Stereoretentive Decarboxylative C-3 Functionalization of Chromone-3-carboxylic Acids via Visible Light Irradiation

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ABSTRACT: Herein, we report a stereoretentive and decarboxylative C-3 functionalization of chromone-3-carboxylic acids with optically active aziridines via visible light irradiation. This metal-free and operationally simple protocol utilizes a simple combination of stable and inexpensive tetrabutylammonium iodide and visible light irradiation. It enables a facile and direct access to chiral 3-substituted chromenones with maintaining the optical purity of starting aziridines.Cross-coupling reactions allowing for efficient carbon–carbon as well as carbon–heteroatom bond formations are of crucial importance in the modern organic chemistry.[1] Among them transition-metal-catalyzed decarboxylative cross-couplings utilizing carboxylic acids as substrates occupy a prominent position.[2] They offer several distinctive advantages related to availability and price of carboxylic acid derivatives, their stability and handling as well as generation of less-toxic carbon dioxide as the by-product that reduces the waste treatment costs. While these methods have proven particularly useful for $C(sp^2)$-$C(sp^2)$ bond formations and were applied for the synthesis of numerous relevant products ranging from pharmaceuticals to organic materials, their application in the $C(sp^2)$-$C(sp^3)$ remains limited. Consequently, there is a need for the development of alternative, transition-metal-free cross-coupling reactions allowing for $C(sp^2)$-$C(sp^3)$ bond formations.

Visible light photocatalysis has recently emerged as a powerful tool expanding the arsenal of bond-forming protocols. Due to its simplicity, economy and environmental friendliness it has received increased attention.[3] Within this research area, the use of carboxylic acids as substrates has become an interesting strategy allowing for the generation of alkyl radicals under mild conditions and opening access to new reaction profiles. Stereoselective processes are challenging and receive special attention. Interestingly, processes involving chiral radical precursors are known in the literature with the memory of chirality phenomenon observed in such processes.[4] Aziridines has recently emerged as a useful group of reactants readily participating in the radical processes resulting in the development new strain-release bond forming reactions.[5] The chromen-4-one and its C-3-substituted derivatives can be found in various bioactive molecules relevant for the life-science industry (Scheme 1, top).[6] Selected examples of bio-relevant C-3-substituted chromen-4-ones are shown in the Scheme 1. Crodimyl possesses muscle relaxant properties and exerts vasodilator effect on coronary blood vessels.[7] Hyperimone B has been reported to exhibit antitumor activity.[8] Iguratimod is an anti-inflammatory small molecule drug used for the treatment of rheumatoid arthritis.[9] Flavoxate was employed as an anticholinergic agent for its antimuscarinic effect.[10]

Given our interest in the development of new synthetic methodologies utilizing chromone-3-carboxylic acids as starting materials,[11] it was envisioned that they should be able to participate in the cross-couplings reaction with aziridines leading to C-3-substituted chromen-4-ones, thus resulting in the unique $C(sp^2)$-$C(sp^3)$ bond forming process. Devised reactivity can be considered as a formal alkenylation of aziridines providing access to homoallylic amines. However, at the outset of our studies challenges related to stereospecificity of the process were considered. We questioned whether the stereochemical information of 1 was possible to be preserved under these reaction conditions following memory of chirality phenomenon.

Herein, we describe a unique, metal-free, visible-light-mediated protocol for the synthesis of chiral 3-substituted chromenones. This method utilizes bench-stable and inexpensive TBAI as a reaction promotor, enabling access to stereoretentive and regioselective construction of a challenging carbon-carbon bonds. The developed approach constitutes attractive strategy for the preparation of structurally diverse molecules and benefits from the operational simplicity.

