Development of a nucleobase-recognition site-conjugated donor-acceptor complex catalyst for base selective trifluoromethylation

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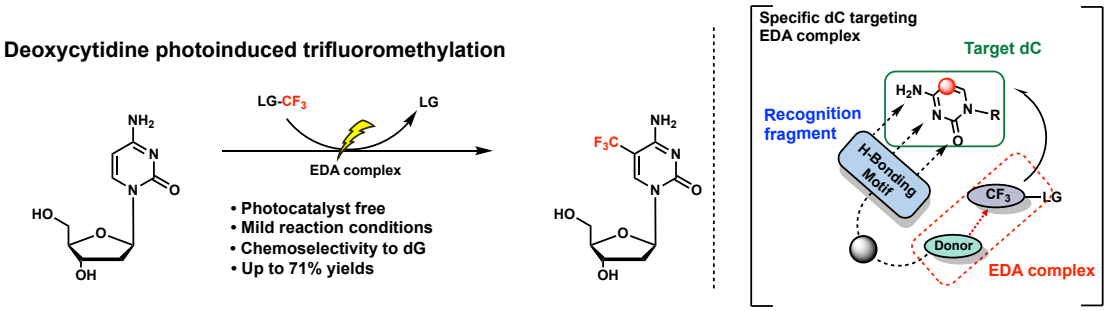
Chemical modification of DNA molecules, a key mechanism in epigenetic regulation, plays crucial roles in gene expression and disease development. Among various DNA modifications, trifluoromethylation has gained significant attention due to its unique electronic effects, steric properties, and lipophilicity. These modifications not only alter DNA's physicochemical properties but also modulate protein interactions. However, traditional synthesis of such nucleoside analogs requires multiple steps of chemical modifications from protected nucleosides. Therefore, developing efficient, mild, and water-compatible methods for direct or late-stage functionalization of nucleosides and oligonucleotides remains highly desirable.[1-3]

Herein, we present a novel selective trifluoromethylation system featuring a dual functional design that combines base recognition with radical generation capabilities. The system employs an organic catalyst that forms electron donor acceptor (EDA) complex with CF_3 sources.[4] Under visible light irritation, the complex undergoes controlled radical generation through single-electron transfer processes. Guided by the base recognition, the targeted nucleosides undergo selective radical modification followed by catalyst-mediated oxidation to achieve trifluoromethylation.

This process utilizes commercially available and an inexpensive CF_3 donor as the trifluoromethyl source and operates under mild conditions. The rigid linkage connecting the base recognition module, significantly enhancing reaction efficiency and the selectivity towards different nucleosides



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