

Decarboxylative Anti-Michael Addition to Olefins Mediated by Photoredox Catalysis

Gabrielle H. Lovett and Brian A. Sparling*

Department of Medicinal Chemistry, Amgen Inc., 360 Binney Street, Cambridge, Massachusetts 02142, United States

(5) Supporting Information

ABSTRACT: Decarboxylative coupling of carboxylic acids with activated olefins has been accomplished using visible light photoredox catalysis. The strategic placement of a radicalstabilizing 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.

R adical-based transformations figure prominently in synthetic chemistry, both for target-directed synthesis¹ 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 decarboxylation⁹ 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 Cs₂CO₃ 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-

 Received:
 June 13, 2016

 Published:
 July 1, 2016

 Table 1. Evaluation of Conditions for the Decarboxylative

 Anti-Michael Addition





catalysts 1 and closely related $[Ir(ppy)_2(dtbby)]PF_6(5)$ 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 ($E_{1/2}^{*III/II} = +1.21$ V for 1 and $E_{1/2}^{*III/II} = +0.66$ 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** predomi-





^{*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.

nated 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

Organic Letters

illustrate the orthogonality of this reaction to traditional crosscoupling methodology.

A mechanism illustrating our rationale for anti-Michael regioselectivity is depicted in Scheme 4, involving the reaction

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



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.

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

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



the reported manufacturing route²¹ 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.

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)

AUTHOR INFORMATION

Corresponding Author

*E-mail: brian.sparling@amgen.com.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge support from the Amgen Internship Program. We thank Paul Krolikowski (Amgen) and Lincoln Ombelets (Amgen) for assistance with NMR spectroscopic studies. We thank Justin Malinowski (Amgen), Erin DiMauro (Amgen), Ben Milgram (Amgen), and James Harvey (Amgen) for insightful discussions.

REFERENCES

(1) (a) Baralle, A.; Baroudi, A.; Daniel, M.; Fensterbank, L.; Goddard, J.-P.; Lacôte, E.; Larraufie, M.-H.; Maestri, G.; Malacria, M.; Ollivier, C. Radical Cascade Reactions. Encyclopedia of Radicals in Chemistry, Biology and Materials, 2012. (b) Rowlands, G. J. Tetrahedron 2010, 66, 1593.
 (c) Rowlands, G. J. Tetrahedron 2009, 65, 8603. (d) Albert, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. Top. Curr. Chem. 2006, 264, 1.
 (e) Gansäuer, A.; Bluhm, H. Chem. Rev. 2000, 100, 2771.

(2) (a) Zhang, N.; Samanta, S. R.; Rosen, B. M.; Percec, V. Chem. Rev. 2014, 114, 5848. (b) Nesvadba, P. Radical Polymerization in Industry. Encyclopedia of Radicals in Chemistry, Biology and Materials 2012, DOI: 10.1002/9781119953678.rad080.

(3) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. Chem. Rev. 1991, 91, 1237.

(4) For recent reviews, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102.

(5) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. J. Am. Chem. Soc. 2014, 136, 10886.

(6) Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. J. Am. Chem. Soc. 2015, 137, 5654.

(7) (a) Peifer, M.; Berger, R.; Shurtleff, V. W.; Conrad, J. C.; MacMillan, D. W. C. J. Am. Chem. Soc. 2014, 136, 5900. (b) Chu, L.; Lipshultz, J. M.; MacMillan, D. W. C. Angew. Chem., Int. Ed. 2015, 54, 7929.

(8) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. J. Am. Chem. Soc. 2015, 137, 624.

(9) Le, C. C.; MacMillan, D. W. C. J. Am. Chem. Soc. 2015, 137, 11938. (10) Melchiorre and co-workers as well as Nicewicz and co-workers have reported intramolecular olefin additions as well as intermolecular heteroatom couplings with similar regioselectivity: (a) Hepburn, H. B.; Melchiorre, P. Chem. Commun. 2016, 52, 3520. (b) Arceo, E.; Montroni, E.; Melchiorre, P. Angew. Chem., Int. Ed. 2014, 53, 12064. (c) Wilger, D. J.; Grandjean, J.-M. M.; Lammert, T. R.; Nicewicz, D. A. Nat. Chem. 2014, 6, 720. (d) Nguyen, T. M.; Manohar, N.; Nicewicz, D. A. Angew. Chem., Int. Ed. 2014, 53, 6198. (e) Nicewicz, D. A.; Hamilton, D. S. Synlett 2014, 25, 1191. (f) Perkowski, A. J.; Nicewicz, D. A. J. Am. Chem. Soc. 2013, 135, 10334. (g) Nguyen, T. M.; Nicewicz, D. A. J. Am. Chem. Soc. 2013, 135, 9588.

(11) (a) Devery, J. J., III; Douglas, J. J.; Nguyen, J. D.; Cole, K. P.;
Flowers, R. A., III; Stephenson, C. R. J. Chem. Sci. 2015, 6, 537.
(b) Keylor, M. H.; Park, J. E.; Wallentin, C.-J.; Stephenson, C. R. J. Tetrahedron 2014, 70, 4264. (c) Wallentin, C.-J.; Nguyen, J. D.;
Stephenson, C. R. J. Chimia 2012, 66, 394. (d) Wallentin, C.-J.; Nguyen, J. D.;
J. D.; Finkbeiner, P.; Stephenson, C. R. J. J. Am. Chem. Soc. 2012, 134, 8875. (e) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.;
Stephenson, C. R. J. J. Am. Chem. Soc. 2011, 133, 4160.

