

SUSTAINABLE CHEMICAL SYNTHESIS: MAKING MOLECULES USING VISIBLE-LIGHT IRRADIATION

DANIEL L. PRIEBBENOW¹

¹Department of Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences,
Monash University, Parkville, Victoria 3052 Australia

Correspondence: Daniel Priebbenow, daniel.priebbenow@monash.edu

ABSTRACT: The discovery of new strategies to increase the sustainability of chemical manufacturing is of critical importance to many sectors. To this end, photochemistry offers significant potential, as the irradiation of molecules and catalysts with visible light (considered a safe and renewable chemical reagent) can provide access to known molecules in a more sustainable fashion or novel molecular scaffolds that cannot be accessed via traditional means. Acyl silanes are a fascinating functional group which, upon irradiation with blue light, undergo rearrangement to generate reactive intermediates. Recent studies into the reactivity of acyl silanes within our research group has led to the discovery of a series of new photochemical methods to access unique molecular scaffolds using only visible-light irradiation, circumventing the use of precious metal catalysts and additives.

Keywords: chemical synthesis, photochemistry, carbene, organic molecules, sustainability

In nature, light irradiation from the sun plays an important role driving highly efficient photochemical processes, including photosynthesis and the formation of Vitamin D. Inspired by the ability of plants to harness the sun's energy, Italian chemist Giacomo Ciamician (1857–1922) was one of the first scientists to explore photochemical reactions (Ciamician & Dennstedt 1881; Ciamician & Plancher 1896; Ciamician & Silber 1901). As a result of his seminal investigations, Ciamician is now considered the pioneer of modern photochemistry with his findings attributed to the eventual invention of technologies such as the solar panel.

Over 100 years ago, the sustainability of the chemical and industrial sectors was already a concern. In 1912, Ciamician delivered a presentation to the VIII International Congress of Applied Chemistry where he advocated for the replacement of fossil fuels and coal with the use of solar energy in which he could already see significant potential (Ciamician 1912). In his presentation, Ciamician began with the following statement:

Modern civilization is the daughter of coal, for this offers to mankind the solar energy in its most concentrated form; that is, in a form in which it has been accumulated in a long series of centuries. Modern man uses it with increasing eagerness and thoughtless prodigality for the conquest of the world and, like the mythical gold of Rhine, coal is to-day the greatest source of energy and wealth. The earth still holds enormous quantities of it, but coal is not inexhaustible. The problem of the future begins to interest us ... Is fossil solar energy the only one that may be used in modern life and civilization? That is the question.

Over a century ago, Ciamician was already considering the possibility of developing an artificial photosynthetic process that harnessed solar energy as a fuel source. To this end, it has recently been estimated that the amount of solar energy that our society can access is over 10,000 times more than that we need. Ciamician challenged the scientists present at his address to consider alternative solutions to the energy problem, wondering:

... whether there are not other methods of production which may rival the photochemical processes of the plants. ... For our purposes the fundamental problem from the technical point of view is how to fix the solar energy through suitable photochemical reactions. ... By using suitable catalyzers, it should be possible to transform the mixture of water and carbon dioxide into oxygen and methane, or to cause other endo-energetic processes.

Ciamician finished his presentation by describing his vision for a society that did not rely on fossil fuels:

On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plants and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is. And if in a distant future the supply of coal becomes completely exhausted, civilization will not be checked by that, for life and

civilization will continue as long as the sun shines! If our black and nervous civilization, based on coal, shall be followed by a quieter civilization based on the utilization of solar energy, that will not be harmful to progress and to human happiness.

While significant advances have been made in our society's ability to harness the sun's energy in a manner that avoids the use of fossil fuel energy, it is not likely that this has been accomplished at the rate initially envisaged by the forward thinking Ciamician.

As synthetic organic chemistry plays a critical role in the discovery of life-saving medicines and functional materials, the development and use of sustainable strategies for chemical synthesis are of critical importance to ensure that society meets the needs of current and future generations. To this end, significant technological and conceptual advances have been made over recent decades to improve the efficiency and sustainability of chemical production across sectors including the agricultural and pharmaceutical industry. However, many of the current state-of-the-art synthetic strategies still require the use of precious metal catalysts including gold, platinum and palladium. The low abundance and high cost of these precious metal catalysts may limit the widespread application of many useful chemical reactions across industry-led medicinal chemistry and pharmaceutical manufacturing programs.

