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Upgrading Malic Acid to Bio-based Benzoates *via* a Diels–Alder-Initiated Sequence with the Methyl Coumalate Platform

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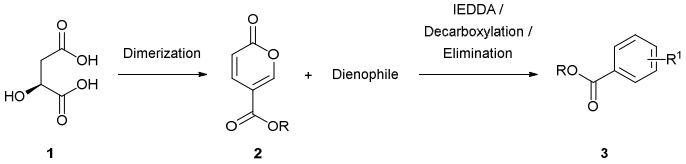
The conversion of naturally-occurring malic acid to the 2-pyrone methyl coumalate was optimized using a variety of acid catalysts. Coupling methyl coumalate with electron-rich dienophiles in an inverse electron-demand Diels–Alder (IEDDA)/ decarboxylation/elimination domino sequence resulted in an investigation of the scope and limitations of the methodology. The thermal, metal-free, and one-pot procedure allows regioselective access to diverse aromatic compounds including tricyclic, biphenyl, and pyridinyl systems for elaboration. A comparison with analogous pyrones demonstrates the striking efficacy of methyl coumalate as a versatile platform for the generation of biorenewable functionalized benzoates.

Substituted benzoates are ubiquitously integrated in many areas of chemistry with bountiful applications as plasticizers,[1] pharmaceutical agents,[2] and novel materials.[3] Dimethyl terephthalate occupies a significant position in the chemical industry since it can be hydrolyzed to terephthalic acid (TPA), a commodity chemical which boasted a global production of 50.7 million tons in 2012, corresponding to a $58 billion market.[4] Either compound can be incorporated as a co-monomer into everyday consumer materials including poly(ethylene terephthalate) (PET) in beverage containers[5] and poly(trimethylene terephthalate) (PTT) in carpet and clothing fibers.[6]

Functionalized aromatic compounds in industry are predominantly procured from petroleum-based resources which will experience continuous price increases as the supply steadily diminishes, and may expire as early as 2040.[7] With the impending forecast of scarce petroleum-based feedstocks, investigating the potential of biomass for specialty and commodity chemicals has become a prime focal area for green chemistry research.[8-10] The microbial fermentation of sugars like glucose provides a rich alternative source of chemical precursors and commodity chemicals.[11-13] Malic acid (**1**), a fermentation product of glucose, readily dimerizes to a key coumalate platform (**2**) from which an inverse electron-demand Diels–Alder (IEDDA) reaction/decarboxylation/elimination sequence constitutes a one-pot, scalable pathway to an expansive array of biorenewable benzoates (**3**) as outlined in Scheme 1.

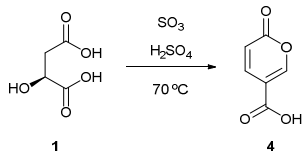
While *L*-malic acid is a naturally-occurring four-carbon carboxylic acid in grapes and apples,[14] industrial methods have focused on metabolically engineering microbial strains[15] to generate sufficient volumes. The conversion of malic acid into coumalic acid (**4**) is well known on a laboratory scale using concentrated sulfuric



Scheme 1 General reaction scheme from malic acid to bio-based benzoates.

acid as the solvent and fuming sulfuric acid, a corrosive dehydrating agent, as the reagent. This transformation, shown in Scheme 2, was reported by von Pechmann in 1891 and appears to be the only reported preparation.[16] Recent articles describe coumalic acid synthesis on a 100 gram scale using the von Pechmann conditions.[17,18]

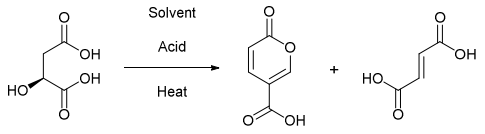
The intermediate in this transformation is formyl acetic acid. Two molecules of this aldehyde acid react to produce one molecule of coumalic acid. Although this reaction is suitable for a multigram laboratory scale, scaling these corrosive reaction conditions to a pilot plant scale is not feasible. Therefore, alternative reaction conditions are needed. The mechanism by which malic acid is transformed into the aldehyde acid was recently studied.[19] There is vigorous gas evolution at the beginning of the reaction. The gas is carbon monoxide, suggesting a direct protonation of the carboxylic acid as an



Scheme 2 von Pechmann coumalic acid synthesis from malic acid (**1**).

