

## Recent development in Photo catalyzed cross-coupling reactions for the synthesis of $\alpha$ -Trifluoromethylated Carbonyls

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### Abstract

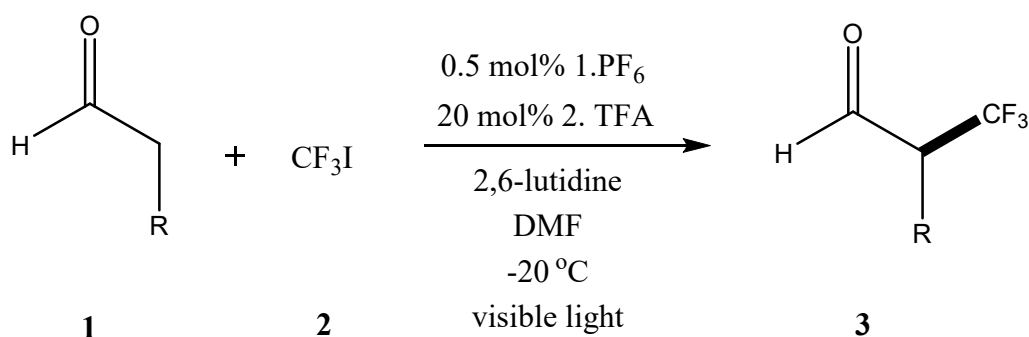
Visible light has received increased attention and research interest in both academics and industry from all around the world.<sup>1</sup> Owing to its natural abundance and renewability it also provides a clean, inexpensive, and eco-friendly source of energy. Various types of photo-catalytic reactions using visible light as an initiator have been described in the past several decades for C–C, C–N, C–O, and C–F, etc bonds formation in different types of coupling reactions.<sup>1</sup> Owing to their great capability towards bond formation of different types, they have been widely used as structural motifs in different areas like pharmaceuticals, agrochemicals, food industries, material sciences, and so on for the synthesis of target molecules. This review provides a brief and concise summary of the recent development in the field of visible light-mediated Photo catalyzed cross-coupling reactions for the synthesis of  $\alpha$ -Trifluoromethylated Ketones.