Visible-light irradiation is considered a 'benign' and renewable chemical reagent. The irradiation of molecules and catalysts with visible light is known to generate high energy reactive intermediates that enable reactions to proceed that are not achievable by other means (i.e. thermal activation). Over the past 15 years, there has been a significant increase in the use of photochemistry in synthetic chemistry labs, inspiring the discovery of many new chemical reactions. In particular the use of visible-light photocatalysis (including photoredox catalysis) has

been widely employed as a safe and efficient method to generate radical intermediates for a range of chemical reactions.

Visible-light photocatalysis has been used to achieve key transformations in the synthesis of active pharmaceutical ingredients (Figure 1) (Cannalire et al. 2021; Douglas et al. 2016; Li et al. 2020). For example, a photocatalysed reaction was developed to address a challenging step in the synthesis of elbasvir (a hepatitis C virus inhibitor). The previous approach used the oxidant potassium permanganate (KMnO_4) which delivered high yields, but led to the formation of undesirable MnO_2 as a byproduct not suitable for long-term manufacturing. A visible-light photoredox catalysed method was developed to replace the KMnO_4 approach using an iridium photocatalyst and tert-butyl peracetate as oxidant (Yayla et al. 2016). A visible-light photoredox catalysed method was also developed to synthesise LY2784544, a selective inhibitor of JAK2-V617F in clinical trials for the treatment of multiple myeloproliferative disorders (Figure 1) (Douglas et al. 2014).

Visible-light photocatalysis has been employed in drug discovery programs via late-stage functionalisation which enables the rapid diversification of lead compounds (e.g. methylation or fluorination) including patented and marketed drugs suitable for repurposing, circumventing the development of new manufacturing pathways (DiRocco et al. 2014). Advances in drug target identification have also been recently made via the discovery of new photocatalytic approaches for mapping the interaction of therapeutic compounds with the cellular environment (Geri et al. 2020; Trowbridge et al. 2022).

In recent years, our research group has been investigating the reactivity and properties of a unique chemical functional group known as acyl silanes (Zhang et al. 2013). We have demonstrated that acyl silanes can be used as directing groups for metal-catalysed C-H

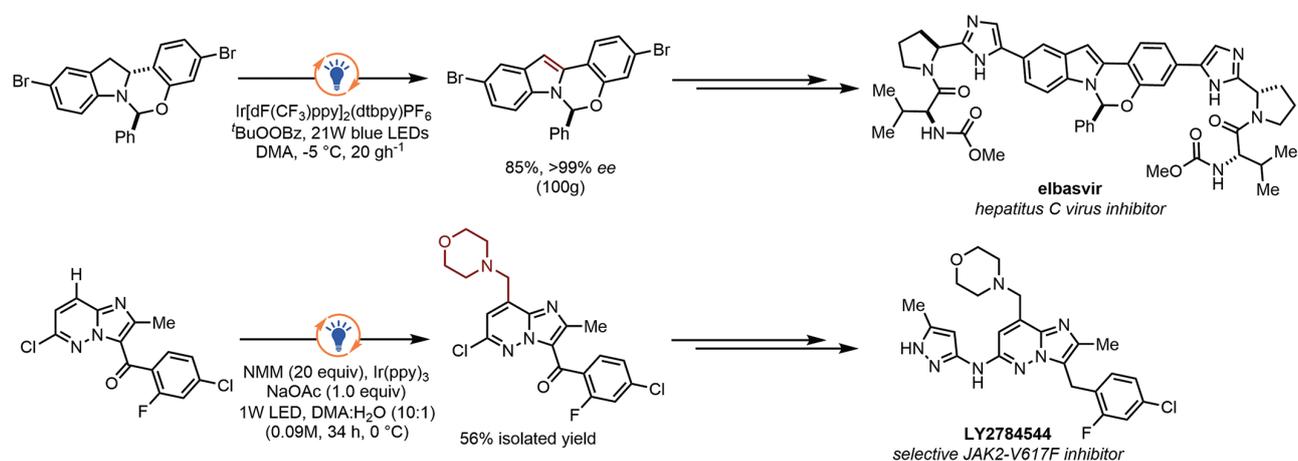


Figure 1: Visible-light photocatalysis has been used in the synthesis of therapeutic compounds.

functionalization (Atkin & Priebbenow 2022; Atkin & Priebbenow 2023; Priebbenow & Hua 2021). Acyl silanes can also undergo the Brook rearrangement when irradiated with blue light (using wavelengths between 390–440 nm). The Brook rearrangement involves a 1,2-silicon transfer process to generate a reactive nucleophilic siloxy carbene intermediate that can participate in a range of intermolecular and intramolecular chemical reactions (Becker et al. 2015; Becker et al. 2014a; Becker et al. 2014b; Priebbenow 2019; Priebbenow 2020).

