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One-pot formal synthesis of biorenewable terephthalic acid from methyl coumalate and methyl pyruvate

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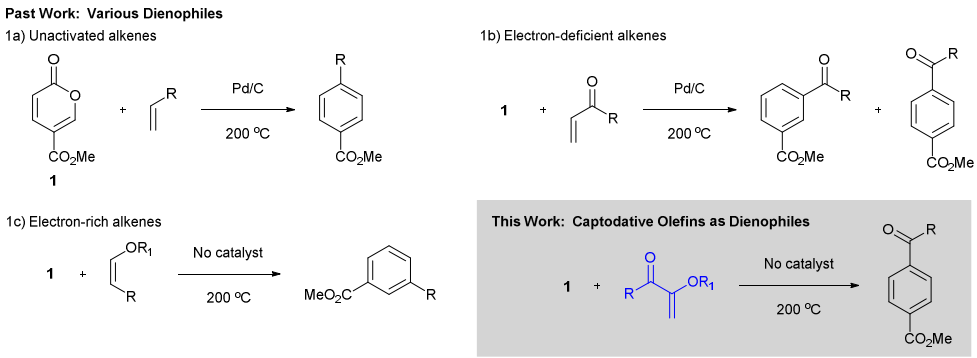
Diverse functionalized aromatic compounds are constructed from captodative dienophiles with exclusive regioselectivity. 100% biorenewable dimethyl terephthalate (DMT) from methyl coumalate and methyl pyruvate is achieved in a one-pot, Diels-Alder/decarboxylation/elimination sequence in nearly quantitative yield. The DMT system is solvent-free and purification is accomplished through recrystallization. DMT hydrolysis reveals the co-monomer terephthalic acid (TPA) as a bio-based drop-in replacement for the polymer industry, avoiding harsh oxidation and petrochemicals.

Functionalized aromatic systems are indispensable commodity building blocks for industry and are embedded within elaborate structures in natural products and unique materials. Aromatics permeate the chemical industry; unfortunately, they are primarily derived from diminishing and volatilely priced petroleum-based sources, with estimates that demand could potentially exceed natural reserves as early as 2040.[1] The rising demand for aromatic compounds, especially polymerization co-monomers like terephthalic acid (TPA) for consumer products, has attracted attention to the critical necessity of developing alternative feedstocks.[2-5] Naturally-occurring materials contain limited aromatic content outside of lignin; moreover, the technology to isolate aromatics effectively from lignin is still in its early stages.[4,6,7] In contrast, upgrading malic acid obtainable through glucose fermentation[8,9] leads to a solution for green aromatics through a key Diels-Alder reaction.

Researchers have efficiently generated aromatic systems through variegated approaches,[10,11] including the acclaimed Diels-Alder reaction which has long been instrumental in building complexity through domino reaction sequences.[12-14] Furthermore, captodative olefins with stabilization arising from an electron-rich and an electron-poor substituent appended to an alkene[15] have been successfully incorporated in radical additions,[16] Friedel-Crafts reactions,[17] 2,3-cycloadditions,[18] and Diels-Alder transformations.[19-21] In the context of 2-pyrones, the Diels-Alder reaction has been extensively explored to install consecutive stereogenic centers in the bicyclic adduct for further elaboration.[22-24] Recently, aromatic systems have been obtained with methyl coumalate (**1**) both with unactivated alkenes[25] and electron-deficient olefins[26] (Scheme 1). In each instance, catalytic palladium was required to effect aromatization. One drawback is that the electron-deficient alkenes or alkynes afforded mixtures of regioisomers.

