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Decarboxylative Anti-Michael Addition to Olefins Mediated by Photoredox Catalysis

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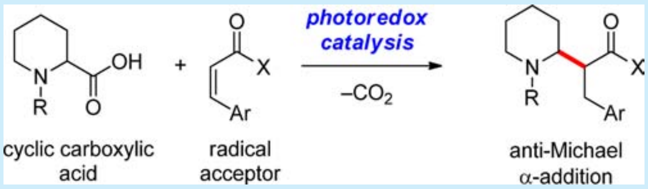
Ⓢ *Supporting Information*



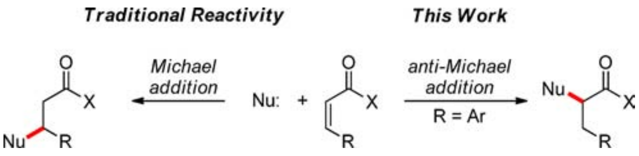
ABSTRACT: Decarboxylative coupling of carboxylic acids with activated olefins has been accomplished using visible light photoredox catalysis. The strategic placement of a radical-stabilizing aromatic group at the β-position of the olefin component biases the regioselectivity of the addition, allowing reliable, facile access to anti-Michael-type products from readily available precursors. The scope of this methodology was demonstrated with a range of carboxylic acids and appropriately substituted olefins and was applied toward a two-step synthesis of the antiarrhythmic agent encainide.

Radical-based transformations figure prominently in synthetic chemistry, both for target-directed synthesis[1] as well as for the manufacture of plastics.[2] The ability of radicals to add to olefins has been a mainstay for the construction of C−C bonds for over 40 years and has been strategically implemented in natural product total synthesis.[3] However, one drawback to this chemistry is the limited pool of radical precursor functionality that can be routinely employed (i.e., halides and alcohol-derived groups such as xanthates) using traditional initiation methodology.

Visible light photoredox catalysis has emerged in recent years as a prodigious hotbed for the development of many new chemical transformations.[4] Activation of a catalyst such as $Ru(bpy)_3Cl_2$ or $[Ir(dFCF_3ppy)_2(dtbbpy)]PF_6$ (**1**) via visible light-promoted metal-to-ligand charge transfer facilitates simultaneous one-electron reductant and oxidant behavior. These activated catalysts may interact in a chemoselective manner with organic substrates via single-electron transfer processes, thus initiating synthetically useful reduction, oxidation, and C−C bond-forming processes. Notably, MacMillan and co-workers have utilized carboxylic acids as "traceless activating groups" in a variety of photoredox bond-forming reactions, such as Michael addition,[5] alkyl fluorination,[6] arylation,[7] vinylation,[8] and anhydride decarboxylation[9] reactions.

This decarboxylative coupling methodology is especially powerful given the stability, variety, and commercial availability of carboxylic acids, which would allow for the rapid generation of chemically diverse libraries. In particular, we were intrigued with MacMillan and co-workers' report of photoredox-mediated decarboxylative Michael additions.[5] In their report, placement of an aryl group on the α-position of the Michael acceptor stabilized the intermediate acyl radical species directly following conjugate addition. Inspired by this tactic, we hypothesized that strategic placement of a radical stabilizing group at the β-position of the acceptor would allow us to access products with opposite regioselectivity (i.e., anti-Michael products). Herein, we explicate our strategy, leading to a regioselective, intermolecular decarboxylative addition of carboxylic acids to aromatic and styrenyl systems mediated by visible light photoredox catalysis, providing products complementary to traditional Michael methodology (Scheme 1).[10−12]

Scheme 1. Comparison of Traditional Michael Addition Reactivity to This Work



We began our investigation with the decarboxylative coupling of Boc-proline (**2**) and *N*-methyl-2-quinolinone (**3**) and were delighted to find that this transformation selectively afforded adduct **4** as the sole observable regioisomer in good yield across a range of conditions (Table 1).[13] Several bases were explored to facilitate this transformation (entries 1−4), of which Cs_2CO_3 provided the highest yield. Akin to other reaction manifolds, the use of cesium salts may be beneficial due to their increased oxidative propensity, high solubility, and weak solvation, among other properties.[14] A screen of polar solvents revealed DMSO to be optimal (entries 4−7).[15] A study of reaction concentration demonstrated increased dilution (i.e., 0.02 M vs 0.2 M of **3**) improved reaction efficiency (entries 4 vs 8). This concentration effect may be due to greater light penetration into the reaction solution at higher dilution, leading to greater photoredox catalytic activity. To further test this hypothesis, we increased the reaction opacity using 3 equiv of Cs_2CO_3 (entry 9) in conditions otherwise identical to entry 4, which led to decreased conversion and isolated yield of **4**. Strongly oxidizing photo-