early step. Interestingly, less than five percent of fumaric acid (**5**) is produced under these acidic conditions. Since a strong acid and heat will be needed to protonate the carboxylic acid, we examined several strong anhydrous acids. The results are collated in Table 1. Concentrated sulfuric acid in dichloroethane afforded coumalic acid in very good yield on a five-gram scale (Table 1, entry 1). Adding a weaker co-acid lowered the reaction yields. The respective anhydrides were employed to remove water, but no significant difference was observed. Acetic acid or trifluoroacetic acid without sulfuric acid present gave small amounts of *O*-acylated products and returned starting material. The more strongly acidic sulfonic acids, triflic acid and nonafluorobutanesulfonic acid, gave coumalic acid in good yields, while methanesulfonic acid gave mixtures of **4** and **5**. Unexpectedly, *para*-toluenesulfonic acid gave a 71% yield of fumaric acid. With the best conditions discovered to date, we scaled up the reaction with triflic acid and obtained an 86% yield of coumalic acid on a five-gram scale (Table 1, entry 7). Solid acid catalysts including Nafion will be evaluated for the conversion in the future.

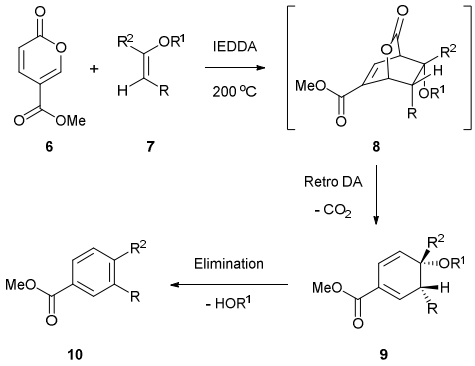
Table 1 Conversion of malic acid into coumalic acid



1 **4** **5**

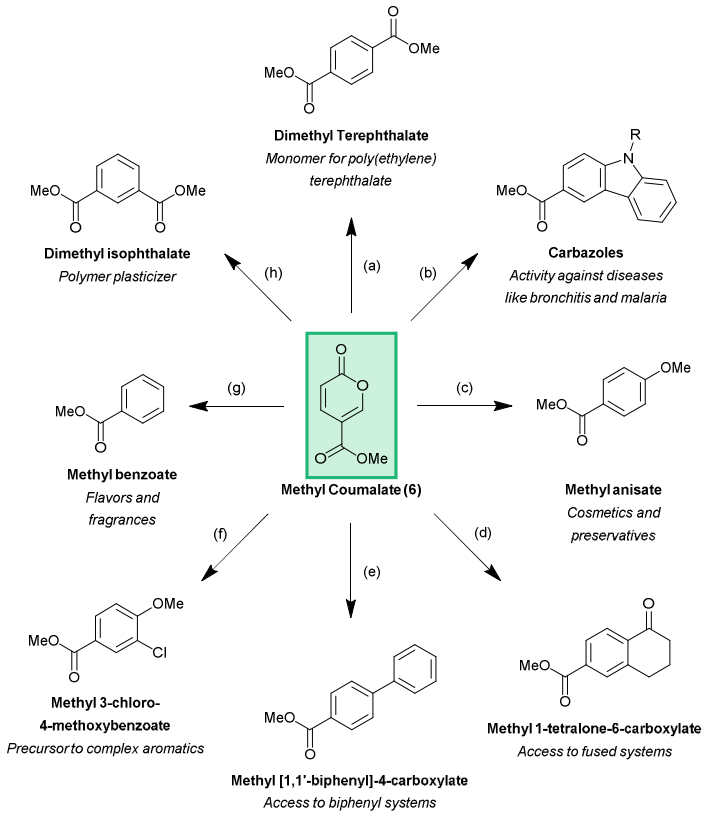
Entry	Acid	Temp. (°C)	Solvent	Additive	Yield **4**[a]	Yield **5**[a]
1	H_2SO_4	100	DCE	None	80[b]	5
2	H_2SO_4	120	AcOH	None	4	3
3	H_2SO_4	120	AcOH	Ac_2O	6	9
4	H_2SO_4	80	CF_3CO_2H	None	51	1
5	H_2SO_4	80	CF_3CO_2H	TFAA	44	0
6	$MeSO_3H$	100	DCE	None	14	25
7	**CF_3SO_3H**	**100**	**DCE**	**None**	**86**[b]	**4**
8	$C_4F_9SO_3H$	100	DCE	None	65	2
9	*p*-TSA	120	None	None	0	71

The reactions can be run with *DL*-malic acid as well. [a]Determined by ^{1}H NMR integration. [b]5 gram scale. DCE = dichloroethane



6 **7** **8** **10** **9**

Scheme 3 Putative mechanism for domino reaction sequence to functionalized aromatics.