Methyl coumalate as a diene represents a convenient bio-based

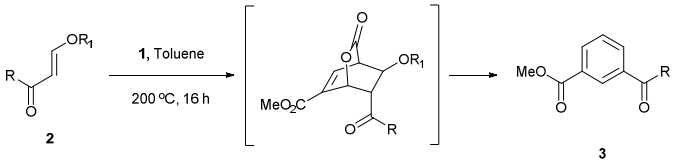


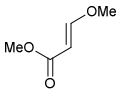
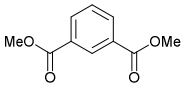
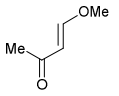
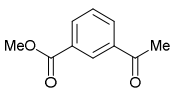
Scheme 1 General reaction summary of literature precedent and current research.

platform for diversification, since it arises from the acid-catalyzed dimerization of naturally-occurring malic acid.[27] The Kraus group recently reported metal-free thermal conditions which convert methyl coumalate to aromatic systems in a one-pot Diels-Alder/decarboxylation/elimination cascade (Scheme 1).[28] The regioselectively obtained aromatic products reflect the compatibly matched electron-deficient methyl coumalate diene with electron-rich dienophiles in an inverse-electron demand Diels-Alder reaction (IEDDA).

While the literature describes the scope of electron-rich, unactivated, and electron-poor dienophiles with methyl coumalate, dienophiles with both an electron-rich and an electron-poor moiety have remained largely uninvestigated. We will present a methodology to couple methyl coumalate with captodative dienophiles to regioselectively generate a broad spectrum of aromatic compounds (Scheme 1), which culminates in an expedient formal synthesis of 100% biorenewable terephthalic acid, a high-volume commodity chemical.

Table 1 *meta*-Selective aromatics from 1,2-substituted dienophiles[a]

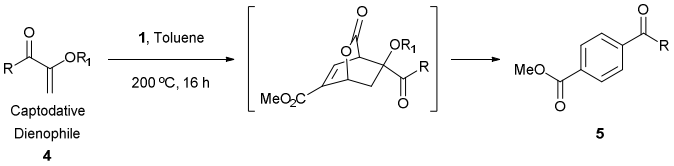


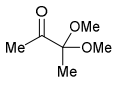
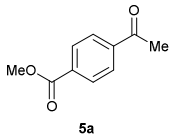
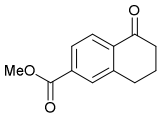
Entry	Dienophile	Aromatic Product	Yield[b] (%)
1	 2a	 3a	83
2	 2b	 3b	92

[a]Reaction conditions: **1** (1 mmol) and **2** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. [b]Isolated yield.

We initially began pairing substituted dienophiles with methyl coumalate (Table 1) to determine whether the additional electron-withdrawing group would mitigate the regioselectivity previously observed with electron-rich vinyl ethers.[28] When methyl *trans*-3-methoxyacrylate (**2a**) is incorporated as the dienophile, only the *meta*-substituted dimethyl isophthalate (**3a**) is produced in 83% yield. The singly obtained regioisomer is attributed to the accompanying selectivity for the bicyclo[2.2.2]octene adduct formed *in situ*. Earlier Diels-Alder approaches with 2-pyrones and electron-deficient alkenes have attempted to target **3a** selectively; however, only mixtures of regioisomers resulted.[29] The newly introduced synthetic strategy provides facile access to **3a** for integration into polymers.[30,31] Consonantly, ketones can function as the electron-withdrawing component in the dienophile, which undergoes similar reactivity (Table 1, entry 2). The resultant 3-acetylbenzoic acid methyl ester (**3b**) is not readily available through commercial suppliers, although it is a building block for anti-obesity[32,33] or cardiovascular drugs.[34] Most approaches to **3b** begin with a di-substituted aromatic system which can undergo further functionalization.[35,36] Although a Diels-Alder sequence has been developed from a butadiene equivalent and an electron-deficient alkyne, two discrete steps are necessary and the Diels-Alder reaction is not completely regioselective.[37] Dienophiles **2a** and **2b** do not conform to the traditional captodative definition where the electron-rich and electron-donating groups exist on the same carbon. However, they are synthetically practical synthons since both substituents provide synergistic electronic stabilization, analogous to the cooperativity of enamine dienophiles.[38]

Table 2 *para*-Selective aromatics from captodative dienophiles[a]

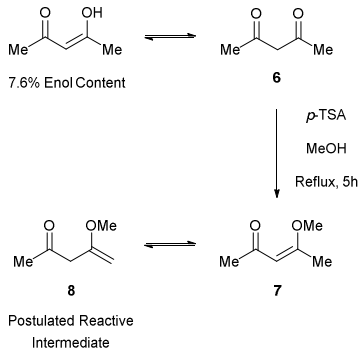


Entry	Captodative Dienophile	Aromatic Product	Yield[b] (%)
1	 4a	 5a	94
2	 4b	 5b	75

[a]Reaction conditions: **1** (1 mmol) and **2** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. [b]Isolated yield.