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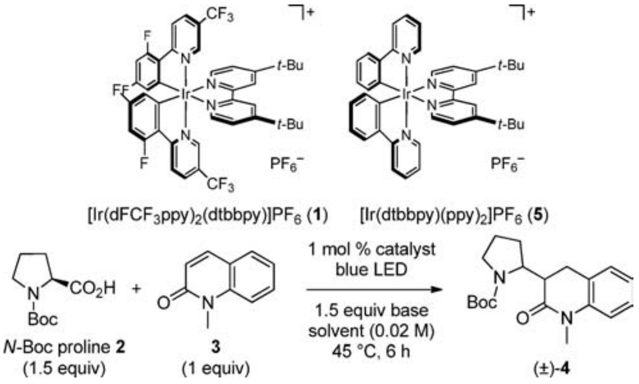
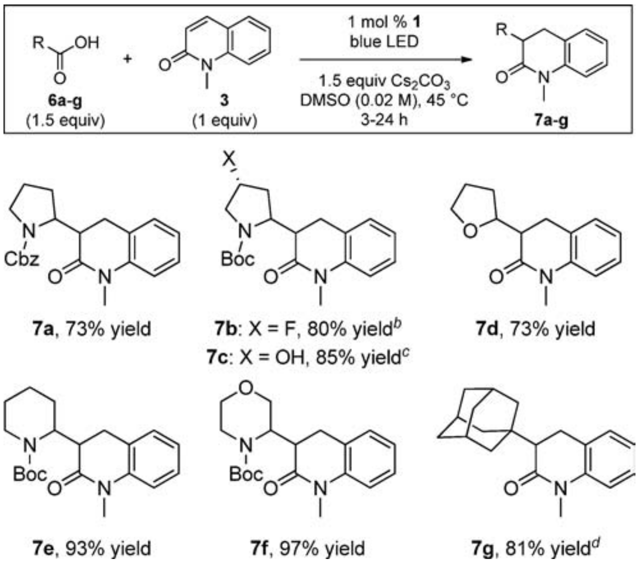
Table 1. Evaluation of Conditions for the Decarboxylative Anti-Michael Addition



entry	catalyst	base	solvent	yield (%)[a]
1	**1**	K_2HPO_4	DMSO	77
2	**1**	CsF	DMSO	81
3	**1**	CsOAc	DMSO	83
4	**1**	Cs_2CO_3	DMSO	89
5	**1**	Cs_2CO_3	DMA	71
6	**1**	Cs_2CO_3	DMF	72
7	**1**	Cs_2CO_3	MeCN	81
8	**1**	Cs_2CO_3	DMSO[b]	70
9	**1**	Cs_2CO_3[c]	DMSO	38
10	**5**	Cs_2CO_3	DMSO	90
11	$Ir(ppy)_3$	Cs_2CO_3	DMSO	trace
12	none	Cs_2CO_3	DMSO	0
13[d]	**1**	Cs_2CO_3	DMSO	0

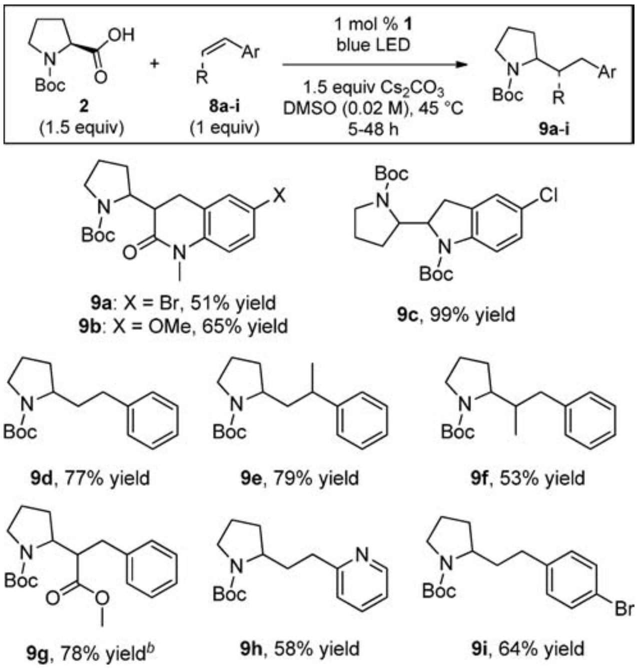
[a] Isolated yield. [b] Reaction run at 0.2 M concentration. [c] 3 equiv Cs_2CO_3 was used. [d] Reaction run in the absence of light.

