Compounds of Interest: 001

Engaging with published research from Oxford Chemistry

Blue-Light Chemistry: Snapping open 3D Carbon Propellers for Better Medicines

This resource has been adapted from:

A General Route to Bicyclo[1.1.1]pentanes through Photoredox Catalysis

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Key Takeaway

A research group at the University of Oxford, in collaboration with Pfizer, has developed an innovative light-driven method to upgrade flat, two-dimensional drug molecules into 3D carbon architectures. This chemical breakthrough promises to revolutionise the synthesis of next-generation medications that are more stable and effective inside the human body.

Exam Links

This article links to the following exam specification topics:

- Radicals and Mechanism Types: **Homolytic fission**, chain reactions
- Transition Metal Catalysis: Variable oxidation states, light absorption
- Structure and Bonding: Covalent bond angles, **ring strain**, molecular shape

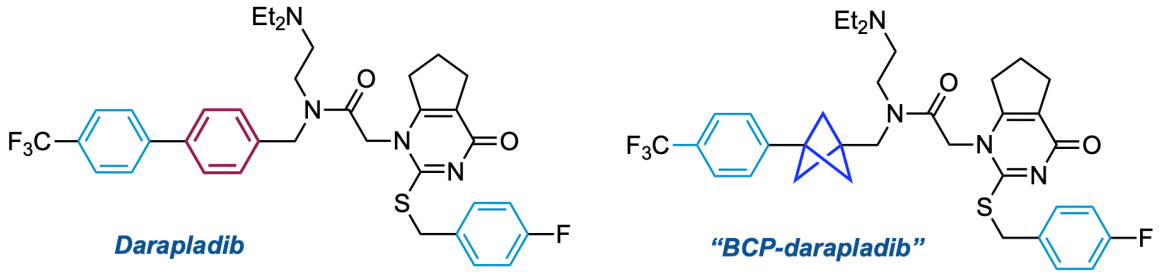


Figure 1: Molecular structures of darapladib (left) and BCP-darapladib (right) with benzene rings shown in light blue and key benzene and BCP rings shown in purple and dark blue respecively.

Introduction

Escape From Flatland

For decades, medicinal chemistry has suffered from a structural issue: many of our most successful pharmaceutical drugs are too flat, built primarily out of two-dimensional aromatic rings like benzene or pyridine. While easy to synthesise, these flat molecules often struggle inside the human body—being poorly soluble in aqueous environments, binding to unintended biological targets and causing side effects, or being rapidly metabolised and destroyed by enzymes in the liver.

To escape this, drug designers want to swap flat rings for molecules with more three-dimensional shape. This is because drug candidates with a

higher fraction of sp^3 carbon atoms – an inherent feature of 3D molecules – have been shown to have a higher probability of success in clinical trials. A perfect candidate is the bicyclo[1.1.1]pentane (BCP) group. Resembling a tiny geometric 3D propeller, the BCP group acts as an ideal **bioisostere** for 1,4-disubstituted (also known as para-substituted) benzene rings, mimicking the size and linear geometry of the aromatic compound but possessing three dimensional shape (see **Figure 1**). Critically, scientists have found that the substitution of a benzene ring with a BCP also maintains the biological activity of the drug candidate, while improving properties such as solubility and membrane permeability, and making it much tougher for metabolic enzymes to break down.

Incorporating these 3D architectures into drug molecules requires a starting material called [1.1.1]propellane, which shares this distinct propeller-shaped structure. [1.1.1]Propellane is a unique saturated hydrocarbon, in that its 'bridgehead' atoms (around which three three-membered rings are attached) appear non-tetrahedral. This makes the molecule highly strained, and by breaking this strained central bond, chemists can 'snap' the propeller open and insert it directly into an organic halide, forming the desired BCP group (see **Figure 2**).

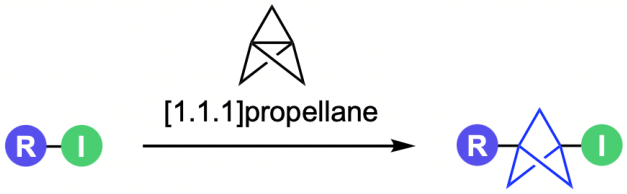


Figure 2: Insertion of [1.1.1]propellane into an organic hallide.

