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Divergent Diels–Alder methodology from methyl coumalate toward functionalized aromatics

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ABSTRACT

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Aromatic systems are prevalent across an extensive spectrum of compounds from components for material science and dyes to crucial precursors for the pharmaceutical industry. However, the functionalized aromatic systems that propagate such complexity are not always accessible from commercial suppliers. Implementing a Diels–Alder approach may conveniently enable improved access to sophisticated aromatic systems.

The Diels–Alder reaction is renowned for efficiently generating intricate systems from simpler substrates¹ and has been applicable across a range of dienes, including 2-pyrones.² In particular, since methyl coumalate (**1**) can be advantageously prepared from malic acid,³ it has emerged as an efficacious and renewable diene to obtain the intermediary bicyclo[2.2.2]octadiene for further functionalization.^{4–6} However, under thermal conditions, a broad range of substituted aromatic compounds are accessible by extrusion of an equivalent of carbon dioxide followed by subsequent elimination.^{2,7} Kraus et al. demonstrated that terminal alkenes required the use of a palladium catalyst to facilitate aromatization (Scheme 1).⁸

When paired with electron-rich olefinic dienophiles, **1** smoothly undergoes inverse electron-demand Diels–Alder reactions with ease followed by aromatization, while maintaining high levels of regioselectivity.^{2,4} We will present a methodology which employs methyl coumalate with substituted vinyl ethers, and more conveniently, ketals or orthoesters, to flexibly generate aromatic systems with increasing structural diversity in high yields (Scheme 2).

We commenced the investigation with cyclic vinyl ethers as dienophiles to generate complexity in the form of bifunctional aromatic systems (Table 1).⁹ By using an excess of commercially available pyran 2a, multiple transformations could be accomplished in the same pot, with a Diels-Alder/decarboxylation/aromatization sequence followed by alcohol protection to provide 3a in 77% yield. The simultaneous alcohol protection is particularly applicable where the presence of a primary alcohol could potentially interfere with other desired synthetic manipulations. Aromatic compound 3a has already proven beneficial as one of the primary starting materials for a cholesterol inhibitor.¹⁰ In similar fashion, the corresponding dihydrofuran **2b** follows the same reaction progression, but with a shorter methylene linker for the protected alcohol **3b**. With the confirmation of dihydrofuran as a viable dienophile, benzofuran 2c was a logical substrate toward more intricate aromatic systems. Unexpectedly, 2c regioselectively furnished para-substituted biphenyl alcohol 3c in 77% yield, as evidenced by the two sets of coupled doublets at 8.13 and 7.59 ppm in the ¹H NMR spectrum. Based on the experimental evidence, it appears that the Diels-Alder adduct exhibits the opposite

An inverse electron-demand Diels-Alder reaction between methyl coumalate and electron-rich

dienophiles produces substituted benzoates. A high-yielding, single-pot procedure transforms readily

accessible vinyl ether, ketal, or orthoester dienophiles into functionalized aromatic systems in a versatile



Scheme 1. General reaction using terminal alkenes to yield aromatic products.







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Scheme 2. General reaction of vinyl ethers toward aromatic systems.

regiochemistry relative to the preceding vinyl ethers, which likely arises from the preferred benzofuran reactivity at the 2-position, adjacent to the oxygen. Previous syntheses of **3c** resulted in low yields.¹¹

As a further extension, substituted pyran **2d** allows the introduction of an additional carbonyl moiety to the aromatic system via the hemiacetal. The resultant **3d** demonstrates the methodology's efficiency as a previous approach required a two-step homologation/oxidation of 3-bromobenzaldehyde.¹² The second carbonyl functionality could also be achieved by converting 2,4-pentanedione to methoxy enone **2e** by an acid-catalyzed procedure.¹³ Surprisingly, exclusive formation of **3e** was observed when **2e** was subjected to the established Diels–Alder conditions, which was confirmed by ¹H NMR data with a singlet at 3.77 ppm for the methylene protons adjacent to the aromatic ring. Presumably, the thermal environment facilitates isomerization of **2e** to the less sterically hindered **2f** dienophile which more readily participates in the ensuing reaction sequence.