Scheme 4 The coumalate platform and valuable applications of resultant benzoates.[29-31] Dienophiles: (a) methyl pyruvate (b) 1-alkyl-3-chloroindole (c) trimethyl orthoacetate (d) 2-methoxycyclohex-2-en-1-one (e) (1,1-dimethoxyethyl)benzene (f) 2-chloro-1,1,1-trimethoxyethane (g) butyl vinyl ether (h) methyl *trans*-3-methoxyacrylate.

The methyl ester of coumalic acid could be made in a single pot from malic acid simply by adding methanol to the reaction after the preparation of coumalic acid was complete. With a ready supply of methyl coumalate (**6**), we explored its potential as a biorenewable diene in a Diels–Alder-initiated strategy to aromatic compounds.

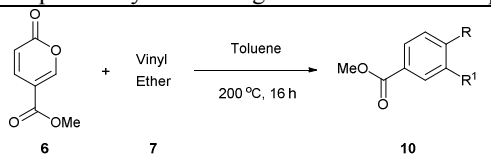
The Diels–Alder transformation efficiently infuses complexity into molecules[20] with high levels of control, and accordingly has been featured in domino reaction sequences.[21-23] Although 2-pyrones have been employed as the diene component in Diels–Alder reactions, researchers have primarily targeted the bicyclo[2.2.2]octadiene intermediate **8** for further manipulation[24-26] (Scheme 3). We had previously reported the reactions of methyl coumalate with electron-deficient alkenes such as methyl acrylate, acrylonitrile, and acrolein. The reactions yielded mixtures of *meta*- and *para*-substituted benzoates, with modest selectivity in favor of the *para*-isomer.[27]

The modest regioselectivity was attributed to the mismatched electronics of the electron-deficient character of methyl coumalate and the dienophile reactants. In contrast, alkyl and remote ether substituents on the dienophile provided *para*-substituted aromatic compounds by creating a more electron-rich dienophile, but required oxidation by palladium on carbon for the final aromatic compound.[28] Generating specific aromatic products reinforced the importance of electronic considerations for the IEDDA reaction.

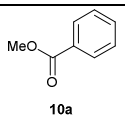
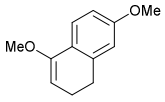
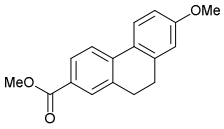
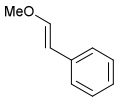
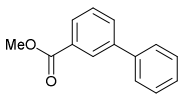
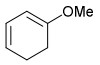
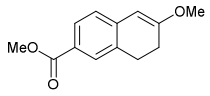
To maintain the high regioselectivity while increasing the functionality of the resulting benzoates, oxygen-containing moieties were introduced directly onto the alkene to increase the electron density and avoid the need for a transition metal catalyst. As predicted, the Diels–Alder adduct was likely followed by a subsequent retro Diels–Alder then elimination in a domino reaction with each conversion contingent on the previously formed *in situ* intermediate (Scheme 3). The Kraus group recently optimized the reaction conditions and published regioselective transformations with bench-stable dienophile equivalents,[29] captodative dienophiles to achieve a formal synthesis of biorenewable terephthalic acid,[30] and substituted indoles to biologically-active carbazole alkaloids.[31] With the advantages conferred by the metal-free thermal conditions, we aimed to design dienophiles with additional functionality to examine the scope and limitations of the methodology, capitalizing on the bio-based coumalate platform we have already initiated to create greener substituted benzoates (Scheme 4).