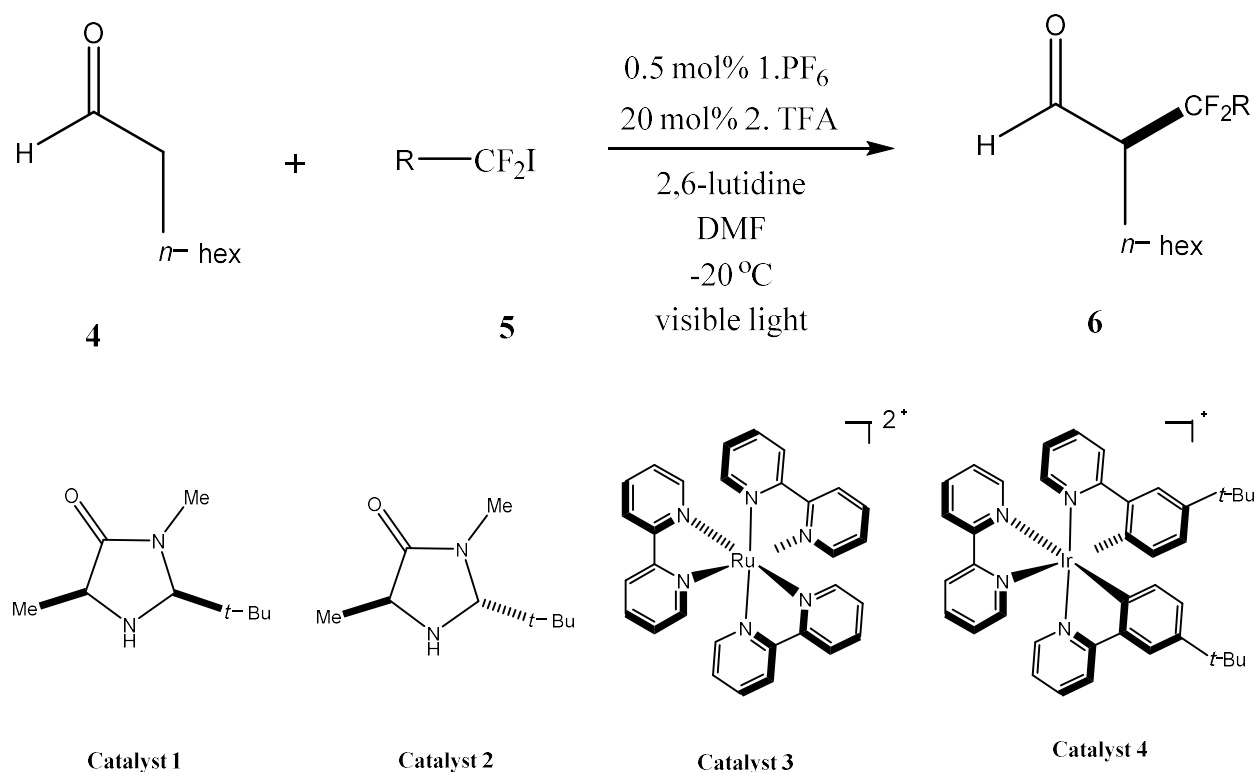
### Introduction

Organofluorides compounds are rare in its naturally occurring form even though the elemental Fluorine is abundantly available in our Earth's crust. Recent advances in catalysis have made the introduction of a trifluoromethyl group in a reliable manner into complex organic molecules easier than ever before.<sup>2</sup> The introduction of a trifluoromethyl group in a molecule undoubtedly belongs among the most relevant and desired transformations in fluorine chemistry. The introduction of trifluoromethyl (CF<sub>3</sub>) groups into organic molecules can impart desirable properties, such as metabolic and thermal stability, lipophilicity, and ability to penetrate the blood-brain barrier thus this type of molecule frequently used as pharmaceuticals and agrochemical compounds as well as in functional organic materials.<sup>3</sup>  $\alpha$ -CF<sub>3</sub> substituted ketones are versatile building blocks for the synthesis of a wide variety of complex CF<sub>3</sub>-containing molecules which are ubiquitous in natural products and synthetic pharmaceuticals. The introduction of a CF<sub>3</sub> group at the  $\alpha$ -position of carbonyl compounds is considered to be a difficult task and thus over the past decade, several research groups involved in the development of numerous efficient methods for carbon–CF<sub>3</sub> bond formation.<sup>4</sup> Among them, Photo catalyzed cross-coupling reactions provide a greener and mild pathway for the synthesis of Trifluoromethylated Ketones. This review provides a brief and concise summary of the recent development in the field of visible light-mediated Photo catalyzed cross-coupling reactions for the synthesis of Trifluoromethylated Ketones.

In 2009, MacMillan and co-workers reported the first enantioselective  $\alpha$ -trifluoromethylation of aldehydes via the successful merger of enamine and organometallic photoredox catalysis. The process was catalyzed by a combination of Ir(ppy)<sub>2</sub>(dtb-bpy)PF<sub>6</sub> as a photocatalyst, (2R,5S)-2-*t*-butyl-3,5-dimethylimidazolidin-4-one·TFA as organocatalyst and 2,6-lutidine under 26 W compact fluorescent light bulb irradiation in DMF solution at -20 °C (**Scheme 1**).<sup>5</sup> In this transformation, Trifluoromethyl iodide (**2**) or perfluoroalkyl iodide (**5**) was used as the alkylation

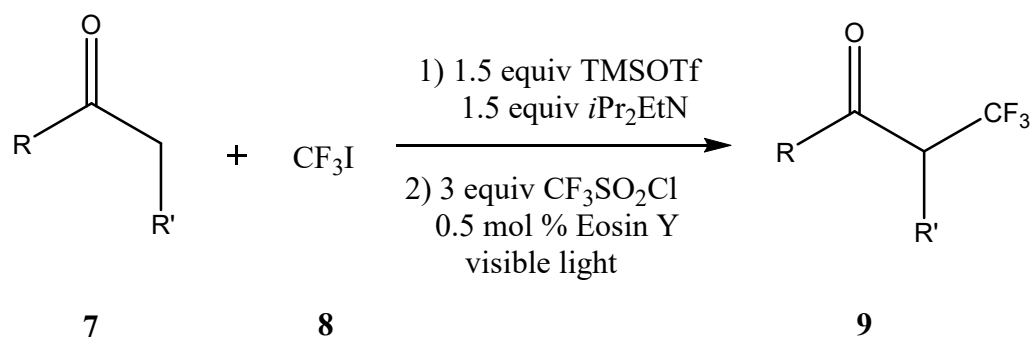
agent for trifluoromethylation of aldehydes (**1,4**) and both the  $\alpha$ -trifluoromethylated (**3**) and  $\alpha$ -perfluoroalkylated aldehydes (**6**) were obtained in up to 89 % yields with 99 % enantioselectivities. Optimization studies revealed that 51 % yield (racemic product) of  $\alpha$ -trifluoromethylated product was indeed possible using a combination of  $\text{Ru}(\text{bpy})_3^{2+}$  (**cat. 3**) and the amine catalyst (**cat. 1**). Control experiments indicated an almost complete loss of catalyst efficiency (<5% yield) when light was omitted. While the use of  $\text{Ir}(\text{ppy})_2(\text{dtb-bpy})^+$  (**cat. 4**) allowed a significant increase in reaction yield (85%) without enantioselectivity at 23°C and up to 52% enantioselectivity can be achieved at -20 °C. Moreover, implementation of the  $\text{Ir}(\text{ppy})_2(\text{dtb-bpy})\text{PF}_6$  (**cat. 4**) as a photocatalyst, (2*R*,5*S*)-2-*t*-butyl-3,5-dimethylimidazolidin-4-one·TFA (**cat. 2**) as organocatalyst provided 99% enantioselectivity up to 79% yield. The authors showed that mild redox conditions are compatible with a wide range of functional groups including ethers, esters, amines, carbamates, and aromatic rings, and the corresponding  $\alpha$ -Trifluoromethylated product was obtained in high yield ( 61-86% ) with enantioselectivity (93-99% ee). Under similar condition a broad range of perfluoroalkyl iodides and bromides also participate in this enantioselective alkylation reaction and corresponding  $\alpha$ - perfluoroalkylated aldehydes was obtained in high yield (67-89%) with enantioselectivity (96-99% ee).





