonosov Moscow State University in 2018 and joined the research group of Prof. Ananikov at the Zelinsky Institute of Organic Chemistry as a Ph.D. student. His current research focuses on the chemistry of HMF and its use in organic synthesis.

Valentine P. Ananikov received his M.Sc degree in 1996 (biochemistry), Ph.D. degree in 1999 (organic chemistry and catalysis), and Habilitation in 2003, and in 2005, he was appointed professor and laboratory head of the Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences. In 2008, he was elected as a member of the Russian Academy of Sciences and in 2019 as Academician of Russian Academy of Sciences. In 2012, he became professor of the Chemistry Department of Moscow State University. He was a recipient of the Russian State Prize for Outstanding Achievements in Science and Technology (2004), an Award of the Science Support Foundation (2005), a Medal of the Russian Academy of Sciences (2000), Liebig Lecturer by German Chemical Society (2010), Balandin Prize for outstanding achievements in the field of catalysis (2010), Organometallics Distinguished Author Award Lectureship by American Chemical Society (2016), Hitachi High-Technologies Award in Appreciation for Novel Approach and Outstanding Contribution to Setting New Standards for Electron Microscopy Applications in Chemistry (2016), and Zelinsky Prize for outstanding achievements in organic chemistry (2020). His research interests are focused on organic chemistry, mechanistic studies, catalysis, sustainable development, and molecular complexity.

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