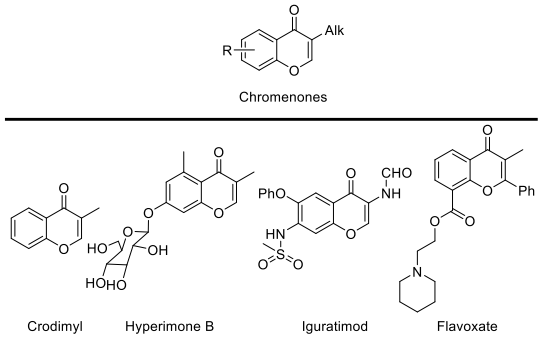
Optimization studies were performed using chromone-3-carboxylic acid 1a and optically active (R)-2-phenyl-1-tosylaziridine 2a as model substrates (Table 1). Initial experiment was performed in NMP as solvent in the presence of tetrabutylammonium iodide (TBAI) as a radical mediator under LED irradiation and under inert atmosphere. To our delight, the desired decarboxylative cross-coupled product 3a was formed in low yield with exclusive regioselectivity (Table 1, entry 1). Importantly, the optical purity of 2a was partially preserved under the reaction conditions. Therefore, solvent screening was initiated to increase both the efficiency and stereospecificity of the process (Table 1, entries 1-5). Among tested solvents, the best results were obtained using anhydrous N,N-dimethylformamide (Table 1, entry 2). Next, the influence of halogen source on the reaction outcome was assessed (Table 1, entries 2, 6-9). Both inorganic and organic iodides initiated the reaction (Table 1, entries 2,6,7). However, worser efficiency and stereospecificity was observed in the case of inorganic salts (Table 1, entries 6,7). Moreover, it was found that the replacement of the counterion with the bromide or fluoride ions suppressed the reactivity (Table 1, entries 8,9). In subsequent investigations, reducing the amount of TBAI from 2 to 1.5-fold excess, yielded the desired product in lower 46% yield (Table 1, entry 10). Using 3-fold excess of TBAI did not improve the reaction efficiency (Table 1, entry 11). In a course of further studies, the concentration effect was evaluated (Table 1, compare entries 12,13). It was found that the decarboxylative cross-coupling reaction proceeded with higher efficiency at higher concentration (Table 1, entry 13) providing 3a with a high 84% yield and with high degree of preservation of optical purity (Table 1, entry 13).

Control experiments revealed that light and TBAI were crucial for this transformation (Table 1, entries 14,15). While the reaction in the dark provided 3a in very low yield, no product 3a formation was identified in the absence of TBAI (Table 1, entries 14 and 15).

Having accomplished the optimization studies, the goal of establishing scope and limitation of the methodology was pursued (Schemes 2 and 3). In the first part of scope studies various chromone-3-carboxylic acids 1a-k were reacted with (R)-2-phenyl-1-tosylaziridine 2a under optimized conditions (Scheme 2). To our delight, the target products 3a-k were obtained in high yields when electron-donating substituents were present on the aromatic ring in 3b-e. In the course of further studies it was found that when electron-withdrawing groups were introduced on the aromatic ring in chromone-3-carboxylic acids 1f-g,k the yield of the reaction was lower. It is worth to note that the developed methodology was efficient for disubstituted carboxylic acids 1i-k. Notably, reactions proceeded with the high degree of preservation of optical purity of 2a in most of the cases. Deterioration of stereospecificity of the process was observed when substituents were present in the 5 or 6 position of the chromone ring system (Scheme 3, compounds 3d,l,j,k) presumably for steric reasons. In the second part of scope studies different aziridines 2 were employed (Scheme 3). It was found that (R)-2-methyl-1-mesylaziridine participated in the reaction providing target product 3l with diminished yield and with excellent stereoselectivity. Subsequently, the influence of the protecting group at the nitrogen atom in 2 was evaluated. While mesyl-protected aziridine 2c reacted smoothly, no product formation was observed for both Boc-protected 2d and unprotected aziridine 2e developed protocol proved to be unsuccessful and desired products were not present in the reaction mixture. Notably, all performed reaction afforded highly enantiomerically enriched products 3a-m confirming that optical purity of the aziridines 2 was maintained during the processes.