The successful generation of *meta*-substituted aromatics stimulated expansion of the captodative dienophiles to favor *para*-substituted aromatic compounds (Table 2). The exploration commences with 3,3-dimethoxy-2-butanone[39] (**4a**) as a captodative dienophile equivalent since ketals are primed to eliminate methanol under the thermal conditions to reveal the dienophile.[28] As predicted, the Diels-Alder reaction sequence forms only *para*-substituted methyl 4-acetylbenzoate (**5a**). This compound has been utilized as an advanced intermediate to synthesize alkaloids[40] and enzyme modulators.[41] Literature precedent majorly focuses on manipulating commercially available aromatic compounds;[42] however, the posited methodology allows functionalized aromatics to be constructed from two non-aromatic substrates. While ketals are obtained in one step from the corresponding ketones, we envisioned that the thermal conditions might induce a shift in the keto-enol equilibrium to allow the enol to react as a captodative dienophile. By employing 2,3-butanedione, the same regioselective aromatic isomer **5a** resulted, albeit in 18% unoptimized yield. The yield likely was limited by the experimentally determined 1.1% enol content at equilibrium based on the entropically disfavored restricted rotation in the enol over the keto form, characteristic of acyclic systems.[43] However, the yield is significantly greater than the 3% observed by crude ^{1}H NMR with acetophenone as the substrate, which lacks captodative stabilization. Among the di-carbonyl systems, α-diones are the most amenable to generate aromatics through the reaction sequence. Although the 1,3-dione acetylacetone (**6**) was calculated to have a higher 7.6% enol content at equilibrium,[43] it was unreactive to the same reaction conditions (Scheme 2). The non-reactivity may imply a predilection for

reaction at the less-substituted olefin **8** through isomerization, which was observed when dienophile **7** was isolated and subjected to the standard reaction conditions.[28]



Scheme 2 Enol content and reactivity of acetylacetone.

Finally, cyclic methoxy enone **4b** cleanly furnishes substituted tetralone **5b** which is not readily available through commercial suppliers. The complementary 1,2-cyclohexanedione was subjected to similar reaction conditions and provided **5b** in a reasonable 36% unoptimized yield likely through an increased thermal enolization from the ambient 4.0% enol content.[43] Captodative dienophiles in the IEDDA with methyl coumalate maintained complete regioselectivity despite their electron-poor constituent, which suggests that the electron-donor is the major contributor to predict regiochemistry. In addition to conserving regioselectivity, captodative olefins have proven their merit as entities that introduce electron-deficient functionality adjoined to the resulting aromatic system.

We then turned to terephthalic acid (TPA) with its *para*-substituted carboxylic acids, which was ultimately the high-value target for our promising technology capitalizing on captodative dienophiles. TPA as a commodity chemical commands a dominant presence since it has been ranked within the six highest domestically produced organic commodity chemicals in 2001 by the US International Trade Commission.[44] On a global scale, production reached 50.7 million tons which translates to a $58 billion market within the last year.[45] The industrial significance of TPA and its ester dimethyl terephthalate (DMT) lies in their ability to act as condensation co-monomers for poly(ethylene terephthalate) (PET).[46] Various companies specifically favor DMT as the co-monomer with ethylene glycol due to its preferential properties.[46-49] PET's societal significance is reflected by its annual production of nearly 60 million tons and its incorporation in numerous consumer applications, with the highest volumes in polyester fibers then in bottles and packaging.[46] While TPA has formidably impacted society and is projected to continue its ascent into the future,[50] its synthesis relies on a harsh oxidation of petroleum-based *p*-xylene,[51] itself isolated from a complex mixture of isomers. In contrast, bio-based captodative dienophiles in conjunction with methyl coumalate may create a sustainable shift toward biorenewable feedstocks.