Studies within our group have focused on harnessing the unique reactivity of siloxy carbenes to develop a series of highly efficient synthetic methods to access valuable molecular building blocks (Figure 2). Advantageously, these chemical reactions require only visible-light irradiation to proceed, circumventing the use of catalysts or additives. For example, we discovered that visible-light-induced siloxy carbenes can react with aryl and alkyl trifluoromethyl ketones via 1,2-carbonyl addition to access fluorinated tertiary alcohol derivatives (Priebbenow et al. 2021). We also discovered that siloxy carbenes underwent C-H insertion into the benzylic position of a tethered benzyl ether (Bunyamin et al. 2022).

Intramolecular photochemical [2+1]-cycloaddition reactions were also discovered that enabled access a series of unique bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane scaffolds (Figure 2) (Bunyamin et al. 2022). This cyclopropanation process required only visible-light irradiation to proceed, avoiding the use of exogenous catalysts or additives and represents a significantly underexplored mode of reactivity for nucleophilic carbenes in chemical synthesis. During this project, a light-induced rearrangement to afford chromanone derivatives was also discovered (Figure 2).

The new photochemical synthetic methods discovered as part of our ongoing investigations into acyl silanes are expected to deliver practical and conceptual advances that enable chemists to design new strategies to synthesise molecules of value in a pharmaceutical setting. These new synthetic strategies are also expected to afford increased sustainability by affording access to important molecules in a manner that avoids the use of expensive precious-metal catalysis or harsh reaction conditions. Efforts to discover new photochemical strategies to access an even greater diversity of molecular frameworks remain ongoing within our group.

Acknowledgements

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Conflict of interest

The author declares no conflict of interest.

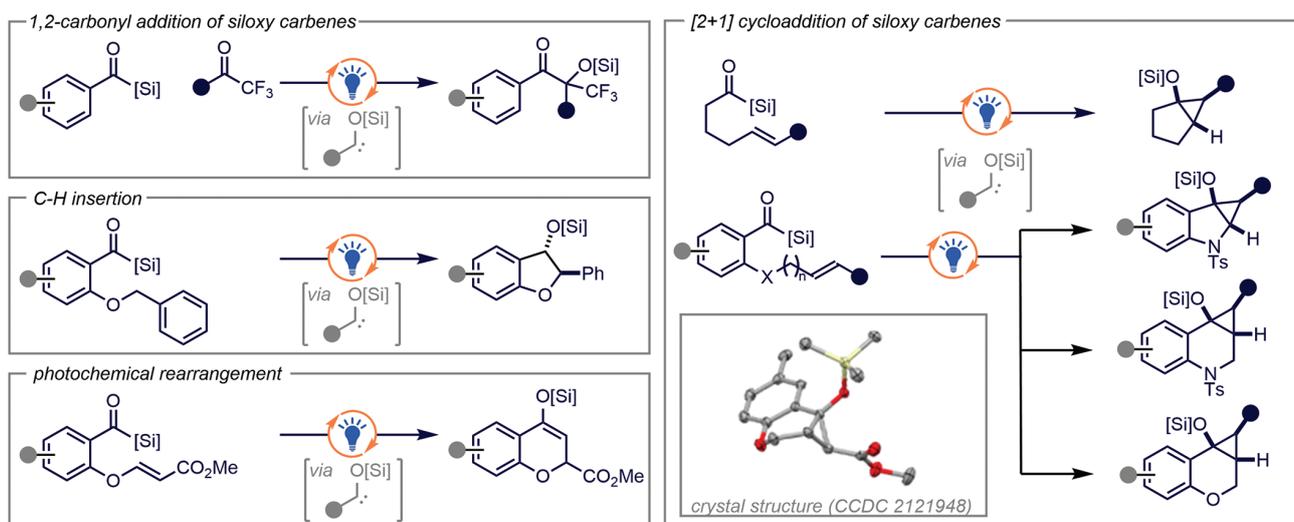


Figure 2: Our group has discovered a range of transformations to access useful molecular scaffolds using only visible-light irradiation. Crystal structure (CCDC 2121948) depicted at 50% probability (hydrogen atoms omitted for clarity): carbon (grey), oxygen (red), and silicon (yellow).

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