Chemoselective Synthesis of Unsymmetrical Disulfides Using Phototropin-Inspired Flavin Photocatalysis

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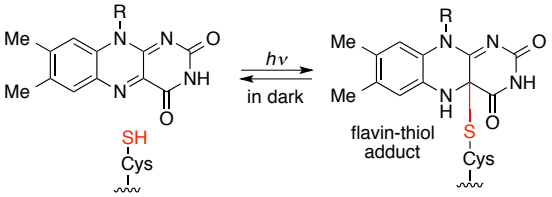
Keywords: *Unsymmetrical Disulfide; Flavin; Aerobic Oxidation; Photocatalysis; Organocatalysis*

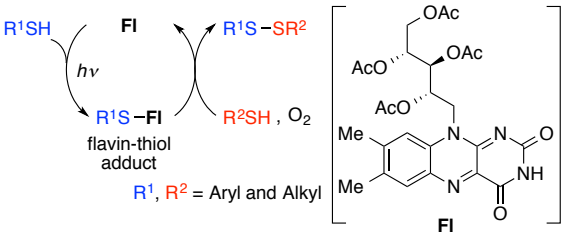
Higher plants have a blue light receptor protein called phototropin in which flavin mononucleotide is contained as a chromophore. The flavin is excited by blue light and forms a covalently bonded flavin-thiol adduct with the cysteinethiol group (Scheme 1)[1]. This photochemical process has attracted a much attention because it exhibits various functions to improve the efficiency of photosynthesis.



Scheme 1. Photoreaction of flavin unit in phototropin

Disulfides, containing two covalently linked sulfur atoms, are one of the important compounds found in natural products and bioactive substances. Despite unsymmetrical disulfides (R^1S-SR^2) are extensively used in pharmaceuticals, the effective synthetic methods have been limited. The direct oxidative crosscoupling of two different thiols is the ideal approach to access unsymmetrical disulfides. However, this system has problems such as the need for excess oxidant, and the competitive generation of two symmetrical disulfides as the by-products. Recently, the crosscoupling of thiols by electrolysis and metal catalysts has been reported.[2] However, the problems including the scope of substrates still remain, thus the development of a more efficient and green method is desired.

In this work, we were inspired by the photochemical process of phototropin and developed the novel green method for the synthesis of unsymmetrical disulfides using flavin-thiol adduct as the catalytic intermediate (Scheme 2). Using a riboflavin tetraacetate (**Fl**) and visible light, we successfully performed the heterocoupling of two different thiols chemoselectively forming the corresponding unsymmetrical disulfide[3]. The scope of the heterocoupling reaction and the reaction mechanism were also investigated by control experiments.



Scheme 2. Chemoselective heterocoupling of thiols

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2) a) P. Huang, P. Wang, S. Tang, Z. Fu, A. Lei, *Angew. Chem. Int. Ed.* **2018**, *57*, 8115. b) L. Song, W. Li, W. Duan, J. An, S. Tang, L. Li, G. Yang, *Green Chem.*, **2019**, *21*, 1432.
3) M. Oka, D. Katsube, T. Tsuji, H. Iida, *Org. Lett.* **2020**, *22*, 9244.