

# Intermolecular Reductive Couplings of Arylidene Malonates via Lewis Acid/Photoredox Cooperative Catalysis

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# **Supporting Information**

**ABSTRACT:** A cooperative Lewis acid/photocatalytic reduction of arylidene malonates yields a versatile radical anion species. This intermediate preferentially undergoes intermolecular radical-radical coupling reactions, and *not* the conjugate addition-dimerization reactivity typically observed in the single-electron reduction of conjugate acceptors. Reported here is the development of this open-shell species in intermolecular radical-radical cross couplings, radical



dimerizations, and transfer hydrogenations. This reactivity underscores the enabling modularity of cooperative catalysis and demonstrates the utility of stabilized enoate-derived radical anions in intermolecular bond forming reactions.

he study of underexplored reactive intermediates, particularly those generated via catalysis, has driven advances in carbon-carbon bond forming reactions, leading to economical synthetic routes and access to important molecular architectures.<sup>1</sup> To this end, strategic bond disconnections based on inverse polarity concepts, termed Umpolung, have been a significant focus of the organic community.<sup>2</sup> While polarity reversal has been an area of considerable interest, strategies to access Umpolung reactivity of conjugate acceptors through catalysis are limited. N-Heterocyclic carbenes (NHCs) have become uniquely suited catalysts for Umpolung reactivity modes, with NHC-homoenolate equivalents representing a thoroughly explored approach toward the polarity-reversed reactivity of conjugate acceptors.<sup>3</sup> The single-electron reduction of conjugate acceptors to generate open-shell anionic species (Scheme 1) represents an older, but less developed strategy to create an enone Umpolung operator.<sup>4</sup> While electrochemical reductive dimerizations of conjugate acceptors have proven robust, examples of cross-coupling variants are rare.<sup>5,6</sup> The development of visible light-driven electrochemistry, i.e. photoredox, has yielded new opportunities for the production of open-shell species under mild conditions. Yoon combined photoredox catalysis with Lewis acid catalysis to pioneer an elegant cooperative catalytic approach to enone Umpolung operators to provide a variety of carbocycles (Scheme 1).<sup>8</sup> Subsequently, modes of substrate activation in photoredox catalysis have been expanded, with Knowles and others demonstrating the utility of proton-coupled electron transfer (PCET) in a variety of C-C and C-N bond forming and breaking reactions.9 Significant challenges posed by this strategy include the requirement of intramolecularity, or for the few examples of intermolecular couplings, a significant excess of one coupling partner must be employed to statistically favor cross-coupled products over homodimerization.<sup>5,6</sup>

Recent reports have begun to address these issues by merging LUMO activation with photoredox catalysis (iminium and Lewis acid, respectively).<sup>10a-c,9h,10d</sup> While these approaches address the intermolecular challenge, cooperative catalytic approaches offer modularity in each catalyst component, thus enabling mechanistic versatility and switchable reactivity (vide infra). In light of these collective challenges, we considered multiple design principles to address these limitations. We surmised that the high energy of an enoate-derived radical anion (e.g., cinnamate) limits its ability to discriminate among potential intermolecular reactions partners.<sup>11</sup> Hence, stabilization of the enoate-derived radical anion might enable hitherto unrealized intermolecular cross-coupling reactions.

A comparison of the reduction potential of benzylidene malonate (1) (literature reports -1.63 V, our measurement -1.57 V vs SCE)<sup>12</sup> and the corresponding cinnamate (-2.3 V)<sup>13</sup> lends credence *a priori* that arylidene malonate (AM)-derived radical anions should be more stable than those derived from previously employed enones. Earlier work has demonstrated that Lewis acids can dramatically raise the reduction potential of benzylidene malonates.<sup>12</sup> Our own cyclic voltammetry studies showed a similarly drastic shift (>1 V, -0.37 vs SCE, 100 mol % Sc(OTf)<sub>3</sub>) of reduction potential when phenyl AM was complexed with scandium triflate (Figure 1).

Tertiary benzylic radical species derived from Hantzsch ester derivatives were chosen as the initial radical coupling partner to explore the parameters for cross-coupling reactions of AMderived radical anions.<sup>14,15</sup> With the initial set of reagents identified, we initiated a set of reaction screens using a variety of photocatalysts and blue LEDs to test our hypotheses, the

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# Scheme 1. Selected $\beta$ -Umpolung Strategies

Catalytic, Two-Electron Approach to Umpolung Enone Reactivity



Single-Electron Approaches to Umpolung Enone Reactivity



This Work: CC reductive intermolecular couplings via redesigned enone



**Design:** The stabilization of anion will result in more persistent radical to enable controlled intermolecular reactivity.