The successful initial trials with vinyl ethers stimulated the extension to ketals or orthoesters to determine if they could function as equivalents of vinyl ether dienophiles (Table 2). Commercially available 2,2-dimethoxypropane (**4a**) smoothly produces **5a** under our established reaction conditions in 89% yield. Presumably, the methoxy group is situated for elimination to first generate 2-methoxypropene in situ. The resulting vinyl ether then reacts with methyl coumalate as previously detailed to furnish substituted aromatic system **5a**, whose spectral data match those of the commercially available compound, and can be carried on to

Table 1

Scope of reactions using vinyl ether dienophiles

Table 2

Scope of reactions using ketals or orthoesters as dienophiles





biologically active materials.^{14,15} Analyzing the overall transformation renders **4a** a regioselective replacement for propyne, with practical implications since **4a** is a liquid at room temperature.





The scope was further explored by preparing ketals from their corresponding ketones, which occurred in nearly quantitative yields and could be used without additional purification. As with 4a, the ketal **4b** derived from acetophenone functions as an equivalent of the phenylacetylene dienophile, both of which result in the same observed regioselectivity for 5b.¹⁶ In effect, 4b provides an alternative entry to substituted biphenyl systems with several applications¹⁷⁻¹⁹ as a metal-free supplement to Suzuki cross-coupling.^{20,21} While the examples thus far concentrate on altering the substituents on the aromatic ring, the methodology was directed toward an annulation strategy to assemble fused bicyclic compounds. The more highly substituted ketal 4c leads to a 1,2disubstituted vinyl ether intermediate to afford 5c in 81% yield. Multiple routes²²⁻²⁴ have employed **5c** as a target, one of which included a Diels-Alder reaction with methyl coumalate, but it involved the inconvenient preparation of a cyclohexyne dienophile.²⁵

The aforementioned aromatic compounds installed functionality with a carbon atom directly attached to the aromatic ring. However, the use of orthoesters allows the introduction of an oxygen bond on the aromatic ring. Commercially available trimethyl orthoacetate (4d) was evaluated as a dienophile to lead to anisole **5d**, with numerous biological applications^{26,27} and potential for deprotection to unmask its phenolic character. More importantly, 4d can be equated to the dienophiles methoxy ethyne or the corresponding ketene acetal. The former is not commercially available, and the latter has literature precedent with 2-pyrones,^{28,29} but is labile. Trimethyl orthopropionate (4e) reacted with 1 to afford a quantitative yield of 5e, cleanly establishing the trisubstituted aromatic ring. On the contrary, an earlier Diels-Alder attempt with 4-methoxy-5-methyl pyrone and methyl propiolate resulted in a non-selective 51:49 mixture of regioisomers.¹⁴ Orthoester 4f provided chloroester **5f**, which has been experimentally purified from a mixture of isomers³⁰ by multi-step routes.³¹ The halogen would rapidly enable the modification to advanced systems, as it has the essential functionality for organometallic coupling. Consequently, the relevance of our Diels-Alder approach with orthoesters is validated with the ability to expeditiously generate tri-substituted aromatic products with substantial applicability.^{32–34}

In summary, we have discovered a novel methodology based on a Diels–Alder sequence between methyl coumalate and readily accessible vinyl ethers, ketals, or orthoesters. Advantageously, all dienophiles are either commercially available or prepared in one step and can be used without purification. The regioselective, high-yielding, and single-pot experimental procedure expediently delivers substituted aromatic systems compared to previous routes that were either not selective for a single target, involved multistep syntheses, or required the use of palladium catalysts. The methodology is a versatile and divergent platform as it can accommodate simplified dienophiles to generate an expansive range of aromatic or biphenyl systems.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02. 083.

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