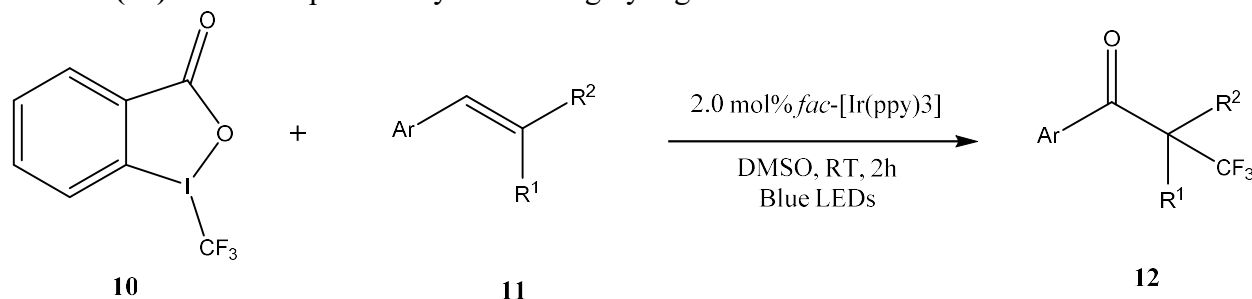
**Scheme 1:** Enantioselective  $\alpha$ -trifluoromethylation of aldehydes via the successful merger of enamine and organometallic photoredox catalysis.

Later, in 2014, Kappe and co-workers demonstrated a continuous-flow procedure for the two-step  $\alpha$ -trifluoromethylation of ketones (**7**) using  $\text{CF}_3\text{SO}_2\text{Cl}$  (**8**) as a source of  $\text{CF}_3$  radicals and Eosin Y as an inexpensive, nontoxic, and readily available photoredox catalyst (**Scheme 2**).<sup>6</sup> The two-step process requires only 20 min for completion, initially, the ketones were transformed into the corresponding silylenolethers in flow and in situ subjected to visible light-induced radical trifluoromethylation. A variety of para- and ortho- substituted acetophenones was successfully trifluoromethylated and gave the corresponding  $\alpha$ -trifluoromethylketones (**9**) up to 87 % yield.



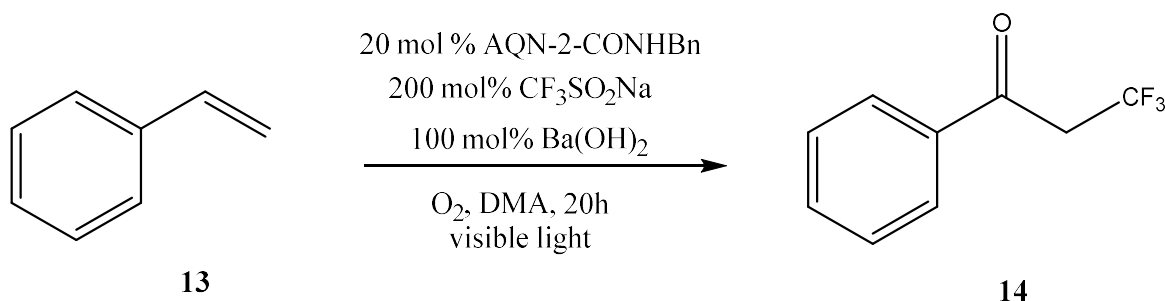
**Scheme 2:** Continuous-flow visible light induced preparation of  $\alpha$ -trifluoromethyl ketones.