Historically, kick-starting this process required harsh conditions such as heat or aggressive chemical initiators, which could degrade or destroy the delicate drug molecules the chemists were trying to upgrade. To allow the reaction to proceed under milder reaction conditions, such as at room temperature, the Oxford team turned to **photoredox catalysis** — a technique where visible light activates a catalyst to drive photochemical reactions *via* single-electron transfers.

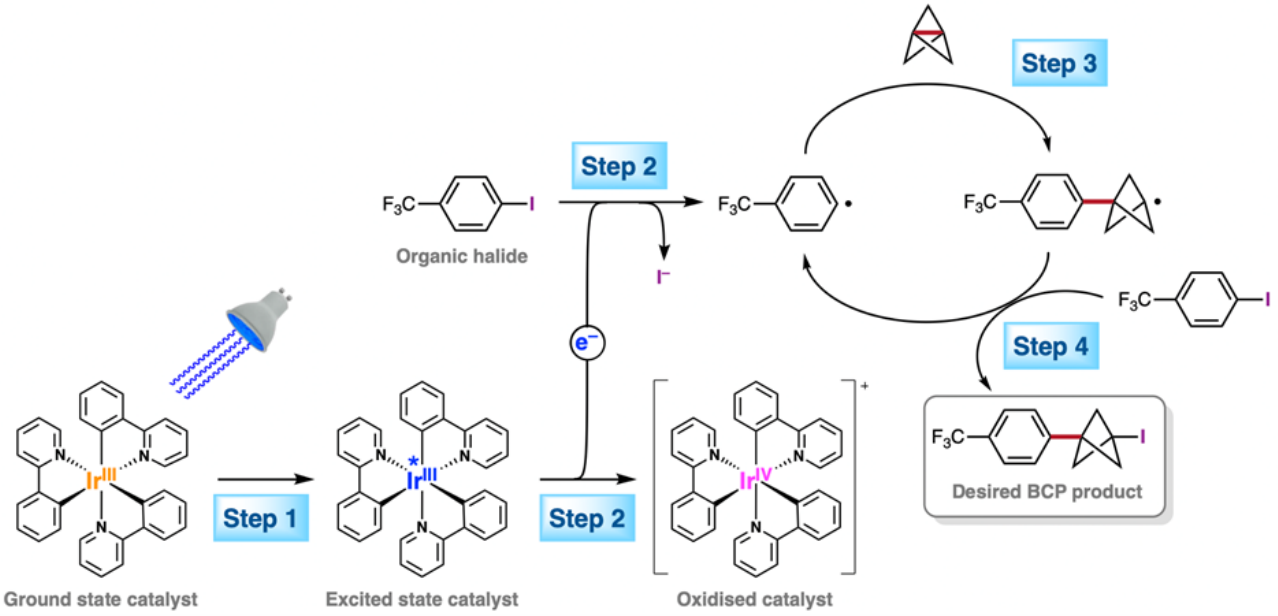


Figure 3: Reaction mechanism of the radical process.

Results and Discussion

The Catalytic Mechanism

Through systematic fine-tuning, the team discovered the perfect recipe to generate and use carbon-centred radicals (species with an unpaired valence electron) in reactions with [1.1.1]propellane. Their optimised system requires:

- An iridium-based catalyst (fac-Ir$(ppy)_3$)
- A simple blue LED light source
- A 2:1 ratio of [1.1.1]propellane to organic halide.

By studying the reaction, the team mapped out a four-step catalytic mechanism (as shown in **Figure 3**):

Step 1: Catalyst Activation – The catalyst absorbs blue light energy, converting it into a higher energy "excited state."

Step 2: Initiation – The excited catalyst transfers a single electron to an organic halide starting material, causing its carbon-halogen bond to break homolytically and form a carbon-centred radical, and an iodide anion.

Step 3: Propagation 1 – This radical attacks the strained propellane, breaking open the central bond to construct a new carbon-carbon bond between the starting material and the BCP framework.

Step 4: Propagation 2 – The opened propeller group (a BCP radical) picks up a halogen atom from another organic halide molecule. This completes the formation of the 3D BCP product and simultaneously generates a new carbon-centred radical, ready to attack another propellane molecule and keep the chain alive.