The investigation of the electron-rich dienophiles commenced with vinyl ethers including those with extended conjugation (Table 2). The simplest vinyl ether for comparison with a compatible boiling point for the reaction conditions was butyl vinyl ether (**7a**), which smoothly provided methyl benzoate (**10a**) in 89% yield. Methyl benzoate can easily be hydrolyzed to benzoic acid, a widespread preservative in food and cosmetics,[32] normally produced through the oxidation of petroleum-derived toluene.[1] While methyl benzoate is naturally present in certain plant species that leads to its application in fragrant oils,[33] utilizing a synthetic route would increase availability while avoiding harsh oxidation conditions. To supplement previously reported aromatic compounds through vinyl ethers,[29] the vinyl ether **7b** of 6-methoxy-1-tetralone was prepared[34] and subjected to the thermal conditions, regioselectively furnishing the fused tricyclic molecule **10b**. The resulting 34% yield reflects the tendency of vinyl ether **7b** to revert to the initial tetralone which was present in the crude ^{1}H

Table 2 Scope of vinyl ethers to generate aromatic compounds[a]



6 7 10

Entry	Vinyl Ether	Aromatic Product	Yield[b] (%)
1	 7a	 10a	89[c]
2	 7b	 10b	34
3	 7c	 10c	51
4	 7d	 10d	72

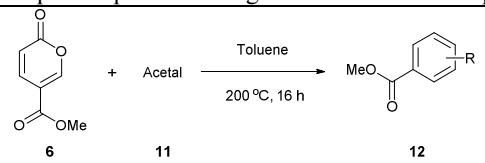
[a]Reaction conditions: **6** (1 mmol) and **7** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. [b]Isolated yield. [c]Reaction conditions involved 1.5 mmol of **7**.

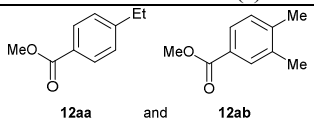
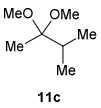
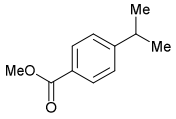
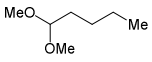
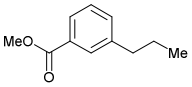
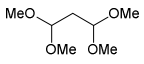
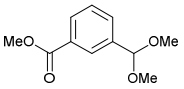
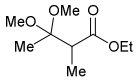
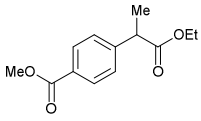
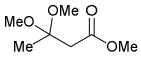
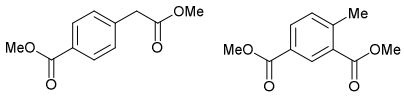
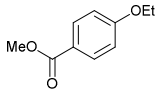
NMR, and also observed to a larger extent with the corresponding dimethyl ketal as the dienophile. Notwithstanding, the cascade reaction quickly established the more complex **10b** backbone, which could potentially lead to anthracene derivatives following oxidation. The methodology conveniently grants entry to biaryl systems including **10c** where further derivitization exposes potential organic materials[35] and treatments for psychotic disorders.[36] By comparison, literature syntheses necessitate the use of transition metal catalysts and starting aromatics with halogen[37] or sulfamate[38] substituents. Finally, vinyl ether systems with extended conjugation was explored with 1-methoxy-1,3-cyclohexadiene (**7d**) which solely afforded **10d**. The chemoselectivity for the more distant alkene was verified in a similar system by Corey[39] to broaden the range of attainable benzoates through the methodology.

As previously reported,[29] ketals were readily prepared from an acid-catalyzed conversion of the corresponding ketone. The thermal conditions led to methanol elimination from the ketal, allowing it to function as a dienophile equivalent that was conveniently used in crude form upon preparation and more stable than its isolated counterpart. The scope and limitations were more thoroughly probed with the ketal **11a** from 2-butanone, to determine whether selectivity would arise (Table

3, entries 1-5). A slight preference for the tri-substituted product **12ab** was detected from *in situ* formation of the more thermodynamically stable dienophile; however, it was part of an inseparable mixture which would not be feasible for incorporation into an efficient synthetic strategy. The analogous cyclic ketal **11b** was similarly utilized as the dienophile, but only starting material was recovered. The non-reactivity was ascribed to the higher likelihood of **11b** to maintain the stable dioxolane rather than elimination to form an *in situ* dienophile. The

Table 3 Scope and limitations of acetal dienophile equivalents to generate aromatic compounds[a]



