

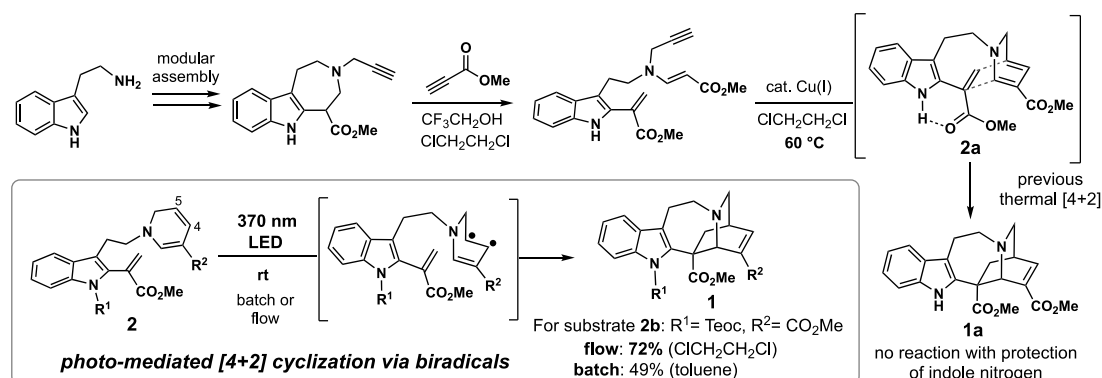
Development and mechanistic studies of photo-mediated [4+2] cycloaddition for rapid assembly of *iboga*-type scaffold

(¹Graduate School of Science, The University of Tokyo, ²Graduate School of Engineering, Tokyo University of Agriculture and Technology) ○Gavin Tay,¹ Soushi Nishimura,¹ Hiroki Kubota,² Hiroki Oguri¹

Keywords: Iboga alkaloids; Photocycloaddition; Dihydropyridine; Multipotent biomimetic intermediate; Photoflow reaction

Iboga-type indole alkaloids are a pharmaceutically significant class of natural products known for its psychoactive and anti-drug addiction properties. In our previous biomimetic synthesis, *iboga*-type scaffold **1a** was assembled via thermal-assisted intramolecular Diels–Alder cycloaddition between the dihydropyridine (DHP) ring and vinylindole methyl acrylate moiety of **2a** in 48% yield.¹ However, the attempted thermal [4+2] cycloaddition of substrates with protection of indole nitrogen resulted in no conversion to form *iboga*-type scaffold **1**. In this study, we achieved the photo-mediated [4+2] cyclization of various substrates with modifications of substituents R¹ and R² for efficient and flexible assembly of the *iboga*-type scaffold **1** at room temperature in the absence of any photocatalysts or sensitizers.

Modular assembly of building blocks to form ene-yne and subsequent Cu(I)-catalyzed 1,6-DHP ring formation² produced cyclization precursor **2** with protection of indole nitrogen.² A representative substrate **2b** (R¹ = Teoc, R² = CO₂Me) exhibits characteristic UV absorption at 365 nm. Photoirradiation at this wavelength region substantially improved the yield of the target *iboga*-type scaffold **1b** up to 72% (batch condition: 48%) with application of micro-flow system. Through computational, spectroscopic, and mechanistic studies, we hypothesize that the photo [4+2] cyclization would be triggered by site-selective activation of C4–C5 double-bond in the DHP unit, which then undergoes a stepwise pathway presumably via open-shelled biradical intermediates. Compared to the thermal cycloadditions, this approach featuring relatively unexplored photo-induced [4+2] cyclizations has been demonstrated to have both broader substrate scopes under milder reaction conditions and practical advantages using series of precursors stable enough to be isolated.



1) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014**, *6*, 57.

2) Mizoguchi, H.; Watanabe, R.; Minami, S.; Oikawa, H.; Oguri, H. *Org. Biomol. Chem.* **2015**, *13*, 5955.