Figure 1. Reduction potential of Ph arylidene malonate (1) in acetonitrile.

results of which are summarized in Table 1. Gratifyingly, a variety of Lewis acids, including magnesium triflate (entry 1) and lanthanum triflate (entry 2), were capable of facilitating the title reaction in the presence of photocatalyst dF-Ir (4), with scandium triflate furnishing the desired cross-coupled product in 62% yield.<sup>16</sup> An excess of nitrile HE radical

#### Table 1. Radical Coupling Conditions



"Yield determined by GC with bibenzyl as internal standard. <sup>b</sup>Yield of isolated product. <sup>c</sup>See Supporting Information (SI) for details.



precursor (1.5 equiv) was required to ensure full conversion of the malonate, as we observed byproducts identified as HEderived radical dimers, in addition to small amounts of saturated arylidene malonate (arising from competing H atom transfer; see the Supporting Information (SI) for full optimization details). A survey of catalysts identified Ir catalyst 4 as optimal, while other commonly used metal photocatalysts greatly diminished the yield. Interestingly, organocatalysts of the dicyanobenzene family<sup>17</sup> performed nearly as well as 4, with diphenyl aniline organocatalyst DPAIPN (6) providing the desired product in a comparable 55% yield. The importance of the arylidene malonate moiety was validated as the potent conjugate acceptor (7) derived from Meldrum's acid showed no conversion under the optimized conditions. Additionally, when the arylidene malonate was replaced with an alkylidene malonate, no reaction was observed. As anticipated for a intermolecular radical coupling process, the reaction proved particularly sensitive to concentration, and all other deviations from the standard conditions led to decreased yields (see SI, Tables 1-3 for additional optimization data).

With the optimal conditions identified, we proceeded to examine the scope of enones that could serve as effective crosscoupling partners, as radical reactions are sensitive to the electronic nature of the reaction partners (Scheme 2).<sup>18</sup> Electron-deficient 4-trifluoromethyl substituted malonate provided the highest yield of cross-coupling product (8) (66%). AMs possessing halogenation at both the 4- and 2-positions underwent coupling with no observed dehalogenation products (9–13). Larger 2-methoxy and 1-naphthyl substrates showed minimal reactivity, likely due to reduced overlap between the enone and aryl  $\pi$ -systems.

Other electron-rich AM substrates proved competent, albeit with slightly diminished yields, with the 3- and 4-methoxy

# Scheme 2. Reductive Coupling Scope<sup>a</sup>



"Reactions on 0.35 mmol scale with 1 mol % dF-Ir and 10 mol % Sc(OTf)<sub>3</sub>. Yields are of isolated product after purification.

products obtained in 55% yield and 51% yield, respectively. Salicyaldehyde-derived arylidene malonate yielded the desired product (**19**) in 51% yield, indicating that locking the phenyl ring in a planar relationship to the enone system does not significantly enhance cross-coupling efficiency. Interestingly the only heterocylic substrate tolerated was the 2,6-dichloropyridine, yielding **17** in a modest 40% yield.<sup>19</sup> This could indicate competitive binding to the Lewis acid by the heterocycle, or instability of the enone-derived radical anion species. Further investigation is underway to rationalize this reactivity.

A variety of substitution on the aryl portion of the nitrile HE derivatives proved competent in the coupling reaction (Scheme 3). The highest yield was obtained with the 4-fluoro substituted derivative 21 (62%). It is unclear if this is the result of a faster rate of cross-coupling or by disfavoring competing side reactions (*vide infra*). Interestingly, the doubly benzylic species also proved competent in the reaction, with the product (26) isolated in 55% yield.

Yoon has demonstrated that photoredox reactions typically presumed to proceed through closed-catalytic photoredox cycles often propagate through chain processes.<sup>22</sup> Our studies indicate the cross-coupling reaction (including the undesired homocoupling side product **28**) to proceed with a quantum yield of 1.0 (see SI for details). Under the standard reaction conditions, a tail-to-tail dimer of phenyl AM (**28**) was isolated (~30% yield, dr = 1:1, Scheme 4).<sup>23</sup>

To investigate whether this dimeric species was the result of radical-radical coupling or radical conjugate addition, the reaction was performed with inversion of the limiting reagent. A nearly identical yield was obtained (59% vs 62% yield) (Table 1, entry 7), indicating that the dimer (28) may *not* be forming through addition of an enone-derived radical anion

# Scheme 3. Scope HE Derivatives in Reductive Coupling Reaction $\!\!\!\!\!^a$



"Reactions were carried out on 0.35 mmol scale with 1 mol % dF-Ir and 10 mol %  $Sc(OTf)_3$ . Yields are of isolated product after purification.