Step 5: Catalyst Regeneration (not shown) – In a varying percentage of cycles (depending on the reaction substrate), the intermediate BCP radical instead transfers its unpaired electron directly back to the oxidised iridium catalyst. This reduces it back to the $+3$ oxidation state in readiness for photoexcitation, and forms a carbocation that goes on to react with an iodide anion to complete the catalytic cycle. The team was able to detect organic molecules that are the product of this catalyst turnover pathway, providing evidence for this proposed reaction mechanism.

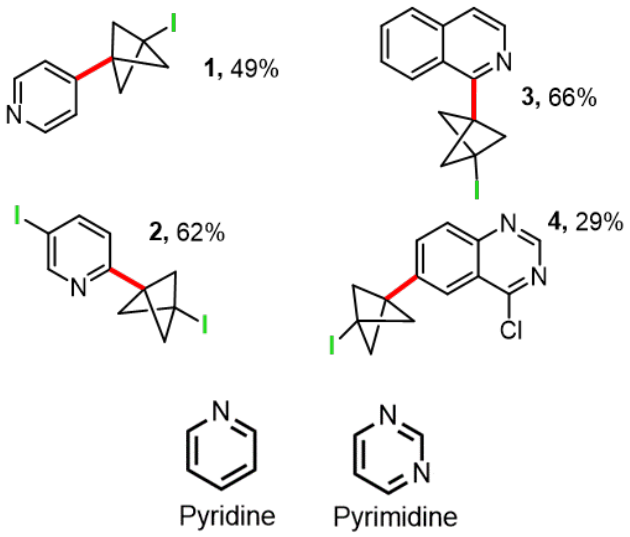
Testing the Limits: From Fragments to Medicines

The team tested their reaction on a large library of 89 different starting materials to evaluate its versatility. This extensive scope demonstrated exceptionally wide utility across several chemical classes, with key examples outlined below. Of particular importance is the tolerance of many different functional groups such as amines, carbonyls and alcohols, which are often found in drug molecules.

1. Drug-Like Building Blocks

Flat, nitrogen-containing rings like pyridines and pyrimidines form the backbone of a large percentage of modern pharmaceuticals. Traditionally, these rings are unreactive under radical conditions. The fact that this photoredox method accommodated them smoothly (see compounds 1–4) — and even allowed chemists to attach BCP groups at multiple different positions on the same ring — is a significant leap forward for drug design.

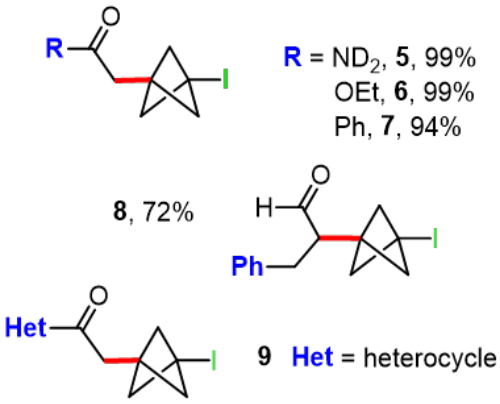
Key Examples



2. Sensitive Functional Groups

The ultimate test of a new organic reaction is its **functional group tolerance**. Harsh, old-fashioned radical methods or highly reactive **organometallic** reagents such as methyllithium (CH_3Li) attack and destroy delicate groups like aldehydes and ketones (see examples 5-9). This new, gentle method completely spared all tested carbonyls, giving yields of up to 99%.

Key Examples

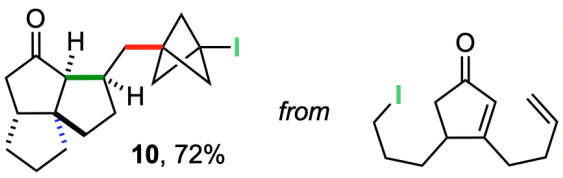


3. Complex Cycles

What happens if the starting material has a carbon-carbon double bond (π-bond) on the opposite end from the halide? The team discovered that the freshly generated radical can loop around and attack the alkene first, creating a brand new ring before it reacts with the propellane group, despite the high reactivity of the latter. In one example, they utilised a starting material with two alkenes to trigger an elegant **cascade reaction** that formed two rings in rapid succession. This built a complex 'triquinane' core

(3 fused cyclopentane rings) before the final radical trapped the propellane (see example 10).

