# SUSTAINABLE SYNTHESIS VIA NOVEL ACTIVATION MODES: ORGANOCATALYSIS AND PHOTOREDOX CATALYSIS

COLIN A. GOULD and DAVID W. C. MACMILLAN[*]

[*]*Department of Chemistry, Princeton University, Princeton, NJ 08540, USA*

## Catalysis for sustainable chemistry

Catalysis impacts society broadly, enabling advancements in diverse areas that range from renewable energy to drug discovery. Indeed, around 35% of gross domestic product (GDP) globally relies on catalysis [1], and over 75% of all industrial chemical transformations and 90% of newly developed processes utilize catalysts [2]. Due to the ubiquitous and essential nature of catalysis, the development of more efficient and environmentally-friendly catalytic processes represents a key step towards a more sustainable future.

Within chemical industry, the pharmaceutical and fine chemical sector is a particularly crucial area for the implementation of sustainable catalysis. Pharmaceutical and fine chemical synthesis is currently reliant on non-sustainable technologies, such as precious metal catalysis [3], and this sector generates over an order of magnitude more waste per product (kg/kg) than other areas of chemical industry (*e.g.*, bulk chemical synthesis or oil refining) [4]. Over the past several decades, significant progress towards the sustainable synthesis of pharmaceuticals and fine chemicals has been achieved through replacing non-sustainable chemistry, reducing waste, and increasing efficiency [5]. For instance, technologies such as base-metal catalysis [6], biocatalysis [7], and organocatalysis [8] have been developed that can be substituted for precious metals in some chemical transformations. As an example, in the manufacturing process of the type 2 diabetes medication Sitagliptin, scientists at Merck developed a biocatalytic transamination reaction to replace a rhodium-catalyzed asymmetric hydrogenation, resulting in a substantial increase in productivity (53% increase in kg/l per day) and yield (10-13% increase) and a reduction in waste (19% decrease), while simultaneously eliminating the need for precious metals in this process [9]. Clearly, the development of more sustainable technologies can render the pharmaceutical and fine chemical sector more environmentally friendly, while simultaneously increasing productivity and efficiency.

In the sections below, I will highlight some of my lab's contributions towards sustainable catalysis, focusing on the areas of organocatalysis [10] and photoredox catalysis [11, 12], and discuss future directions in these areas.

## My recent research contributions

My lab focuses on the development of novel activation pathways that enable new chemical transformations, including work in the fields of organocatalysis [10] and photoredox catalysis [11, 12]. In particular, synthetic methodologies developed by my lab utilize native functional groups such as carboxylic acids [13, 14], alcohols [15], and even C−H bonds [16, 17, 18] as versatile cross-coupling handles to enable the expedited synthesis of complex molecules from abundant, bench-stable precursors. Such methodologies have been rapidly adopted by the fine chemical and pharmaceutical industry, enabling more efficient and sustainable syntheses of target compounds.

For example, the fragrance company Firmenich currently synthesizes a target compound—Lily of the Valley (Fig. 1)—through a single-step chemical reaction that is promoted by the combination of an organocatalyst and a photocatalyst [19], an approach that was first developed in my lab [20]. This organophotocatalytic process allows the initial six-step route to Lily of the Valley to be reduced to a single step, starting from a biomass-derived precursor, (−)-β-pinene, and a feedstock chemical, propanal. The optimized route eliminates toxic or energetic reagents (*i.e.*, peroxy acids and pyridinium chlorochromate), while also minimizing the waste generated during the synthesis, resulting in a significantly more sustainable process overall.

