

Current Trends in Electrochemical Oxidation of Arenes And Olefins

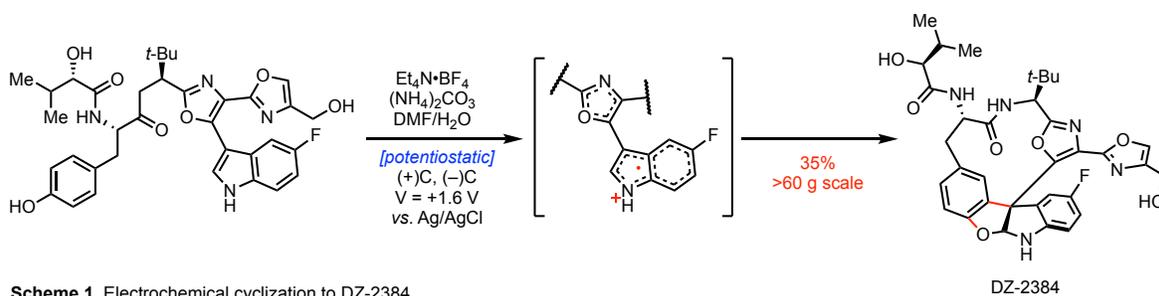
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INTRODUCTION

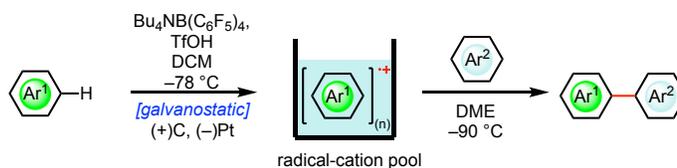
Recently, there has been much renewed interest in harnessing the power of electrochemical processes for organic chemistry. As an alternative to traditional stoichiometric or catalytic redox reactions, electroorganic methods are inexpensive to run, generate no stoichiometric byproducts or waste, and can be highly scalable. Most significantly, electrochemical reaction conditions are often very mild, with a high chemoselectivity and functional group tolerance, because the electroorganic chemist can dial in precisely the correct potential for the desired redox transformation. Accordingly, anodic oxidation has proven to be one of the most chemoselective techniques for generating radical cations from arenes and olefins, and these highly reactive species have found wide application in organic methodology development and total synthesis¹.

ANODIC OXIDATION OF ARENES



Direct functionalization of arene C–H bonds under electrochemical conditions is facile for electron-rich arenes given their low oxidation potentials, and appropriate tuning of electrical potential affords specific arene and heterocycle selectivity not possible with chemical reagents. The selective anodic oxidation of an indole in a complex molecule containing free alcohols, electron-rich heterocycles, and phenols was achieved by Harran and co-workers on a 60 g scale in a dramatic late-stage cyclization to produce DZ-2384, a novel microtubule-targeting diazonamide analogue in currently preclinical development at Diazon Pharmaceuticals (Scheme 1.)².

Transition-metal and chemical oxidant-free biaryl heterocoupling can be achieved through use of a "radical-cation pool" strategy, in which a

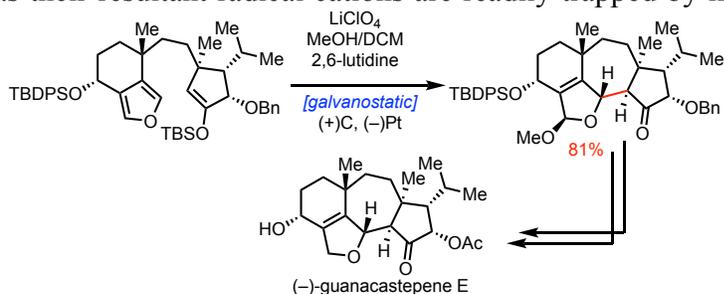


stoichiometric quantity of aryl cation radicals are first generated through electrolysis at $-78\text{ }^{\circ}\text{C}$,

whereupon addition of an electron-rich arene under nonoxidative conditions at $-90\text{ }^{\circ}\text{C}$ affords exclusively heterocoupled biaryl products in high yield and without overoxidation (Scheme 2)³.

ANODIC OXIDATION OF OLEFINS AND ENOL ETHERS

Anodic olefin couplings of enol ethers serves as a powerful umpolung strategy in synthesis, as their resultant radical cations are readily trapped by ketene acetals, electron-rich arenes, allyl



Scheme 3. Anodic olefin coupling with a furan in Trauner's synthesis of (-)-guanacastepene E

silanes, alcohols, amides, and other enol ethers. These reactions have seen broad application in synthesis through intramolecular cyclization reactions, such as in Trauner's synthesis of guanacastepene E,

where the anodic coupling of a silyl enol ether and a furan furnishes a 7-membered ring and two stereocenters in 81% yield (Scheme 3)⁴.

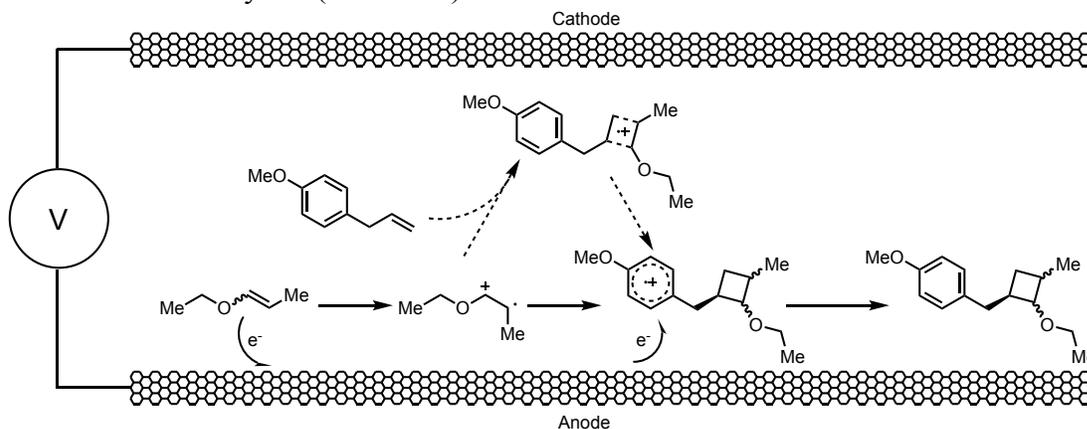


Figure 1. Electrocatalytic [2+2] cycloaddition of olefins

The reaction of olefins with enol ether radical cations reversibly generates transient "cyclobutane radical cation" intermediates. Chiba and coworkers observed that such cycloadducts could be isolated if one of the olefin components contained an electron-rich arene component. Such "redox tags" act as single electron donors to trap the olefin cycloadducts, and subsequently undergo *anodic reduction* via electron back transfer, thus rendering this process electrocatalytic⁵. Chiba further demonstrated that the *retro*-[2+2] of the radical cation intermediate could be controlled, thus enabling electrochemical enol ether/olefin cross metathesis⁶.

References:

- [1] Baran et al. *Chem. Rev.*, **2017** Article ASAP.
- [2] Harran et al. *ACIE*, **2015**, *54*, 4818
- [3] Wang et al. *ACIE*, **2017**, *56*, 3009
- [4] Trauner, et al. *J. Am. Chem. Soc.* **2006**, *128*, 17057
- [5] Chiba, et al. *Org. Lett.* **2009**, *11*, 1033
- [6] Chiba, et al. *ACIE*, **2006**, *45*, 14