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CHEMISTRY

A Light Touch Catalyzes Asymmetric Carbon-Carbon Bond Formation

The cooperation between a photoactivated catalyst and an organocatalyst enables a so far elusive stereoselective synthetic transformation.

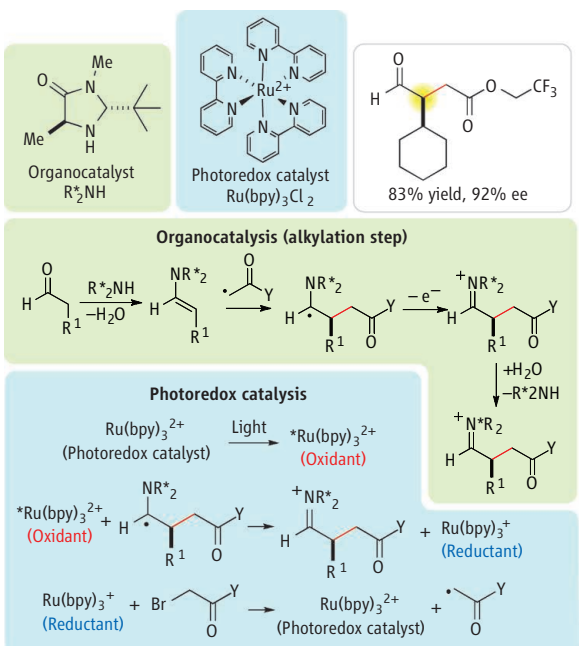
Philippe Renaud and Paul Leong

One of the most formidable tasks in organic synthesis is the formation of carbon-carbon bonds, in part because the activation of the carbon atoms requires the control of highly reactive species. Not only must these reactions form the correct bond connectivity, but they usually need to produce one enantiomer (the left- or right-handed arrangement of functional groups around each carbon atom that acts as a stereogenic center). The α-alkylation of carbonyl compounds (those containing a C=O group) with alkyl halides is a classical method, but it works much better for ketones (two alkyl groups on the C=O) than for aldehydes (one alkyl and one H on the C=O) and often requires stoichiometric amounts of additional reagents to direct the handedness at the stereocenter. On page 77 of this issue, Nicewicz and MacMillan report a remarkable approach for the enantioselective α-alkylation of aldehydes that not only is catalytic but uses a photoredox cycle to control the formation of highly reactive intermediates (*1*).

Prior to this work, asymmetric versions of these α-alkylation reactions that yield preferentially one enantiomer relied heavily on the use of chiral auxiliaries, which help direct the stereochemistry of the product (*2*). However, chiral auxiliaries, in contrast to catalysts, are used in stoichiometric amounts, and additional steps are required for their attachment and removal. These considerations alone render the chiral auxiliary approach unsuitable for large-scale applications. Consequently, the development of catalytic systems that generate enantiomerically pure compounds by using a minimal amount of an environmentally friendly catalyst is a field of intensive research (*3*).

Given that aldehydes are among the most widely used building blocks in organic synthesis, α-alkylation reactions of aldehydes that are both catalytic and enantioselective would be highly desirable. Despite extensive efforts, such reactions have remained elusive until recently (*4*). The problem is that alkyl halides are only modestly reactive toward nucleophiles (reagents that form a new chemical bond by donating both bonding electrons), which necessitates the use of highly reactive aldehyde enolates. Because aldehyde enolates are difficult to prepare and are expected to react faster with the starting aldehydes than with an alkyl halide, a truly catalytic cycle is nearly impossible to achieve.

Nicewicz and MacMillan have proposed a solution to this challenging problem in which the difficult and slow ionic alkylation step (a two-electron process) has been replaced by rapid steps based on less stable open-shell molecules involving one-electron pathways. MacMillan's and Sibi's groups had already introduced the concept of organo-SOMO catalysis (one-electron processes that make use of SOMOs, singly occupied molecular orbitals) for enantioselective α-allylation (*5*, *6*), α-vinylation (*7*), and α-oxygenation (*8*) of aldehydes. However, a stoichiometric amount of oxidant is required to generate the



Asymmetric catalysis via one-electron steps. The steps of the organocatalytic reaction (green shading) are carefully intertwined with the photoredox cycle of $Ru(bpy)_3^{2+}$ (blue shading). The photoexcited state of $Ru(bpy)_3^{2+}$ readily oxidizes the radical resulting from the coupling of the activated alkyl halide and the enamine, which is generated by condensation of the aldehyde with the organocatalyst. The bulky chiral organocatalyst directs the approach of these reactants so that alkyl group R^1 has a preferred stereochemistry; hydrolysis recovers the final product. The photocatalyst, now $Ru(bpy)_3^{+}$, reduces the alkyl halide by one electron to create the radical (the activated species with an odd electron) as well as the initial $Ru(bpy)_3^{2+}$. (**Upper right**) A typical product, its yield, and enantiomeric excess (ee).

