

Introduction

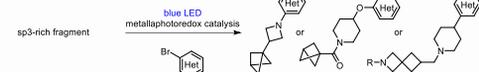
Compounds and intermediates in medicinal chemistry often present a bias toward the presence of multiple aromatic rings, as palladium-cross-coupling reactions have emerged as robust and versatile methodologies. Although synthetically tractable, such sp^2 -rich compounds exhibit lower metabolic stability and less desirable physical-organic properties compared to their sp^3 -rich counterparts. Following the mantra *escape from flatland*, SpiroChem identified visible light photochemistry and photoredox catalysis as an enabling technology to generate complexity from simple building blocks and give access to sp^3 -rich fragments and building blocks.

Two strategies were benchmarked by optimizing reported reactions: Dearomatization/cycloaddition reactions, and fragment coupling between a sp^3 -rich fragment and a (hetero)aromatic halide.

Strategy 1: Dearomatization or cycloadditions



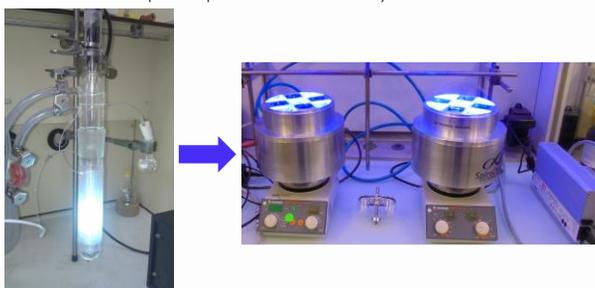
Strategy 2: Fragment coupling



Photochemistry by direct or sensitized irradiation

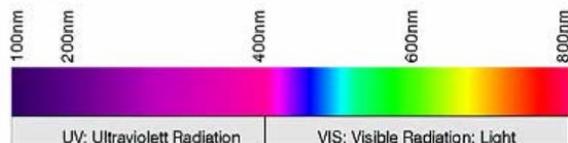
Photochemistry has been used for centuries in the field of synthetic organic chemistry, but direct irradiation with high-energy photons prevented wide adoption of this technology for fine chemical synthesis, because of functional group compatibility issues.

Some substrates can react after direct absorption of visible light, leading to better controlled reactivity. When that is not possible, *energy transfer* from a catalyst excited by visible light such as benzophenone derivatives or metal complexes can promote excitation and reactivity.



Broad UV mercury lamp (200+ nm)

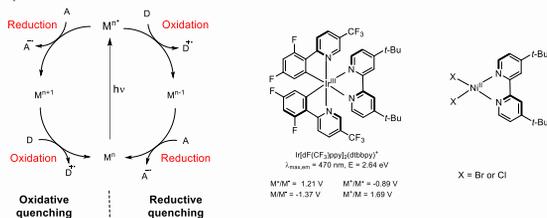
Blue light high-power LED reactors (450 nm)



(Metalla)Photoredox catalysis

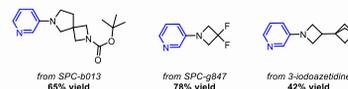
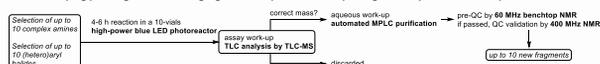
In recent years, development of *photoredox catalysis* enabled a large variety of redox transformations to be performed with visible light, unlocking many interesting reactions which were deemed not applicable in complex synthetic settings.³

Metallaphotoredox catalysis is the combination of metal catalysis and photoredox catalysis, and often expands the scope of traditional metal-catalyzed cross-couplings or enables them at lower temperatures.⁴

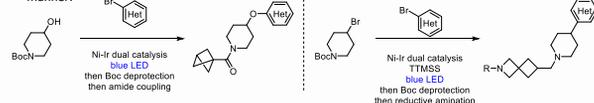


Fragment coupling

Technological advances in photoreactor design facilitated reliable and reproducible experimentation. We used a *high-power blue LED photoreactor* to set up to 10 experiments in parallel and probe the reactivity of spirocyclic and strained heterocyclic building blocks under previously reported reaction conditions (Nickel-photoredox dual catalysis). Interesting fragments could thus be rapidly accessed, identifying privileged or challenging reaction partners and paving the way for further exploration.⁵

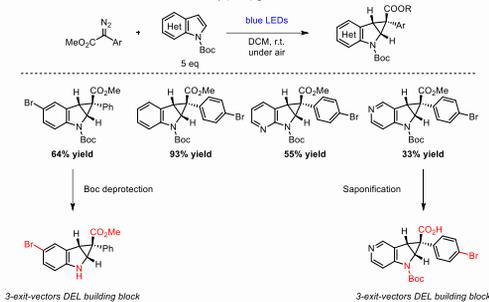


During a confidential client project, we validated and expanded the scope of *nickel-photoredox dual catalyzed C-O and C-C couplings* of simple piperidine derivatives with a complex heteroaryl bromide derivative. The products were then Boc-protected and capped with a sp^3 -rich building-block by amide coupling or reductive amination. A diverse library could thus be accessed in an efficient and modular manner.

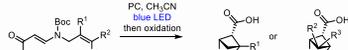


Dearomatizations and Cycloadditions

Inspired by a report by Davies¹, we decided to investigate the direct reaction of donor-acceptor diazo compounds with (aza)indoles upon blue light irradiation to generate densely substituted cores. Upon irradiation, the diazo compound formed a carbene which reacted selectively on the electron-rich ring to give the corresponding cyclopropane with full diastereoselectivity. Boc deprotection or saponification of selected examples gave 3-exit-vectors building blocks which could be useful for DNA-Encoded-Library (DEL) generation.



UV-A-initiated [2+2] cycloadditions to form nitrogen-containing bicyclic scaffolds were reported, but had poor scalability and functional group compatibility.² During a confidential client project, we developed and optimized this reaction by leveraging an *energy transfer strategy* using a photocatalyst and blue light. The process was then further optimized elsewhere to provide multi-gram quantities of the diastereo- and enantiopure compounds.



References

1. I. D. Jurberg, H. M. L. Davies, *Chem. Sci.*, **2018**, 9, 5112-5118.
2. G. R. Krow, G. Lin, S. B. Herzon, A. M. Thomas, K. P. Moore, Q. Huang, P. J. Carroll, *J. Org. Chem.*, **2003**, 68, 7562-7564.
3. C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.*, **2013**, 113, 5322-5363.
4. A. Y. Chan *et al.*, *Chem. Rev.*, **2022**, 122, 2, 1485-1542.
5. Q. Lefebvre, C. Salomé, T. C. Fessard, *Beilstein J. Org. Chem.*, **2020**, 16, 982-988.

Conclusion

Using visible-light photochemistry and photoredox catalysis, complex sp^3 -rich products could be synthesized from simple, "flat" starting materials, with complete atom-economy. They could be used in the field of DNA-Encoded-Libraries or as cores for diversification in a confidential project.

Metallaphotoredox catalysis was used for fragment coupling between heteroaromatics and small saturated heterocycles such as (spirocyclic)azetidines and piperidine derivatives. The products obtained could be used in the field of Fragment-Based-Libraries or could be further functionalized to generate high-value large molecules in a confidential project.