(12) Several regioselective, intermolecular C-C bond formation processes have been reported previously, but these typically suffer from harsh reaction conditions or specific prefunctionalization. For examples, see: (a) Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. J. Am. Chem. Soc. 2015, 137, 8700. (b) Shih, Y.-C.; Tsai, P.-H.; Hsu, C.-C.; Chang, C.-W.; Jhong, Y.; Chen, Y.-C.; Chien, T.-C. J. Org. Chem. 2015, 80, 6669. (c) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. Org. Lett. 2014, 16, 1876. (d) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. J. Am. Chem. Soc. 2013, 135, 10946. (e) Pan, S.; Matsuo, Y.; Endo, K.; Shibata, T. Tetrahedron 2012, 68, 9009. (f) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. Angew. Chem., Int. Ed. 2009, 48, 792. (g) Boto, A.; De León, Y.; Gallardo, J. A.; Hernández, R. Eur. J. Org. Chem. 2005, 2005, 3461. (h) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. J. Am. Chem. Soc. 2002, 125, 6462. (i) Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A. J. Am. Chem. Soc. 1999, 121, 6509. (j) Martin, S. F.; Barr, K. J. J. Am. Chem. Soc. 1996, 118, 3299. (k) Hernandez, A. S.; Thaler, A.; Castells, J.; Rapoport, H. J. Org. Chem. 1996, 61, 314. (1) Lochead, A. W.; Procter, G. R.; Caton, M. P. L. J. Chem. Soc., Perkin Trans. 1 1984, 2477. (m) Radwan, A. S.; Melek, F. R.; Negm, S. J. Prakt. Chem. 1980, 322, 475.

(13) Given the complex mixture of diastereomers and rotamers present in 4, unambiguous NMR structure elucidation of regioselectivity was conducted on other substrates. See Supporting Information for details. (14) For other instances of "cesium effects", see: (a) Lee, M.; Chang, S. *Tetrahedron Lett.* 2000, 41, 7507. (b) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. Org. Lett. 1999, 1, 1893. (c) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. J. Am. Chem. Soc. 1997, 119, 10539. (d) Rauhe, B. R., Jr.; McLarnon, F. R.; Cairns, E. J. J. Electrochem. Soc. 1995, 142, 1073.

(15) Polar solvents generally performed well due to their capacity to stabilize charged and radical intermediates.

(16) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A., Jr.; Milliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712–5719.

(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.

(18) Reversible addition of radicals to olefins has been studied extensively. For example, see: (a) Babiarz, J. E.; Cunkle, G. T.; DeBellis, A. D.; Eveland, D.; Pastor, S. D.; Shum, S. P. J. Org. Chem. 2002, 67, 6831. (b) Tanner, D. D.; Zhang, L. J. Am. Chem. Soc. 1994, 116, 6683. (c) Julia, M. Acc. Chem. Res. 1971, 4, 386 Additionally, when the photoredox coupling of 2 and *trans-β*-methylstyrene (8f) was run to partial conversion, recovered 8f had partially isomerized to provide a mixture of *trans-* and *cis-β*-methylstyrene, which may indicate reversible olefin addition during the reaction.

(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**.

(20) (a) Echt, D. S.; Liebson, P. R.; Mitchell, L. B.; Peters, R. W.; Obias-Manno, D.; Barker, A. H.; Arensberg, D.; Baker, A.; Friedman, L.; Greene, H. L.; Huther, M. L.; Richardson, D. W. CAST Investigators. *N. Engl. J. Med.* **1991**, 324, 781. (b) Harrison, D. C.; Winkle, R.; Sami, M.; Mason, J. *Am. Heart J.* **1980**, *100*, 1046.

(21) (a) Dillon, J. L.; Spector, R. H. (Bristol-Myers Company, USA). U.S. Patent 4,800,226, January 24, 1989. (b) Madding, G. D. (Mead Johnson & Company, USA). U.S. Patent 4,394,507, July 19, 1983.

(22) Photoredox chemistry has been used in industrial-scale applications. For more information, see: (a) Yayla, H. G.; Peng, F.; Mangion, I. K.; McLaughlin, M.; Campeau, L.-C.; Davies, I. W.; DiRocco, D. A.; Knowles, R. R. *Chem. Sci.* 2016, 7, 2066. (b) Ciriminna, R.; Delisi, R.; Xu, Y.-J.; Pagliaro, M. Org. Process Res. Dev. 2016, 20, 403. (c) Porta, R.; Benaglia, M.; Puglisi, A. Org. Process Res. Dev. 2016, 20, 2. (d) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. Angew. Chem., Int. Ed. 2014, 53, 4802. (e) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. Angew. Chem., Int. Ed. 2012, 51, 4144. (f) Andrews, R. S.; Becker, J. J.; Gagné, M. R. Angew. Chem., Int. Ed. 2012, 51, 4140.