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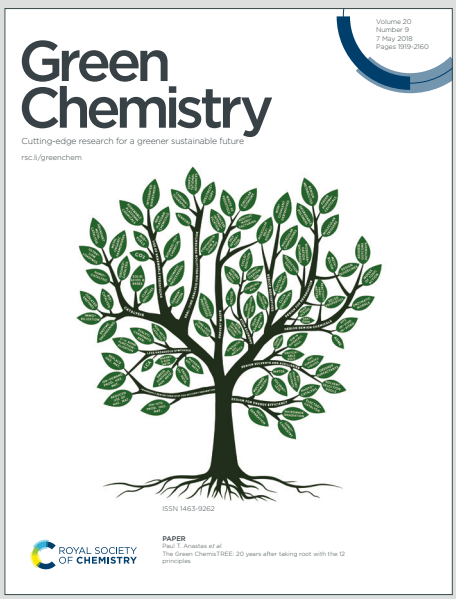

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ARTICLE

Eco-friendly organocatalyst- and reagent-controlled selective construction of diverse and multifunctionalized 2-hydroxybenzophenone frameworks for potent UV-A/B filters by cascade benzannulation

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The organocatalyst- and reagent-controlled highly selective synthesis of diversely functionalized novel 2-hydroxybenzophenone frameworks, such as 2-hydroxy-3'-formylbenzophenones, 7-(2'-hydroxybenzoyl)-2-naphthaldehydes, and 2-hydroxybenzophenones, under green conditions, for the development of potent UV-A/B filters is described. The organocatalyzed benzannulation reactions proceed individually *via* [3+3] cycloaddition for the synthesis of 2-hydroxy-3'-formylbenzophenones and [4+2] cycloaddition for 2-hydroxybenzophenones. With this methodology, an unprecedented double benzannulation allows one-pot construction of diverse 7-(2'-hydroxybenzoyl)-2-naphthaldehydes *via* [3+3+4] cycloaddition. This protocol features a broad substrate scope, high functional-group tolerance, and operational simplicity in an environmentally benign green solvent. The synthesized compounds are successfully utilized for further transformations and well characterized as potent UV-A/B filters.

Introduction

The 2-hydroxybenzophenone framework is ubiquitous in a wide range of natural products and biologically active molecules.[1] This moiety has been used as a valuable building block in the synthesis of various pharmaceuticals and natural products.[2] Molecules bearing 2-hydroxybenzophenone skeletons display a wide range of biological activities, such as antimicrobial,[3] anti-inflammatory,[4] antioxidant,[5] anticancer,[6] anticoccidial,[7] anti-HIV,[8] and antitubulin activities.[9] In particular, they have widely been used as valuable chemical auxiliaries,[10] sun-protection materials[11] and as important precursors for the synthesis of chiral ligands[12] and fluorophores.[13] Owing to their importance and usefulness, several synthetic methods for the synthesis of 2-hydroxybenzophenones have been developed. Typical methods include Fries rearrangement of phenyl esters (Scheme 1A)[14] and Friedel–Crafts acylation of phenols (Scheme 1B).[15] These two reactions provided undesired *para*-isomers, which were generally difficult to separate and purify. Apart from these reactions, transition-metal-catalyzed direct C–H hydroxylation of benzophenones (Scheme 1C)[16] and oxime ethers (Scheme 1D)[17] have been used for the preparation of 2-hydroxybenzophenones. Despite the significant achievements of these methods, there are still drawbacks in the requisite preparation of pre-functionalized starting materials, undesired dihydroxylation, two-step reaction conditions, and high loading of noble metals and strong oxidants. In this context, eco-friendly and atom-economic synthetic methods are still highly desirable.

Recently, organocatalysts have been gradually introduced in organic syntheses owing to their valuable advantages of being less toxic, less polluting, more eco-friendly, and more economically viable than stoichiometric organic reagents and organometallic catalysts.[18] In addition, transformations in green solvents have been widely adopted by synthetic chemists because of the increasing demand and motivation to develop sustainable and environmentally benign protocols with regard to safety, health, pharmaceutical, industrial, and environmental concerns.[19]

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*Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data, X-ray crystallographic structure and data for **5** (CCDC 1991823) and **34** (CCDC 1991825). See DOI: 10.1039/x0xx00000x]*