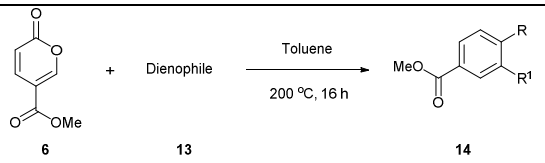
Entry	Acetal	Aromatic Product(s)	Yield[b] (%)
1	 **11a**	 **12aa** and **12ab**	73 2:3[c]
2	 **11b**	–	0
3	 **11c**	 **12c**	40
4	 **11d**	 **12d**	43
5	 **11e**	 **12e**	0
6	 **11f**	 **12f**	76
7	 **11g**	 **12ga** and **12gb**	76 2:1[d]
8	 **11h**	 **12h**	48

[a]Reaction conditions: **6** (1 mmol) and **11** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. [b]Isolated yield, with the exception of entry 1. [c]An inseparable mixture of regioisomers resulted in a 2:3 ratio of **12aa**:**12ab**, as determined by integration of the crude ^{1}H NMR. [d]A mixture of regioisomers resulted in a 2:1 ratio of **12ga**:**12gb**, as determined by integration of the crude ^{1}H NMR.

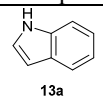
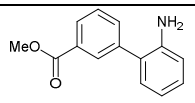
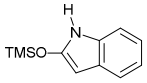
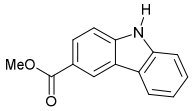
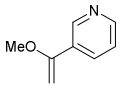
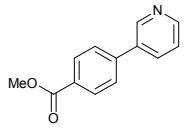
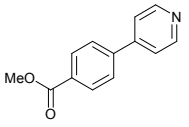
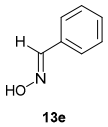
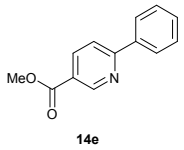
exclusive regioselectivity returned once the ketal was adjacent to an isopropyl group in **11c**, which would only form one productive dienophile to provide aromatic product **12c** in 40% yield. In contrast, earlier preparations resorted to a metal-catalyzed Negishi coupling[40] or oxidation[41] before continuing the synthesis for a potential treatment of Alzheimer's disease.[42] The methodology could also be extended to acetals of aldehydes including 1,1-dimethoxypentane (**11d**) in 43% yield. In general, the total yield is lower relative to most of the parallel ketal systems as by-products appeared under the reaction conditions from decomposition of the acetal and regeneration of the starting aldehyde. However, the resultant **12d** demonstrated that acetals of aldehydes are suitable substrates and can alternatively be used to generate aromatic compounds without incrementally functionalizing benzene derivatives. The double acetal of malonaldehyde **11e** seemed to be an interesting substrate that might lead to **12e**; unfortunately, the predicted vinyl ether from the elimination of one equivalent of methanol conceivably isomerized *in situ*. The supposition was mirrored by the crude ^{1}H NMR which contained a complex mixture of aromatic peaks, suggesting the formation of multiple aromatic products.

After developing the scope and limitations of acetal and ketal dienophile equivalents in the IEDDA-initiated approach, we were inspired to broaden the breadth of ketals that would create alkenes adjacent to carbonyl systems (Table 3, entries 6-8). Precedent research in our group established that alkenes with both electron-deficient and electron-donating groups in conjunction with methyl coumalate produced regioselective aromatic systems in good yield, including the industrially valuable dimethyl terephthalate.[30] In accordance with previous findings, the ketal of ethyl 2-methylacetoacetate **11f** as a dienophile equivalent regioselectively constructed **12f** in 76% yield without transesterification during the reaction. Literature precedent for the preparation of **12f** depended on a palladium coupling of the methyl 4-iodobenzoate with a ketene silyl acetal.[43] The 2-methyl substituent imparted regioselectivity to the transformation as the ketal **11g** of methyl acetoacetate afforded a 76% overall yield of isomers. Although **12ga** was the major product from the analogously less-substituted dienophile, a fraction of the more substituted *in situ* alkene reacted under the thermal conditions to provide **12gb** in a 2:1 ratio. Lastly, commercially available 2,2-diethoxypropanenitrile (**11h**) smoothly supplied methyl 4-ethoxybenzoate (**12h**) in 48% yield. The slightly depressed yield presumably originates from the mitigating effect of the strongly withdrawing cyano group on the captodative dienophile created in the reaction medium. While pyrones have been exploited in the literature to synthesize **12h**, the reaction of methyl coumalate and ethoxyethyne only furnished 9% of the desired compound.[44] In a normal electron-demand Diels–Alder reaction, 4-ethoxy-2-pyrone was combined with methyl propiolate but mixtures of regioisomers resulted, and **12h** was the minor product relative to the *meta*-substituted compound in a 23:77 ratio of *para*- to *meta*- isomers.[45] Furthermore, pharmaceutically-active agents against tuberculosis[46] and cancer[47] have been elucidated after derivitizing the **12h** aromatic system. We have expounded additional ketal and acetal dienophile equivalents for incorporation into the methodology, which sometimes were not effective reactants, but mostly aligned with the IEDDA principles to regioselectively yield aromatic products.