Scheme 2. Decarboxylative Additions to 3: Scope of the Carboxylic Acid Component[a]



[a] All products are equimolar mixtures of racemic diastereomers unless stated otherwise. [b] Product is a 2.3:1.3:1.1:1.0 mixture of diastereomers. [c] Product is approximately a 1.4:1.4:1.0:1.0 mixture of diastereomers. [d] Product is an inseparable 2:1 mixture of coupling product and oxidized quinolinone. See Supporting Information for details.

Scheme 3. Decarboxylative Additions of Boc-Proline (2): Scope of the Radical Acceptor Component[a]



[a] All products are equimolar mixtures of racemic diastereomers unless stated otherwise. [b] Reaction provided a 5.7:1 mixture of regioisomers. The minor regioisomer is the Michael-type product resulting from addition to the β-position. See Supporting Information for details.

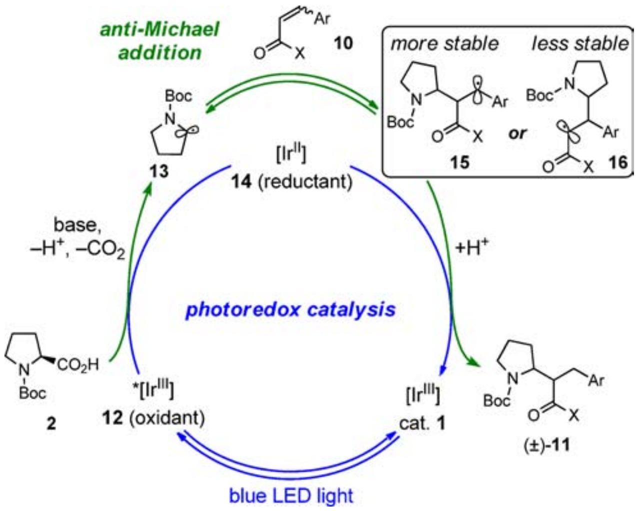
catalysts **1** and closely related $[Ir(ppy)_2(dtbbpy)]PF_6$ (**5**) were more efficient than the strongly reducing photocatalyst $Ir(ppy)_3$, which failed to induce decarboxylation (entries 4 vs 10−11). We utilized **1** in subsequent studies given its stronger oxidizing properties ($E^{*III/II}_{1/2}$ = +1.21 V for **1** and $E^{*III/II}_{1/2}$ = +0.66 V for **5** vs saturated calomel electrode in MeCN).[16] In the absence of catalyst (entry 12) or light (entry 13), no product was observed. Without active cooling, the reactions reached thermal equilibrium at 45 °C; yields were not adversely affected when run at this temperature when compared to room temperature. Additionally, yields were not significantly different when the reaction was conducted open to the atmosphere or under the rigorous exclusion of oxygen.

Having found optimal conditions for the synthesis of **4**, we surveyed a variety of carboxylic acid radical precursors (**6a**−**g**) in coupling reactions with quinolone **3** (Scheme 2). Acids bearing an α-heteroatom substituent gave good yields for this transformation, including 5- and 6-membered heterocyclic rings (**7a**−**f**).[17] Proline derivatives bearing a small 3-substituent provided only modest levels of diastereoselection in products **7b** and **7c**. Alicyclic carboxylic acids may also be utilized in this methodology, such as adamantoic acid (**6g**) to afford **7g**.

