A Triple Catalysis for Alkyl-Alkyl Coupling: An Advance toward the Ideal Synthesis

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The efficient forging of C(sp\(^3\))–C(sp\(^3\)) bonds in a catalytic fashion remains a challenge in organic synthesis. In a recent issue of Nature, MacMillan and coworkers have devised a polarity-match-based cross-coupling of \(\alpha\)-hetero-substituted alkanes with alkyl bromides via photoredox, nickel, and hydrogen-atom-transfer triple catalysis.

Think of the formation of alkylated N-Boc-Prozac from N-Boc-Prozac. How would you perform this reaction in one step? Considering the employed reaction conditions in Scheme 1, one immediately realizes the intriguing novelty of the highlighted approach: using a new catalytic mixture under visible-light irradiation to couple two C(sp\(^3\)) moieties with excellent site selectivity. Clearly, this transformation would not be possible with last century’s organic chemistry. As just reported in Nature by the MacMillan group,\(^1\) this feat is another milestone in combining photoredox catalysis with concurrent catalytic cycles, which dates all the way back to the seminal merging of photoredox catalysis with organocatalysis for the asymmetric alkylation of aldehydes by Nicewicz and MacMillan.\(^2\)

Alkyl-alkyl cross-coupling is a very powerful approach for the straightforward connection of functionalized fragments.\(^3\) Traditional cross-couplings have so far relied mainly on the transition-metal-catalyzed reaction of an organometallic nucleophile with an electrophile or the more recently developed reactions between two electrophiles or two nucleophiles. However, all approaches suffer from drawbacks. In the first case, you need a tamed nucleophile to enable sufficient functional-group compatibility; in the latter cases, you have to combine electrophiles or nucleophiles with different reactivity profiles, which requires overstoichiometric amounts of reducing or oxidizing agents. An emerging strategy—single-electron transmetalation,\(^4\) which consists of merging the photocatalytic formation of radical entities with a catalyzed cross-coupling\(^5\)—alleviates these issues and therefore alters the conventional paradigm for running cross-coupling reactions. Recent examples include C(sp\(^3\))–C(sp\(^3\)) cross-coupling reactions employing carboxylic acids\(^6\) or silicates as radical precursors.\(^7\) Extending this transformation by including a selective C–H activation step, the holy grail of organic synthesis, to generate the radical intermediate represents a major advance.\(^1\)

To accomplish this breakthrough, MacMillan and colleagues implemented a triple catalytic manifold. In the first catalytic cycle, they obtained an alkyl radical species by an intermolecular hydrogen atom transfer (HAT) reaction. Polar effects in HAT reactions have been known for a long time.\(^8,9\) Here, the judicious use of the quinuclidinium radical cation as an electrophilic H abstractor allows the highly selective generation of radical entities at the most electron-rich C–H bond and not the weakest ones.\(^10\) Thus, the polarity matching, though possibly thermodynamically unfavorable, promotes the efficient generation of radical intermediates in the \(\alpha\)-position for heteroatoms such as oxygen, nitrogen, and sulfur.

A second, classical visible-light photoredox catalysis cycle using the iridium photocatalyst \(\text{Ir[dF(CF}_3\text{)ppy}_2(\text{dtbbpy})\text{PF}_6}\) with a long-lived \((t = 2.3 \, \mu s)\) and appropriate oxidizing \((E^{red}_{1/2} \, \text{[Ir(III)/}\text{Ir(II)}] = +1.21 \, V \text{versus SCE})\) excited state serves as the central gear for intertwining the involved catalytic cycles. It shuttles electrons and allows the oxidation of quinuclidine into the quinuclidinium radical cation by reductive quenching of the excited iridium(III) photocatalyst and presumably the reduction of a nickell(I) species into the nickell(0) catalytic species of the third organometallic cross-coupling catalytic cycle. The nickell(0) species is trapped by the alkyl radical intermediate to generate a new nickell(I) complex, which engages in oxidative addition with the alkyl bromide. The resulting Ni(III) intermediate undergoes reductive elimination to liberate the alkyl-alkyl cross-coupling product and restore the Ni(I) species.

This selective sp\(^3\) C–H alkylation reaction is particularly powerful for the functionalization in the \(\alpha\)-position of amines, ethers, and thioethers, all of which are ubiquitous functional groups in pharmaceuticals. The mildness of the reaction conditions allows for a broad scope of substrates. Selected examples are shown in Scheme 1: cyclic amines, ethers, and thioethers could...
be used in addition to acyclic amines and thioethers as C–H partners. Even a methyl group of tetramethylurea could be alkylated. In terms of electrophiles, primary or secondary bromides reacted efficiently. Particularly striking is the methylation of N-protected pyrrolidine or its direct coupling to a gem-difluorocyclobutyl group. In addition, the low catalyst loading is remarkable: only 1 mol % of photocatalyst, 2 mol % of nickel, and 10 mol % of quinuclidine are required. Besides both cross-coupling partners—the alkyl bromide and the α-amino (or α-oxo and α-thio) alkane—only potassium carbonate is present as the stoichiometric reagent.

In conclusion, this work by the MacMillan group constitutes a significant advance for organic synthesis. It alters our way of thinking in constructing C(sp³)–C(sp³) bonds and paves the way for new retrosynthetic disconnections. The developed methodology relies on three intertwined catalytic cycles that are each established but whose judicious combination is a key novelty.