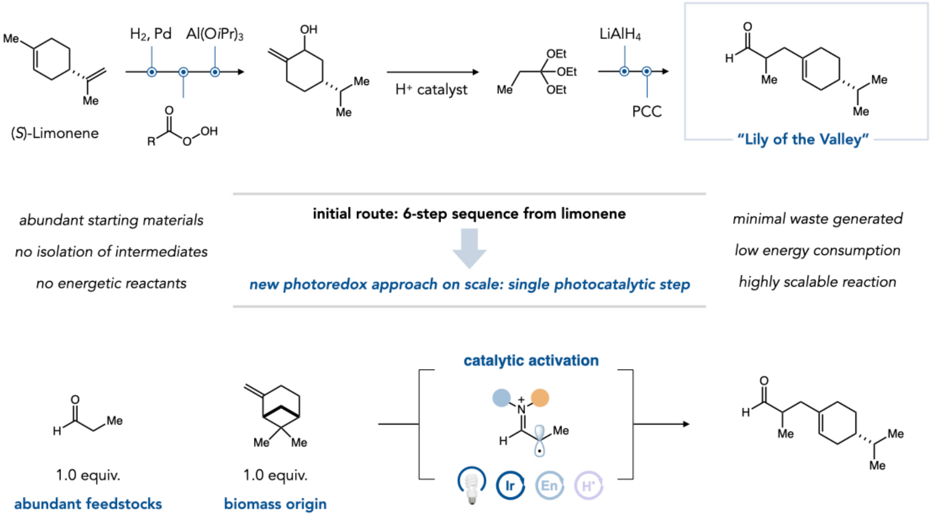

**Fig. 1.** Expedited synthesis of Lily of the Valley through the merger of organocatalysis and photoredox catalysis.

## Outlook to future developments

Since their development, organocatalysis and photoredox catalysis have been rapidly adopted by both academia and industry, however, most methodologies that utilize these activation modes are designed for small-scale processes (*i.e.*, <1 gram output). Translating more of these methodologies to an industrial scale is thus an essential goal, and, excitingly, significant progress is currently being made in this direction [21, 22]. I am optimistic about the long-term adoption of these activation modes at the commercial scale by chemical industry, and I believe that this constitutes an important route towards making catalysis more efficient and more sustainable.

## References

1. Z. Ma, F. Zaera, *Encyclopedia of Inorganic Chemistry- Heterogeneous Catalysis by Metals*, John Wiley & Sons, Ltd, 1 (2005).
2. S. Bhaduri, D. Mukesh, *Homogeneous Catalysis: Mechanisms and Industrial Applications*, John Wiley & Sons, Ltd, 1 (2014).
3. A. O. King, N. Yasuda, *Organometallics in Process Chemistry: Topics in Organometallic Chemistry* **6**, Springer, 205 (2004).
4. R. A. Sheldon, *J. R. Soc. Interface* **13**, 20160087 (2016).
5. R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **17**, 1479 (2013).
6. J. D. Hayler, D. K. Leahy, E. M. Simmons, *Organometallics* **38**, 36 (2019).
7. J. P. Adams, M. J. B. Brown, A. Diaz-Rodriguez, R. C. Lloyd, G.-D. Roiban, *Adv. Synth. Catal.* **361**, 2421 (2019).
8. B. Han, X.-H. He, Y.-Q. Liu, G. He, P. Cheng *et al.*, *Chem. Soc. Rev.* **50**, 1522 (2021).
9. C. K. Saville, J. M. Janey, E. C. Mundorff, J. C. Moore, S. Tam *et al.*, *Science* **329**, 305 (2010).
10. D. W. C. MacMillan, *Nature* **455**, 304 (2008).
11. M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **81**, 6898 (2016).
12. A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards *et al.*, *Chem. Rev.* **122**, 1485 (2022).
13. Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle *et. al.*, *Science* **345**, 437 (2014).
14. C. P. Johnston, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature* **536**, 322 (2016).
15. Z. Dong, D. W. C. MacMillan, *Nature* **598**, 451 (2021).
16. J. D. Cuthbertson, D. W. C. MacMillan, *Nature* **519**, 74 (2015).
17. M. H. Shaw, V. W. Shurtleff, J. A. Terrett, J. D. Cuthbertson, D. W. C. MacMillan, *Science* **352**, 1304 (2016).
18. I. B. Perry, T. F. Brewer, P. J. Sarver. D. M. Schultz, D. A. DiRocco *et. al.*, *Nature* **560**, 70 (2018).
19. C. Chapuis, International Patent PCT/EP2017/083377 (2018).
20. J. A. Terrett, M. D. Clift, D. W. C. MacMillan, *J. Am. Chem. Soc.* **136**, 6858 (2014).
21. F. Xu, *Organocatalysis for Asymmetric Synthesis: From Lab to Factory*, John Wiley & Sons, Ltd, 1 (2013).
22. K. C. Harper, E.-X. Zhang, Z.-Q. Li, T. Grieme, T. B. Towne *et. al.*, *Org. Process Res. Dev.* **26**, 404 (2022).