Table 4 Scope and limitations of nitrogeneous dienophiles to generate aromatic alkaloids[a]



6 13 14

Entry	Dienophile	Aromatic Product	Yield[b] (%)
1	 13a	 14a	0
2	 13b	 14b	0[c]
3	 13c	 14c	0[d,e]
4	 13d	 14d	23[e]
5	 13e	 14e	18

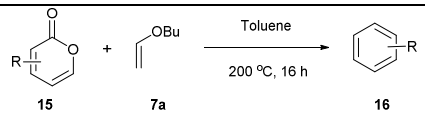
[a]Reaction conditions: **6** (1 mmol) and **13** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. [b]Isolated yield. [c]Dienophile reversion to oxindole observed. [d]Dienophile reversion to 3-acetylpyridine observed. [e]Tar formation observed during the reaction.

While the aforementioned dienophilic partners appended either carbon or oxygen-containing substituents onto the aromatic ring, we strived to introduce nitrogenous units into the final aromatic system (Table 4). Initially, we used indole (**13a**) as the equivalent of the benzofuran system, the latter of which efficiently provided methyl 2'-hydroxy-[1,1'-biphenyl]-4-carboxylate in 77% yield.[29] The oxygen in benzofuran served as a vinyl ether for the IEDDA and also the alkoxy leaving group for aromatization, which could potentially be extrapolated to the indole system. However, partnering methyl coumalate (**6**) with **13a** only returned starting material instead of the biphenyl aniline derivative **14a**. Undeterred, we then targeted the related carbazole skeleton as variants have been incorporated as materials[48] and oxidized versions of 3-methylcarbazole expressed beneficial biological activity.[49] Progress to the carbazole scaffold began with the enol silyl ether of commercially-available 1-methyl-2-oxindole (**13b**) which was activated to encourage the IEDDA with methyl coumalate. The better siloxy leaving group was expected to prevent potential ring-opening to the aniline structure, but carbazole **14b** was not realized as **13b** regressed to the starting oxindole. The TBS cognate fared similarly and the initial oxindole was observed in the crude ^{1}H NMR. Designing 1-alkyl-3-chloroindole dienophiles led to successfully achieving the desired carbazole backbone and signaled the first successful IEDDA reaction of substituted indoles with methyl coumalate.[31] We then embarked on an initiative to access pyridinyl systems through our methodology, starting with pyridine-containing dienophiles. The methyl vinyl ether of 3-acetylpyridine **13c** was employed as the dienophile but did not give rise to the anticipated **14c** as the 3-acetylpyridine reappeared over the course of the reaction. Surprisingly, 4-vinylpyridine (**13d**) under thermal conditions led to the biphenyl system **14d** in 23% yield, which might have been hindered by tar formation in the reaction; however, up to 51% yield can be obtained with the addition of Pd/C to facilitate the oxidation.[50] While pyridinyl systems had shown some utility as dienophiles, we endeavored to explore whether the methodology could fashion pyridines from oximes. We were rewarded when *E*-benzaldehyde oxime (**13e**) led to **14e** in 18% yield, indicating that the added electron density from the oxygen aided the regioselectivity and water lost during the reaction led to the installation of aromaticity in the pyridine ring. The crude ^{1}H NMR suggested that the reaction primarily resulted in the desired pyridine which leads to uncertainties about the mass loss although some tars were detected during the reaction. Arriving at **14e** most importantly highlights the breadth of the domino reaction series with methyl coumalate

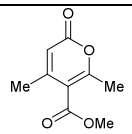
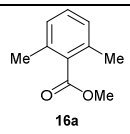
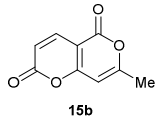
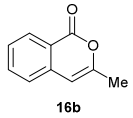
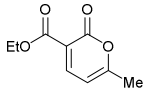
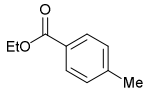
which can accommodate oxime dienophiles to construct the pyridine core.