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radicals. This requirement represents a major drawback in terms of atom economy and waste production.

To address this limitation, Nicewicz and MacMillan have investigated ruthenium bipyridine complexes, which are well-established photoredox catalysts. Under irradiation with blue light, tris(bipyridine)ruthenium(II), $Ru(bpy)_3^{2+}$, forms a more reactive species, $*Ru(bpy)_3^{2+}$, an excited state in which an electron on the metal transfers to the bpy ligand, where it has enhanced oxidative and reducing power relative to the ground state (*9*).

Nicewicz and MacMillan elegantly combined this photoredox process (see the figure, blue shading) with organo-SOMO catalysis so that the desired transformation can occur in the correct sequence to generate enolate radicals by a reductive process, and, after coupling with the chiral enamine, oxidize the reaction product. Here, the radical needed in the organo-SOMO catalysis is obtained by a one-electron transfer that reduces an α-bromocarbonyl compound with a Ru(I) species, $Ru(bpy)_3^{+}$. The enolate radical possesses an electrophilic character and adds efficiently to the electron-rich chiral enamine (the aldehyde-organocatalyst condensation product) to form an intermediate 1-aminoalkyl radical. This radical is readily oxidized by the excited $*Ru(bpy)_3^{2+}$ back to the corresponding iminium ion, which upon hydrolysis yields the final product; the oxidation step also regenerates the $Ru(bpy)_3^{+}$ ion so that the photoredox catalytic cycle can begin again.

A key feature is that the alkylation step proceeds stereoselectively because of the presence of the chiral secondary amine organocatalyst, which, after condensation with the aldehyde, gives an enamine that helps direct the approach of the incoming radical. Despite the delicately intertwined organo-photoredox catalytic cycles, this reaction is technically simple. It can be performed even with a household 15-W fluorescent light, with no external heating or cooling of the reaction mixture. For example, typical reaction conditions use a relatively high organocatalyst loading (20 mol %) with a minute amount of the photoredox catalyst (0.5 mol %). Indeed, alkylation of a series of aliphatic aldehydes with bromomalonates, α-bromoesters, and α-bromo-β-ketoesters occurs in excellent yield (63 to 93%) and with high stereochemical control (enantiomeric excess up to 99%) in all cases, even where two stereocenters are created (see the figure, upper right panel).

The selectivities for one enantiomer rival those observed for the classical ionic and concerted reactions, dispelling the previous notion that the high reactivity of radicals precludes their use in catalytic asymmetric synthesis. The cooperation of organo-SOMO catalysis and photoredox catalysis offers many possibilities for asymmetric transformations. A burgeoning field of research is likely to emerge from this seminal work.

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BIOCHEMISTRY

Not Comparable, But Complementary

New studies increase the number of protein-protein interactions but show little overlap. This is not a bad thing, though.

Lars Juhl Jensen[1,2] and Peer Bork[1,3]

It took many years between the introduction of DNA sequencing technologies in the mid-1970s and completion of the first genome sequences in the mid-1990s. Connecting the one-dimensional "parts lists" encoded within genomes—the proteins—into two-dimensional interaction maps is an even more daunting task, despite the introduction in the late 1980s of the yeast two-hybrid assay to identify protein–protein interactions (*1*) and high-throughput versions of this technology at the turn of the millennium (*2*, *3*). On page 104 in this issue, Yu *et al.* (*4*) identify 1809 interactions in the model organism budding yeast, of which more than 1500 are new relative to the early yeast two-hybrid studies (*2*, *3*). Together with the 2770 interactions recently determined by Tarassov *et al.* by a protein complementation assay (*5*), almost all of which are new, the number of binary interactions has more than tripled relative to earlier analyses (*2*, *3*). These studies bring us closer to a complete map of biophysical interactions in a single organism, and hence to the ultimate goal of functional understanding of the cellular machinery in space and time (*6*).

To document the quality of the identified interactions, the two groups performed extensive quality assessments, both on an absolute scale and relative to earlier large-scale studies. According to their estimates, only a few percent of the newly identified interactions are false-positives, which is more than an order of magnitude lower than suggested by previous quality assessments of large-scale yeast two-hybrid experiments (*7*, *8*). However, a direct comparison of those numbers is difficult and potentially confusing because each group used a different "gold standard" of known interacting and noninteracting protein pairs. Whereas Yu *et al.* take into account the genome-wide estimate for the number of interacting protein pairs relative to noninteracting ones, the standard used by Tarassov *et al.* is more than 40-fold enriched for interactions. This implicitly lowers the number of false-positives and hence inflates the estimated precision, which drops from 98.2% to around 50% if corrected for this bias. However, the latter value is overly pessimistic because the authors' reference set disfavors binary interaction assays.

A comparison of numbers becomes even more difficult when considering assays such as tandem affinity purification (*9*), which copurify proteins that are parts of the same complex. Four years after the first large-scale

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