Key Examples



4: Pharmaceutical Examples

To prove the real-world utility of their discovery, the team also tested **late-stage functionalisation** — attaching BCP groups directly onto completed, commercially available pharmaceuticals. They successfully bolted 3D BCP groups directly onto structures such as Penicillin G (an antibiotic), and Metronidazole (an antibacterial) with yields of up to 94% (see **Figure 4**). Instead of pharmaceutical companies having to build new 3D drug variants from scratch over many tedious, costly steps, scientists can now take an existing, proven drug and safely add a 3D propeller group to it as a final, single-step upgrade.

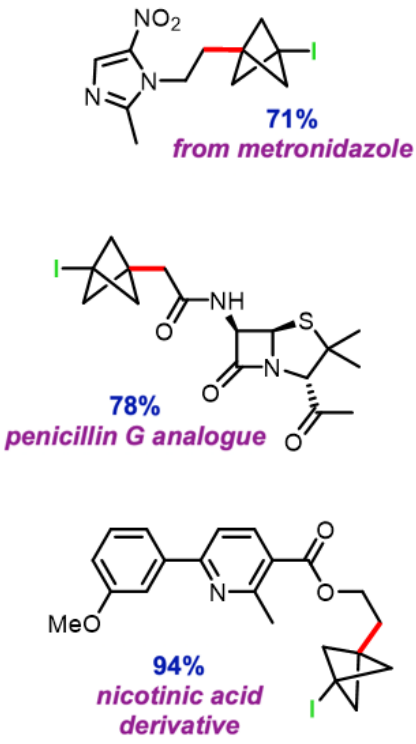


Figure 4: Molecular structures of BCP functionalised metronidazole (upper), penicillin G (middle), and nitronic acid derived compound (lower) alongside the product yields.

By effectively building a bridge out of "flatland," this photoredox revolution equips drug designers with a powerful new toolkit to construct the safer, more resilient, and decidedly more three-dimensional medicines of tomorrow.

Conclusion: Key Points

- A traditional reliance on benzene rings results in many pharmaceutical drugs being structurally flat, making them vulnerable to metabolic breakdown and off-target side effects, as well as being poorly soluble in the body.
- Bicyclo[1.1.1]pentane (BCP) propeller-shaped groups serve as 3D "**bioisosteres**" that mimic benzene rings while improving a drug's efficacy and bodily stability.
- Making BCPs from [1.1.1]propellane traditionally required very harsh conditions that are incompatible with sensitive druglike molecules.
- The University of Oxford team developed a room-temperature method using an iridium photoredox catalyst activated by simple blue LED light.
- The reaction utilises single-electron transfers to create radicals that snap open the propellane group, creating a huge range of pharmaceutically useful products.

Helpful Explainer: What is a Radical?

In standard covalent bonding, pairs of electrons are shared between atoms. However, under certain conditions, a covalent bond can break by **homolytic fission**—where each bonding atom takes one electron from the shared pair. This process generates free radicals: chemical species containing an unpaired valence electron. Radicals are reactive and short-lived because the formation of a **molecular orbital**, containing a pair of electrons, is more energetically stable. Once formed, they routinely drive chain reactions consisting of three main phases: initiation, propagation, and termination. These steps are often driven by the formation of a strong bond and/or more stable radical, at the expense of a weak bond and/or less stable radical.

A Classic Example: CFCs and Atmospheric Ozone Depletion

You may already be familiar with radical chain reactions from studying Chlorofluorocarbons (CFCs) such as CF_2Cl_2 in atmospheric chemistry:

Initiation: High-energy UV light breaks a C-Cl bond homolytically to form a chlorine radical:
$CF_2Cl_2 + \text{UV light} \rightarrow \cdot CF_2Cl + \cdot Cl$

Propagation: The chlorine radical attacks an ozone molecule (O_3), destroying it while regenerating another radical ($\cdot ClO$) to keep the destructive chain cycle going:
$\cdot Cl + O_3 \rightarrow \cdot ClO + O_2$
$\cdot ClO + O_3 \rightarrow \cdot Cl + 2\,O_2$

Termination: Two radicals collide and react to form a stable, non-radical molecule, removing radicals from the system and stopping the chain reaction:
$\cdot Cl + \cdot Cl \rightarrow Cl_2$ (or $\cdot Cl + \cdot ClO \rightarrow Cl_2O$)

While CFCs show how destructive radical chain reactions can be in the atmosphere, organic chemists can harness this same high reactivity in the lab — using radicals as powerful tools to rapidly construct complex 3D molecules like BCPs.