We next examined the scope of radical acceptors with *N*-Boc proline **2** as the nucleophile (Scheme 3). Quinolinones **8a**,**b** and indole **8c** provided coupling products **9a**−**c** in good yields. The reactivity of exocyclic olefin acceptors was also explored. Coupling with anti-Markovnikov selectivity was achieved using styrene and styrenyl derivatives (**8d**−**i**). Substitution at the styrenyl α- and β-positions was tolerated to afford **9e** and **9f**. It is interesting to note that the anti-Michael product **9g** predominated in the reaction with methyl cinnamate (**8g**) over the traditional Michael-type product. 2-Vinylpyridine (**8h**) was also a competent coupling partner in this reaction to give **9h**. The efficiency of coupling reactions producing **9i** as well as **9a** and **9c** illustrate the orthogonality of this reaction to traditional cross-coupling methodology.

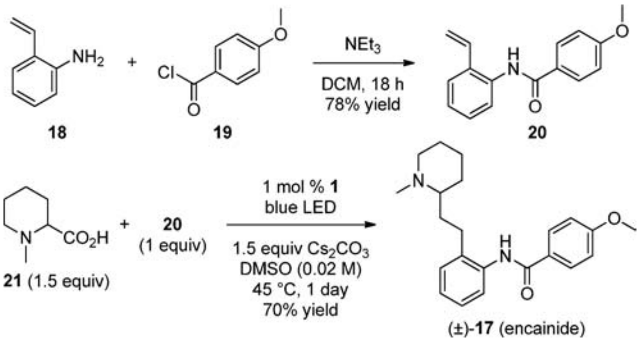
A mechanism illustrating our rationale for anti-Michael regioselectivity is depicted in Scheme 4, involving the reaction of Boc-protected proline (**2**) with an olefin **10** to form adduct **11** using photoredox catalyst **1**. Upon activation of **1** with blue LED light to excited-state species **12**, base-mediated decarboxylative single-electron oxidation affords radical **13** and reduced Ir species **14**. Reversible addition[18,19] of radical **13** to acceptor **10** gives rise to two possible regioisomers, **15** or **16**. Formation of the α-coupled product **15** should be thermodynamically preferred owing to benzylic radical stabilization, which cannot occur in regioisomer **16**. This radical stabilization biases against addition of the nucleophilic radical species to the more electrophilic position of the olefin. Single-electron reduction and protonation of **15** affords product **11** and regenerates the ground-state Ir catalyst **1**, completing the photoredox cycle.

Scheme 4. Proposed Mechanism for the Photoredox-Catalyzed Anti-Michael Addition



To further illustrate the value of this methodology, we performed a 2-step synthesis of encainide (**17**), a discontinued class Ic antiarrhythmic agent (Scheme 5).[20] Acylation of 2-vinylaniline (**18**) with 4-anisoyl chloride (**19**) gave radical addition precursor **20**. Without any modifications to our photoredox coupling protocol, we obtained encainide in 70% yield through the coupling of *N*-methyl DL-pipecolic acid (**21**) with **20**. Considering that three steps of the four total utilized in the reported manufacturing route[21] of this drug are devoted to coupling and modification of similar fragments (i.e., aldol condensation, dehydration, and reduction), this photoredox coupling methodology is superior both in terms of step- and redox-economy.[22] Further, this chemistry may be utilized to quickly generate a library of encainide analogues.

Scheme 5. Two-Step Synthesis of the Antiarrhythmic Drug Encainide



In summary, photoredox catalysis was utilized to facilitate decarboxylative coupling of cyclic carboxylic acids and a wide range of radical acceptors with anti-Michael selectivity. For styrenyl substrates, anti-Markovnikov addition products were reliably obtained. Among other functionality, highly substituted β-alkoxy- or β-aminocarbonyl motifs may be accessed using this methodology. The reaction is operationally facile to execute, and its mild reaction conditions tolerate a wide variety of functionality. Given its orthogonality to traditional carbon—carbon bond-forming processes, such as Pd-catalyzed cross-coupling and Michael additions, this methodology may be particularly useful for the parallel synthesis of compound libraries and generally useful to the synthetic community as a whole.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01712.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Acyclic acids bearing an α-heteroatom (e.g., *N*-Boc-glycine) as well as secondary alicyclic acids (e.g., cyclohexanecarboxylic acid) also work using this methodology albeit with lower yields.

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(19) This reversible addition may also have a kinetic component governed by the Bell−Evans−Polanyi principle in which the difference in activation barriers for the formation of **15** and **16** correlates to the difference in thermodynamic stability between **15** and **16**.

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