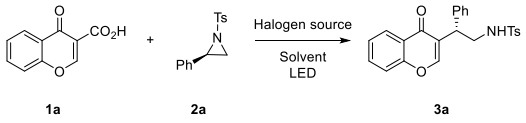
To assign the absolute configuration of target products 3, the single crystal X-ray analysis of 3c was performed (Scheme 4, top) indicating that the reaction proceeded with retention of absolute configuration of the starting aziridine 2.[12] The configuration of all remaining products 3 was established by analogy. Given the obtained very interesting result, the mechanism of developed approach was proposed.[13] The reaction is initiated by the opening of the aziridine ring in 2a by iodide anion acting as nucleophilic catalyst. The iodide 4a interacts with 1a[14] to form photoactive EDA-complex EDA-1 with strong absorption in the visible region (bathochromic shift observed in the UV-VIS spectra of TBAI+1a+2a+DMF). Visible-light irradiation of EDA-1 induces SET and produces radical 5a that undergoes decarboxylation to sp^2-centered radical 10a. In parallel, anion radical 6a undergoes elimination to benzylic radical 7a that participates in halogen atom transfer to give 4a. It interacts with 2a to give a second EDA-complex EDA-2 (second maximum of absorption observed in the UV-VIS spectra of reaction mixture after 30 minutes). Visible-light irradiation of EDA-2 leads to second SET resulting in radical cation 8a. The latter acts as precursor of benzylic radical 9a that is configurationally stable due to the donation of electrons from the negatively charged nitrogen atom (memory of chirality phenomenon). Cross-coupling between radicals 9a and 10a results in new C-C bond formation that proceeds with retention of configuration at the chiral center originating from aziridine 2a. Notably, both SET processes are facilitated by their irreversibility associated with elimination of iodide anion or carbon dioxide molecule.[15] Importantly, the formation of selected reaction intermediates was confirmed by MS studies. Furthermore, radical 7a was captured by the experiment with TEMPO confirming its formation in the course of the reaction.

In conclusion, we have successfully developed the first stereoretentive TBAI-promoted transformation between chromone-3-carboxylic acids and aziridines under visible-light irradiation.` This process proceeds through the formation of radical intermediates and leads to the formation of biologically relevant and enantioenriched C-3-substituted chromenones. The reaction benefits from broad scope, operational simplicity as well as highly stereospecific character with retention of configuration being the outcome of the process. The mechanism of the reaction was confirmed by experimental studies involving mass spectroscopy.



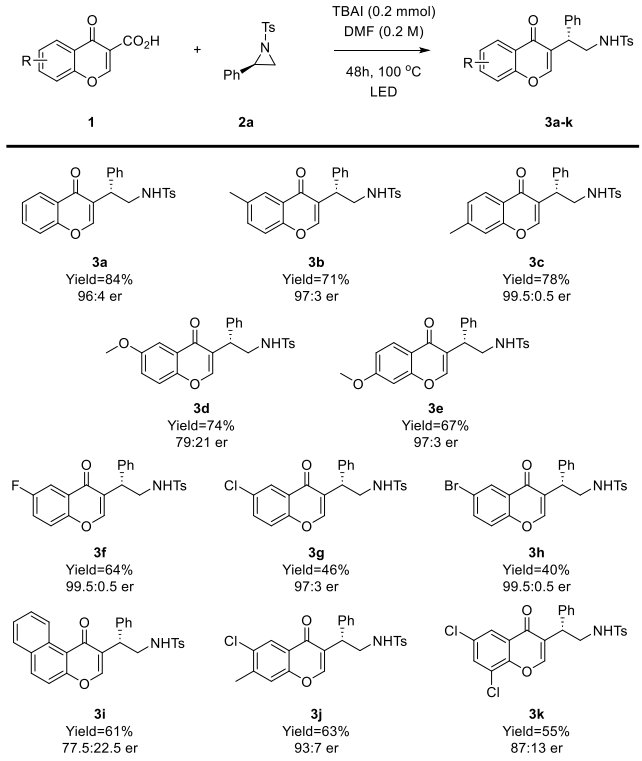
Scheme 1. Representative examples of naturally occurring chromenone derivatives.

Table 1. Stereoretentive, decarboxylative C-3 functionalization of chromone-3-carboxylic acids 1 – optimization studies