Glossary

Bioisostere: A molecule with a similar size and shape to another chemical group, used in drug design to swap out structural sections without losing biological activity.

Cascade Reaction: A chemical domino effect where multiple bonds are broken and formed sequentially in a single reaction without adding extra reagents.

Functional Group Tolerance: A measure of how gentle a reaction is; specifically, whether it can build a target bond without accidentally destroying other sensitive chemical groups on the same molecule.

Heterocycle: A cyclic compound which contains at least one heteroatom as a member of the ring.

Homolytic Fission: The breaking of a covalent bond where one electron goes to each atom of the bond, creating radicals.

Late-Stage Functionalisation: The strategy of altering or upgrading a highly complex molecule (like a finished drug) at the very final step of synthesis, which is much more efficient than making each new molecular target from scratch.

Molecular Orbital: a region in space in a molecule where there is a high probability of finding bonding electrons. At a simplified, descriptive level, a molecular orbital forms by the combination of atomic orbitals of the atoms linked by a covalent bond.

Organometallic: A molecule which contains one or more direct bond between a carbon atom in an organic group and a metal atom.

Photoredox Catalysis: A type of catalysis that uses visible light energy to activate a catalyst, which then drives chemical reactions *via* single-electron transfers.

Ring Strain: A type of chemical instability that occurs when covalent bond angles are forced to deviate from their ideal, lowest-energy geometries, storing massive potential energy.

Common Structural Abbreviations

Me = CH_3 (methyl)
Et = CH_3CH_2 (ethyl)
Ph = C_6H_6 (phenyl, derived from benzene)

The Lit Lab: Discussion Questions

Comprehension Questions (Checking the Basics)

1. **The Light Control:** In the optimisation phase, when the researchers turned off the blue LED lights, the reaction ground to a complete halt, but could be restarted by switching the LEDs back on again. Using the four-step mechanism cycle, explain exactly why the chemical chain reaction cannot proceed in the dark, and why switching the lights back on enabled the reaction to progress further.
2. **The Geometry of Strain:** Look at the structure of [1.1.1]propellane described in the text. Standard 4-bonded carbon atoms prefer a tetrahedral bond angle of 109.5°. Why does the inverted geometry of propellane store so much "potential energy," and how does Step 3 of the mechanism exploit this to drive the reaction forward?
3. **The Power of the Catalyst:** Look at the section on Chemically Sensitive Functional Groups. When making Aldehyde 8, the photoredox blue-light method achieved a 72% yield, whereas traditional chemical radical initiators managed only 38%. Based on the text, why does the photoredox method give such a drastically higher yield when dealing with delicate molecules like aldehydes?

Thought-Provoking Questions (Thinking Like a Researcher)

1. **The Dilemma of the Oligomer:** The researchers found that adding too much propellane caused the groups to polymerise into long chains of BCPs that are not useful in this context. If you were a chemist in the lab trying to prevent these groups from attacking one another, what adjustments could you make to the concentration of the solvent or the rate at which you drip the propellane into the flask?
2. **Evaluating the Late-Stage Upgrade:** Imagine you are a medicinal chemist at Pfizer evaluating the BCP-upgraded version of Penicillin G. While the 94% chemical yield is a triumph, what biological tests must this new 3D drug variant pass before it can ever be approved for patients?
3. **The Catalyst Challenge:** Iridium is a transition metal belonging to the platinum group, making it incredibly rare and highly expensive. For this blue-light method to be scaled up to manufacture metric tons of medication cheaply in a factory, what features would an ideal "next-generation" catalyst need to have? Can you think of alternative elements on the periodic table that chemists might investigate? Can you think of other, greener methods that might be used to promote the reaction?

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