



## Single Electron Processes Enabling Organic Synthesis

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In traditional cross-coupling reactions, a three-step catalytic cycle mechanistically based on 2-electron processes is employed: oxidative addition of a halide at Pd<sup>0</sup> or Ni<sup>0</sup>, transmetalation of an organometallic nucleophile with the oxidative addition intermediate, and reductive elimination, which releases the coupled product and regenerates the Pd<sup>0</sup> or Ni<sup>0</sup> catalyst. Although such methods are highly effective for C<sub>sp2</sub>-C<sub>sp2</sub> coupling, extension to 2° and 3° C<sub>sp3</sub>-hybridized organoboron reagents in particular has proven challenging owing primarily to lower rates of transmetalation, which is rate limiting in many alkylmetallic cross-coupling protocols operating under the traditional mechanistic manifold. To date, strategies aimed at facilitating the transmetalation of C<sub>sp3</sub> cross-coupling reactions with functional group-tolerant organoboron or organosilicon reagents employ harsh reaction.

The limitations of the transmetalation in cross-coupling reactions are inherent to the mechanism of this process at the most fundamental level, and thus predispose many C<sub>sp3</sub>-hybridized alkylmetallic reagents for failure. Described is a novel, single electron mechanistic paradigm for cross-coupling that avoids this problem. Thus, dual catalytic cycles are established: a photoredox catalytic cycle, generating radicals from appropriate precursors, and a cross-coupling catalytic cycle that funnels these radicals into a base metal catalytic cycle that effects the cross-coupling. The nature of the cross-coupling cycle, in which high-energy radical intermediates engage the cross-coupling catalyst, insures a cascade of low energy events leading to product, avoiding the high energy of activation associated with previous cross-coupling protocols.

Described will be our efforts to develop a suite of radical precursors for cross-coupling with a variety of electrophiles, emphasizing the tolerability of the developed conditions to an unprecedented array of functional groups. The value of generating radicals in a process that is *synchronized and catalytic* will be emphasized, both in dual catalyzed processes and in radical/polar crossover processes where a subsequent catalytic transformation is not utilized. Finally, applications to DNA-encoded library synthesis will be presented.