Methyl coumalate has been documented as a bio-based diene for the IEDDA/decaroxylation/elimination cascade sequence from which numerous aromatic systems have been derived when combined with varying dienophiles. We translated the principles that governed the successful trials with methyl coumalate to other 2-pyrones to further develop the reach of the methodology with butyl vinyl ether (Table 5). The methyl ester of dehydroacetic acid (**15a**) is structurally homologous to methyl coumalate but with additional methyl groups that could influence the reaction.

Table 5 Studies of 2-pyrone dienes to generate aromatic compounds[a]



15 7a 16

Entry	Diene	Aromatic Product	Yield[b] (%)
1	 15a	 16a	54
2	 15b	 16b	45[c]
3	 15c	 16c	42

[a]Reaction conditions: **15** (1 mmol) and **7a** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. [b]Isolated yield. [c]Yield calculated based on recovered starting material as the reaction was stopped after 16 h for practical purposes rather than continuing the reaction until all starting material was consumed.

The slight modifications introduced additional sterics and a more muted electron-withdrawing character of **15a** which affected performance in the domino reaction, evidenced by the 54% yield of **16a**. The same 2-pyrone **15a** was also coupled in the past with ethyl vinyl ether at a lower temperature over a longer time frame to attain the Diels–Alder adduct along with **16a**, where the adduct was quantitatively converted to **16a** upon standing.[51] We then turned to **15b**, another bio-based pyrone arising from the condensation of malic acid and triacetic acid lactone,[52] the latter of which also can be upgraded from glucose. Although **15b** contained two potential 2-pyrone diene moieties, the IEDDA-initiated sequence chemoselectively provided isocoumarin **16b** with 45% conversion of the more electron-deficient pyrone unit. Finally, the electronics of the 2-pyrone system was investigated with an ester at the 3-position in **15c**. In conjunction with butyl vinyl ether (**7a**), ethyl 4-methylbenzoate (**16c**) was cleanly isolated in 42% yield, corroborating the claim that the electron-withdrawing functionality more effectively yields product compared to the 3-position.[53] The additional 2-pyrone dienes upheld the precepts of the IEDDA along sterics, chemoselectivity, and electronics to regioselectively generate aromatic compounds.

Conclusions

The cascade reaction sequence of methyl coumalate and dienophiles in an IEDDA/decarboxylation/elimination methodology has created a metal-free entryway to a broad spectrum of functionalized benzoates. Optimizing the acid-catalyzed route to methyl coumalate from naturally-occurring malic acid led to the emergence of a bio-based diversification platform. The main determinant for the successful one-pot cascade was designing electronically coordinated dienophiles to complement the electron-deficient methyl coumalate diene to regioselectively assemble targeted aromatic systems. A systematic analysis into the scope and limitations of the methodology revealed challenges for the system with readily prepared acetals adjacent to both primary or secondary carbons and certain nitrogen-containing systems. However, the examination unearthed successful access to tricyclic, biphenyl, and pyridinyl frameworks which supplemented our previous research to characterize the expanse of the methodology emanating from methyl coumalate. While the most detailed explorations arose from methyl coumalate, other 2-pyrone dienes reinforced the concepts of sterics, chemoselectivity, and electronics of the IEDDA-initiated sequence consistent with the methyl coumalate results. From industrially-relevant pharmaceuticals to plastics, a myriad of possibilities is achievable through the domino reaction of methyl coumalate as an alternative route for biorenewable functionalized aromatics to advance the goals of green chemistry and approach the reality of a sustainable future.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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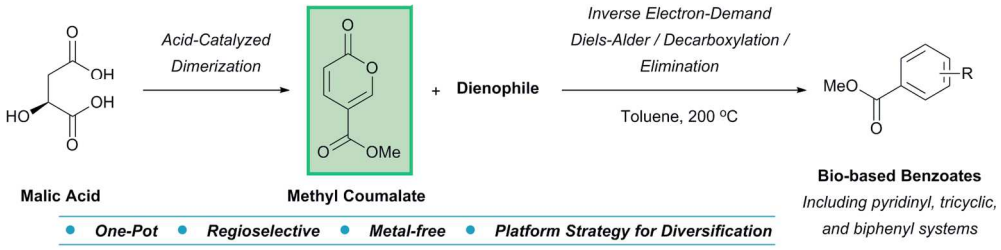

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