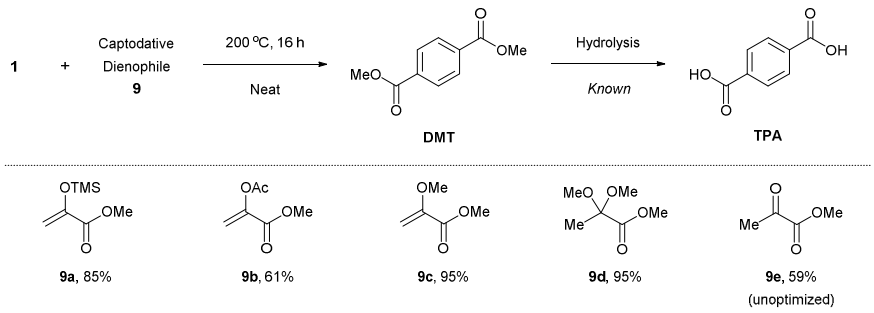
With potential to profoundly impact the process for a high-volume commodity chemical, the reaction conditions were specifically optimized for DMT using the enol silyl ether of methyl pyruvate (**9a**) as delineated in Table 3. Methyl pyruvate was identified as an exemplary dienophile since its preparation involves an esterification of pyruvic acid, the major natural product from the glycolysis cycle. In general, the effectiveness of the systematic changes in reaction conditions was analyzed by comparing the ratio of the characteristic DMT methyl ester peak at 3.95 ppm to the methyl ester peak of the limiting reagent methyl coumalate at 3.88 ppm in the crude ^{1}H NMR spectra. The reaction sequence is concentration-dependent (Table 3, entries 2 and 11) and allowing the Diels-Alder/aromatization sequence to proceed without solvent allows the reaction to occur with fewer equivalents of the dienophile but with similar completion. Along the parameter of the dienophile : diene ratio (Table 3, entries 3-5 and 10-11), an excess of 3.0 equivalents of the dienophile **9a** was necessary for complete consumption of methyl coumalate (**1**) at 0.5M, but an excess of 1.5 equivalents was sufficient under neat conditions. The effect of temperature was next investigated (Table 3, entries 2-6 and 11), and decreasing the temperature to 150 ^{o}C was effectual in the absence of solvent. Finally, the optimal reaction conditions are collated in Table 3, entries 11-12, to eliminate the dependence on aromatic solvents. Both sets of conditions completely consume the limiting reagent, depending on the preference to run the reaction at a lower temperature or utilize higher equivalents of the dienophile.

Table 3 Reaction optimization trials

Entry	Conc. (M)[a]	Temp. (^{o}C)	Time (h)	Equiv. of **9a**	Ratio of DMT : **1**[b]
1	0.5	200	16	3.0	1 : 0
2	0.5	150	18	3.0	1 : 0.48
3	0.5	100	17	3.0	1 : 4.00
4	0.5	200	17	1.5	1 : 0.53
5	Neat	150	16	1.5	1 : 0.12
6	Neat	125	18	1.5	1 : 0.72
7	Neat	150	6	1.5	1 : 0.50
8	Neat	150	3	3.0	1 : 0.49
9	Neat	150	1	1.5	1 : 1.31
10	Neat	150	17	1.0	1 : 1.12
11	**Neat**	**150**	**16**	**3.0**	**1 : 0**
12	**Neat**	**200**	**16**	**1.5**	**1 : 0**

[a]Entries 1-4 were run with toluene as the solvent. [b]Ratios determined by integration of crude ^{1}H NMR.

