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

Jennifer J. Lee\textsuperscript{a} and George A. Kraus\textsuperscript{*a}

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 volatily priced petroleum-based sources, with estimates that demand could potentially exceed natural reserves as early as 2040.\textsuperscript{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.\textsuperscript{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.\textsuperscript{4,6,7} In contrast, upgrading malic acid obtainable through glucose fermentation\textsuperscript{8,9} leads to a solution for green aromatics through a key Diels-Alder reaction.

Researchers have efficiently generated aromatic systems through variegated approaches,\textsuperscript{10,11} including the acclaimed Diels-Alder reaction which has long been instrumental in building complexity through domino reaction sequences.\textsuperscript{12-14} Furthermore, captodative olefins with stabilization arising from an electron-rich and an electron-poor substituent appended to an alkene\textsuperscript{15} have been successfully incorporated in radical additions,\textsuperscript{16} Friedel-Crafts reactions,\textsuperscript{17} 2,3-cycloadditions,\textsuperscript{18} and Diels-Alder transformations.\textsuperscript{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.\textsuperscript{22-24} Recently, aromatic systems have been obtained with methyl coumalate (1) both with unactivated alkenes\textsuperscript{25} and electron-deficient olefins\textsuperscript{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 feedstock for domains ranging from optoelectronics to biopharmaceuticals.\textsuperscript{9} The history of aromatics and their application in the commercial world is a treasure trove of chemistry.\textsuperscript{27,28} For instance, the production of polystyrene from styrene is a critical component of the petrochemical industry, and solely relies upon steam cracking of ethane.

### 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. 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). 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Aromatic Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>3a</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>3b</td>
<td>92</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (1 mmol) and 2 (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. *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-butane as a captodative dienophile equivalent since ketals are primed to eliminate methanol under the thermal conditions to reveal the dienophile. As predicted, the Diels-Alder reaction sequence forms only *para*-substituted methyl 4-acetobenzoxate (5a). This compound has been utilized as an advanced intermediate to synthesize alkaloids and enzyme modulators. Literature precedent majorly focuses on manipulating commercially available aromatic compounds; 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-butanezidione, 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. However, the yield is significantly greater than the 3% observed by crude *1H 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, it was unreactive to the same reaction conditions (Scheme 2). The non-reactivity may imply a predilection for

<table>
<thead>
<tr>
<th>Entry</th>
<th>Captodative Dienophile</th>
<th>Aromatic Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>4a</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>4b</td>
<td>75</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (1 mmol) and 2 (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. *Isolated yield.
reaction at the less-substituted olefin 8 through isomerization, which was observed when dienophile 7 was isolated and subjected to the standard reaction conditions.\(^9\)

**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-cyclohexanedicarboxylic acid 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 target for our promising technology capitalizing on captodative olefins. TPA and its ester dimethyl terephthalate (DMT) lies in their ability to act as condensation co-monomers for poly(ethylene terephthalate) (PET).\(^6\) Various companies specifically favor DMT as the core of its 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.\(^50\) While TPA has formidably impacted applications, with the highest volumes in polyester fibers then in bottles and packaging, its societal significance is reflected by its annual production of nearly 60 million tons. By contrast, DMT is a key component of PET and its ester dimethyl terephthalate (DMT) lies in the ability to act as a condensation co-monomer for poly(ethylene terephthalate) (PET).\(^6\)

With the optimal reaction conditions in hand, five captodative dienophiles were explored to flexibly generate DMT (Scheme 3), which can undergo facile hydrolysis to TPA.\(^52\) At the outset, the enol silyl ether of methyl pyruvate (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\(^53,54\) (9b) became the next dienophiolic 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\(^55\) (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

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**Table 3** Reaction optimization trials

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Equiv. of 9a</th>
<th>Ratio of DMT : 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>200</td>
<td>16</td>
<td>3.0</td>
<td>1 : 0</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>150</td>
<td>18</td>
<td>3.0</td>
<td>1 : 0.48</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>100</td>
<td>3</td>
<td>3.0</td>
<td>1 : 4.00</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>200</td>
<td>17</td>
<td>1.5</td>
<td>1 : 0.53</td>
</tr>
<tr>
<td>5</td>
<td>Neat</td>
<td>150</td>
<td>16</td>
<td>1.5</td>
<td>1 : 0.12</td>
</tr>
<tr>
<td>6</td>
<td>Neat</td>
<td>125</td>
<td>18</td>
<td>1.5</td>
<td>1 : 0.72</td>
</tr>
<tr>
<td>7</td>
<td>Neat</td>
<td>150</td>
<td>6</td>
<td>1.5</td>
<td>1 : 0.50</td>
</tr>
<tr>
<td>8</td>
<td>Neat</td>
<td>150</td>
<td>3</td>
<td>3.0</td>
<td>1 : 0.49</td>
</tr>
<tr>
<td>9</td>
<td>Neat</td>
<td>150</td>
<td>1</td>
<td>1.5</td>
<td>1 : 1.31</td>
</tr>
<tr>
<td>10</td>
<td>Neat</td>
<td>150</td>
<td>17</td>
<td>1.0</td>
<td>1 : 1.12</td>
</tr>
<tr>
<td>11</td>
<td>Neat</td>
<td>150</td>
<td>16</td>
<td>3.0</td>
<td>1 : 0</td>
</tr>
<tr>
<td>12</td>
<td>Neat</td>
<td>200</td>
<td>16</td>
<td>1.5</td>
<td>1 : 0</td>
</tr>
</tbody>
</table>

Entries 1-4 were run with toluene as the solvent. Ratios determined by integration of crude \(^1H\) NMR.

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With optimal reaction conditions in hand, five captodative dienophiles were explored to flexibly generate DMT (Scheme 3), which can undergo facile hydrolysis to TPA.\(^52\) At the outset, the enol silyl ether of methyl pyruvate (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\(^53,54\) (9b) became the next dienophiolic 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\(^55\) (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
single step from methyl pyruvate, equally affords high yields of DMT. We postulated that the <10% enol content of pyruvic acid in CCl₄, stabilized by intramolecular hydrogen bonding, 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 typically under the reaction 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 methodology exceptionally addresses the immediate global issue of rapidly depleting petrochemicals and highlights bio renewable feedstocks as a green innovation toward the chemical building blocks of a sustainable future.

Acknowledgments
We would like to thank the NSF Engineering Center for Biorenewable Chemicals which was awarded NSF grant EEC-0813570 and SusTerea Biorenewables, LLC for support of this research.

Notes and references
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41  All characterization data for 2-acetoxyacrylate (9b) matched those previously reported. Z. Zhang, B. Ma, Q. Zhu, Y. Ding, C. Wang and W. Song, Synth. Commun., 2012, 42, 3053-3060.
42  2-methoxyacrylate (9c) and methyl 2,2-dimethoxypropanoate (9d) were prepared according to the following literature precedent; all characterization data matched those previously reported. A. B. Cooper, Y. Nan, Y. Deng, G. W. ShippS, N.-Y. Shih, H. Y. Zhu, J. M. Kelly, S. Gudipati, R. J. Doll, M. F. Patel, J. A. Desai, J. J.-S. Wang, S. Palival, H.-C. Tsai, S. B. Boga, A.-B. Alhassan, X. Gao, L. Zhu and X. Yao, WO Pat., 105 500 A1, 2009.
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