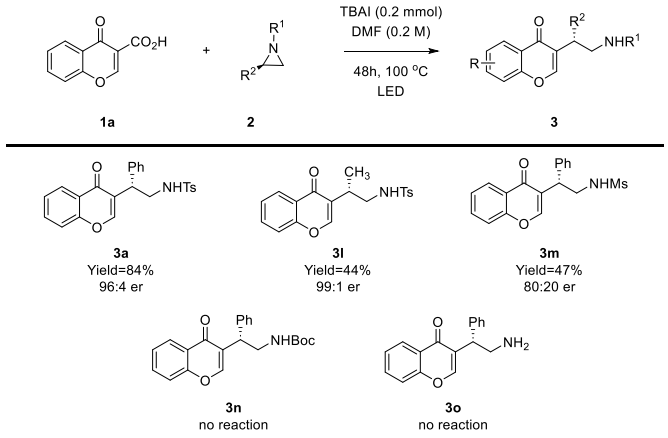


	Solvent	Halogen source (equiv.)	Yield (%)	er
1	NMP (0.05)	TBAI (2.0)	24	89:11
2	DMF (0.05)	TBAI (2.0)	81	94:6
3	DMSO (0.05)	TBAI (2.0)	11	n.d.
4	1,4-Dioxane (0.05)	TBAI (2.0)	48	n.d.
5	Toluene (0.05)	TBAI (2.0)	62	88:12
6	DMF (0.05)	KI (2.0)	49	86:14
7	DMF (0.05)	NaI (2.0)	38	n.d.
8	DMF (0.05)	TBABr (2.0)	14	n.d.
9	DMF (0.05)	TEAF (2.0)	<5	n.d.
10	DMF (0.05)	TBAI (1.5)	46	95:5
11	DMF (0.05)	TBAI (3.0)	73	95:5
12	DMF (0.09M)	TBAI (2.0)	56	96:4
13	DMF (0.2M)	TBAI (2.0)	84	96:4
14[b]	DMF (0.2M)	TBAI (2.0)	11	n.d.
15	DMF (0.2M)	-	<5	n.d.

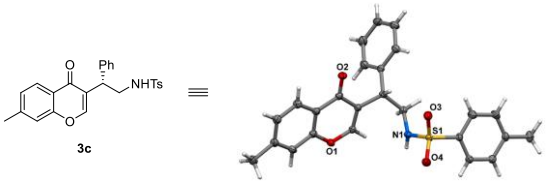
[a] Reaction conditions: alkene 1a (0.1 mmol), (R)-2-phenyl-1-tosylaziridine 2a (2.5 equiv.), halogen source (2.0 equiv.), solvent (0.05M) 50 W blue LED irradiation (440 nm), 100 °C, 48 h. TBAI = tetrabutylammonium iodide; TBAF = tetrabutylammonium fluoride; TBABr = tetrabutylammonium bromide; n.d. = not determined, [b] – reaction performed in the dark.

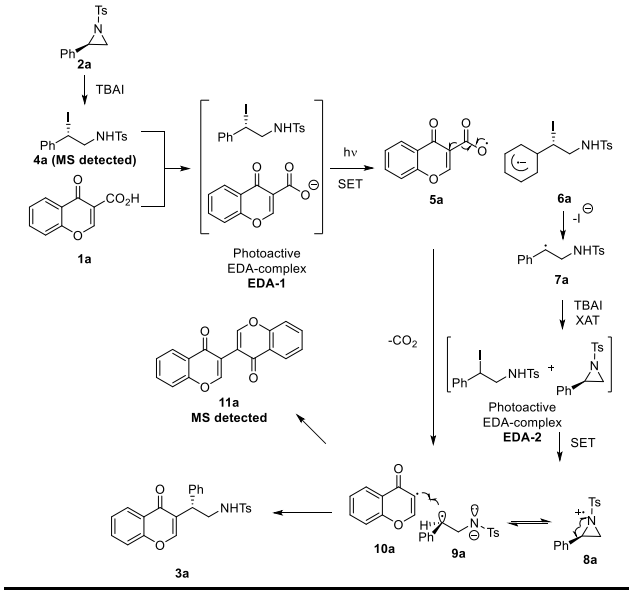


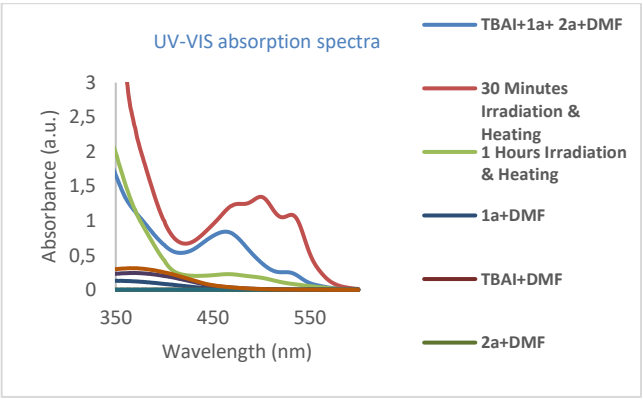
Scheme 2. Stereoretentive, decarboxylative C-3 functionalization of chromone-3-carboxylic acids 1 – scope of chromone-3-carboxylic acids 1



Scheme 3. Stereoretentive, decarboxylative C-3 functionalization of chromone-3-carboxylic acids 1 — scope of aziridines 2







Scheme 4 Stereoretentive, decarboxylative C-3 functionalization of chromone-3-carboxylic acids 1 – mechanistic considerations

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