The oxidative trifluoromethylation of unactivated alkenes/alkynes is a highly efficient and rapidly growing novel strategy for the synthesis of  $\alpha$ -trifluoromethylated ketones. Recently, Akita and co-workers have reported a highly efficient synthetic route to  $\alpha$ -CF<sub>3</sub>-substituted carbonyl compounds from aromatic alkenes (**11**) and Togni's reagent (**10**) by combining photoredox-catalyzed trifluoromethylation and oxidation mediated by an alkoxy-sulfonium ion (**Scheme 3**).<sup>7</sup> In this photocatalytic approach Togni's reagent was used as a precursor of CF<sub>3</sub>-radical and Dimethyl sulfoxide (DMSO) served as a key and mild oxidant. A variety of aromatic alkenes with different functional groups, such as halogen, ester, acetal, boronic ester, hydroxy, and pyridyl groups were tolerated to the photocatalytic ketotrifluoromethylation and corresponding  $\alpha$ -CF<sub>3</sub>-substituted ketones (**12**) obtained up to 87% yield in a highly regioselective fashion.



**Scheme 3:** Keto-trifluoromethylation of alkenes.

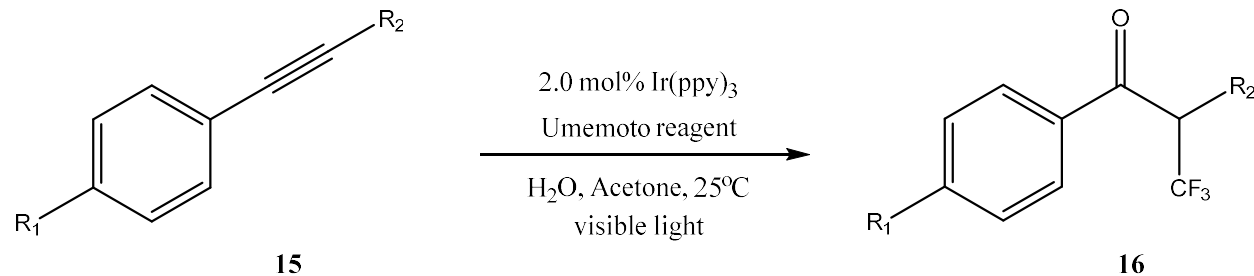
Very recently, Itoh and co-workers reported a mild, efficient, and metal-free oxidative methodology for the transformation of styrenes (**13**) and Langlois reagent (CF<sub>3</sub>SO<sub>2</sub>Na) into  $\alpha$ -trifluoromethyl carbonyls (**14**) utilizing anthraquinone as an organic photoredox catalyst (**Scheme 4**).<sup>8</sup> Control experiments support that visible light, photocatalyst, and air, are all essential for the completion of reaction. The reaction worked well with styrenes bearing electron-donating substituents, electron-withdrawing substituents, and a wide range of functional groups including bromo, chloro, acetal, TBS, ethers, esters, cyano, and  $\alpha,\beta$ -substituted olefins, etc well tolerated under reaction condition. It gave the corresponding  $\alpha$ -trifluoromethylated in good to excellent yield.



**Scheme 4:** Organocatalytic keto-trifluoromethylation of styrenes

In 2018, Han et al developed the first direct synthesis of  $\alpha$ -CF<sub>3</sub> substituted ketones from internal and terminal alkynes via oxidative trifluoromethylation using visible light catalysis (**Scheme 5**).<sup>9</sup> The operational simplicity, mild reaction condition, broad scope of functional group tolerance, and

the synthesis of various CF<sub>3</sub>-incorporated heterocyclic compounds provide an alternative route to the construction of  $\alpha$ -CF<sub>3</sub> substituted ketones.



**Scheme 5:** Oxidative Trifluoromethylation of Alkynes

The wide applications of  $\alpha$ -Trifluoromethylated Ketones in pharmaceuticals, agrochemical compounds and functional organic materials show the importance of  $\alpha$ -Trifluoromethylated Ketones. Over the past several years, a number of efficient methods are available for the synthesis of such type of wonderful molecules. In this review, we reported the recent development of photo-catalyzed cross-coupling reactions for the synthesis of  $\alpha$ -Trifluoromethylated Ketones.

### Conclusions and perspectives

For progress in pharmaceuticals and agrochemical compounds as well as in functional organic materials.  $\alpha$ -CF<sub>3</sub> substituted ketones are versatile building blocks for the synthesis of a wide variety of complex CF<sub>3</sub>-containing molecules. Formation of the bond C-CF<sub>3</sub> is pivotal and the formation mechanism of this bond should be mild, eco friendly and high yield. Efficient catalyst is being introduced through rigorous experimental process for such synthesis. Initially metal catalyst was major player and now emphasis is given to use more economical, mild, ecofriendly and widely available catalyst like light (photo catalyst). More and more researches are reported in using this path. One thing is clear that the potential of trifluoromethylation reaction under the process of radicals is great, and it still has a long way to go. We anticipate significant future growth in this field and the synthetic community will design novel transformations in the coming few years.

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