Scheme 4. Controlling the Reactivity of Arylidene Malonate Derived Radicals



<sup>*a*</sup>Reaction on 0.30 mmol scale with 2 mol % DPAIPN and 1.5 equiv of DIPEA. <sup>*b*</sup>Reaction on 0.30 mmol scale with 1 mol %  $Ir(ppy)_3$  and 1.5 equiv of NBu<sub>3</sub>. <sup>*c*</sup>Yields are of isolated product after column chromatography. <sup>*d*</sup>Observed by LC/MS.

(III) to unreacted AM or its Lewis acid complex, but by dimerization of these species.<sup>24</sup> Intrigued by this result, conditions were sought to promote this dimerization. Interestingly, using reductive quenching of the photocatalyst (same mechanism as previous reaction) with tertiary amines as the terminal reductant yielded only saturated malonate (27) in 75% yield (Scheme 4).<sup>2i</sup>

Employing  $Ir(ppy)_3$  in an oxidative quenching cycle (direct reduction of the AM-Lewis acid complex by the excited state of the photocatalyst) afforded significant quantities of the dimeric product with saturated malonate only observed in small quantities.<sup>25</sup> Notably, alkylidene malonates again proved unreactive in attempted cross-couplings under these conditions. Only the dimer of phenyl AM (**28**) was observed when the alkylidene malonate was used in a 2-fold excess. This strongly suggests that the observed dimerization arises from radical—radical combination of the AM-derived radical anions species rather than radical-conjugate addition to unreacted AM. It is important to note that chalcones exclusively show dimerization under similar conditions,<sup>26</sup> highlighting the unique reactivity of AM derived radical anions.

Interestingly, electron-donating groups (4-OMe-Ph) led to increased yields of dimeric products (**30**) while the electrondeficient 4-CF<sub>3</sub>-Ph AM yielded minimal product (**31**), as the saturated AM was the major product. This lack of dimerization could account for its superior performance in the benzyl radical cross-coupling reaction. These linear enone dimerization products have previously been prepared in poor to modest yields via electrochemical methods, demonstrating the mechanistic flexibility engendered by cooperative catalysis.<sup>23,27</sup>Additionally, the malonate dimer product **30** can be smoothly processed to 3,4 disubstituted cyclopentanone **32** in 69% yield via a one-flask Krapcho/Dieckmann sequence (eq 1).



Based on the data collected, we propose the following reaction pathways for the radical cross-coupling reaction with HE derived benzylic radicals (Scheme 5). Upon irradiation, the photoexcited iridium species oxidizes the nitrile HE A, yielding radical cation B. This species fragments into the tertiary radical





coupling partner C and the protonated pyridine species D. Concurrently, the reduced iridium species transfers an electron to the Lewis acid-arylidene malonate complex, producing radical anion G. Radical-radical coupling of C and G yields the enolate complex H which is then protonated by D, thus liberating the Lewis acid and providing the desired product I.

Arylidene malonates form stabilized radical anions with reactivity divergent from high energy reductive species generated from conventional enones. This radical anion can undergo challenging and productive reductive intermolecular radical-radical cross-coupling reactions to yield vicinal tertiary and quaternary centers. Further exploration of the reactivity of the corresponding radical anion demonstrated that adjusting components of the cooperative catalytic system could provide 3,4-diaryl adipic ester derivatives (28, 30) via radical dimerization, as well as hydrogenated to yield cinnamic ester products. This platform provides a foundation for further development of  $\beta$ -Umpolung-like reactivity via photoredox catalysis. Investigations toward new cross-coupling reactions as well as the development of enantioselective variants using AMs are ongoing.

#### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b02893.

Detailed experimental procedures, characterization data, and copies of NMR spectra (PDF)

# **Accession Codes**

CCDC 1835353, 1835355, and 1835357 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/ data\_request/cif, or by emailing data\_request@ccdc.cam.ac. uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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