With the optimal reaction conditions in hand, five captodative dienophiles were explored to flexibly generate DMT (Scheme 3), which can undergo a facile hydrolysis to TPA.[52] At the outset, the enol silyl ether of methyl pyruvate[53] (**9a**) was isolated through recrystallization after subjection to the reaction conditions in Table 3, entry 12, which resulted in 85% yield. Although recrystallization is a convenient purification method conducive for industrial scale, pure DMT spontaneously sublimes on the walls of the sealed flask during the reaction as captured in Figure 1. Recognizing that the enol silane would not be feasible for industrial-scale reactions, 2-acetoxyacrylate[54,55] (**9b**) became the next dienophilic partner, with a straightforward acid-catalyzed preparation from acetic anhydride and methyl pyruvate. The desired *para*-substituted DMT was the major product, along with 3% dimethyl isophthalate (DMI), presumably due to the heightened electron-withdrawing nature of the dienophile as a whole. Conversely, 2-methoxyacrylate[56] (**9c**) generated DMT regioselectively in 95% yield without formation of DMI. While advantageous, generating **9c** from methyl pyruvate involved isolating the ketal then eliminating one equivalent of methanol under acidic conditions. We were interested in assembling DMT as rapidly as possible with the fewest modifications of bio-based methyl pyruvate, which successively led to using the crude ketal directly. Strikingly, methyl 2,2-dimethoxypropanoate[56] (**9d**), which is only a



Scheme 3 Captodative dienophiles to generate dimethyl terephthalate

Figure 1 DMT sublimation during the reaction.

single step from methyl pyruvate, equally affords high yields of DMT. We postulated that the <10% enol content of pyruvic acid in CCl_4, stabilized by intramolecular hydrogen bonding,[57] would allow even more direct access to DMT with methyl pyruvate (**9e**). The hypothesis was corroborated by the 59% yield which may be elevated if left for a longer period of time since methyl coumalate was not completely consumed during the standard 16 hours. Utilizing a ketone adjacent to the ester functions as a better captodative dienophile assumedly due to the placating electron-withdrawing effect of the ester compared to a ketone as observed in previous cases with an adjacent ketone. Since unaltered methyl pyruvate presents itself as a captodative dienophile equivalent to successfully achieve DMT, it adds another dimension of flexibility and convenience to the biorenewable methodology.

In summary, captodative dienophiles coupled with the methyl coumalate platform distinctively provide a regioselective route to functionalized aromatic systems through a one-pot domino Diels-Alder/decarboxylation/elimination sequence. Previously, only electron-neutral or electron-rich groups were plausible dienophile substituents to promote the electron-matched components under IEDDA conditions; however, captodative dienophiles allow access to electron-withdrawing substituents directly on the resultant aromatic structure. Flexibility is inherent in designing captodative dienophiles to generate either *para*- or *meta*-substituted aromatic compounds, depending on the relative placement of the electron-withdrawing and electron-donating group across the olefin. Furthermore, diversified aromatic systems can be accessed through the combination of non-aromatic precursors without being limited by the availability of aromatic compounds for incremental functional group manipulation. Implementing the strategy in the case of methyl coumalate and methyl pyruvate leads to a 100% biorenewable formal synthesis to the mass market commodity chemical terephthalic acid, although dimethyl terephthalate itself is preferred as a co-monomer in industry. Advantageously, an additional petroleum-based solvent is avoided for DMT and a versatile approach to accommodate varying dienophiles provides high yields and rapid assembly of DMT. From an industrial perspective, the methodology features a facile purification by recrystallization, and introduces a potentially scalable drop-in replacement for DMT or TPA that bypasses the harsh oxidation of *p*-xylene. The methodology exceptionally addresses the immediate global issue of rapidly depleting petrochemicals and highlights biorenewable alternative feedstocks as a green innovation toward the chemical building blocks of a sustainable future.

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Notes and references

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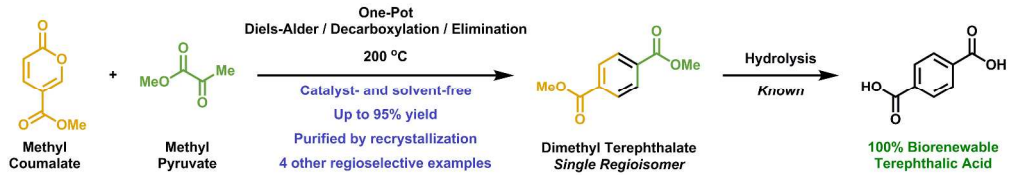

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