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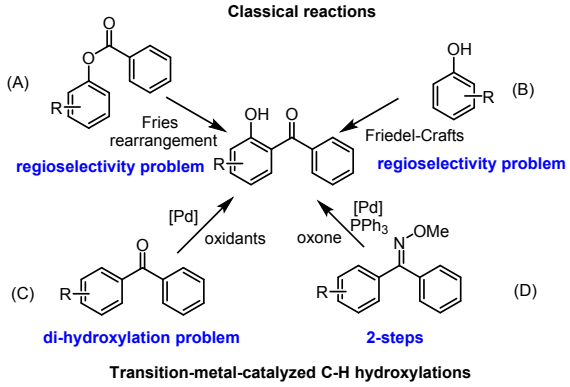
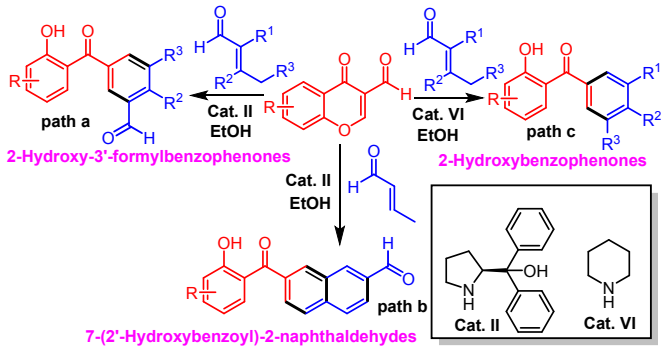


Scheme 1. Reported strategies for 2-hydroxybenzophenone synthesis.



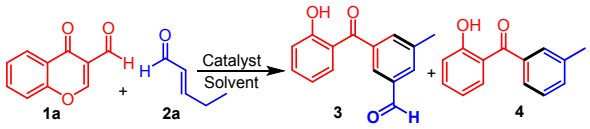
Scheme 2. Organocatalyst-controlled direct construction of divergent and novel 2-hydroxybenzophenone frameworks.

We previously reported In(III)-catalyzed reactions of 3-formylchromones with β-enamino esters for the synthesis of simple 2-hydroxybenzophenones bearing dicarboalkoxy groups.[20] In a continuation of our studies on the development of new green methodologies for potent UV-A/B filters, this paper reports the atom-economical organocatalyst-controlled selective construction of diversely functionalized novel 2-hydroxybenzophenone frameworks, such as 2-hydroxy-3'-formylbenzophenones (path a), 7-(2'-hydroxybenzoyl)2-2-naphthaldehydes (path b), and 2-hydroxybenzophenones (path c), by cascade benzannulations *via* [3+3], [3+3+4], and [4+2] cycloadditions in a green solvent (Scheme 2).

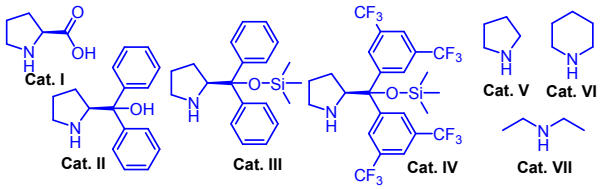
Results and discussion

We first examined the reaction of 3-formylchromone (**1a**) with *trans*-2-pentenal (**2a**) by using different organocatalysts and solvents (Table 1). After the initial attempt in the presence of 20 mol% of L-proline (Cat. **I**), products **3** and **4** were isolated in 23 and 34% yields, respectively (entry 1). With 20 mol% of (*S*)-diphenyl(pyrrolidin-2-yl)methanol (Cat. **II**), which bears bulky groups, the yield of **3** was increased to 78%, whereas **4** was isolated in 5% yield (entry 2). If (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (Cat. **III**) or (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl) oxy)methyl)pyrrolidine (Cat. **IV**), bearing even more bulky groups, were employed, the yield of product **3** was not improved (entries 3 and 4). However, with pyrrolidine (Cat. **V**), piperidine (Cat. **VI**), and diethylamine (Cat. **VII**) as the catalyst, product **4** was obtained in 68, 76, and 55% yields, respectively, and compound **3** was not isolated (entries 5–7). To optimize the formation of products **3** or **4**, various solvents such as DMSO, CH_3CN, H_2O, and EtOH were screened in the presence of Cat. **II** (entries 8–14) or Cat. **VI** (entries 15–20) under various temperature and catalyst loading conditions. The best result (91%) for **3** was achieved by using 10 mol% of Cat. **II** in EtOH at 60 °C for 22 h (entry 13) and that (85%) for **4** was obtained with Cat. **VI** (20 mol%) in EtOH at 80 °C for 15 h. The structures of **3** and **4** were identified by an analysis of their spectral data. The ^{1}H NMR spectrum of **3** showed a singlet methyl peak at δ=2.51 ppm, a singlet peak of the formyl group at δ=10.04 ppm, three aromatic singlet peaks at δ=7.93, 7.89, and 7.73 ppm, and a phenolic OH peak at δ=11.86 ppm. In the case of **4**, the ^{1}H NMR spectrum showed a methyl peak at δ=2.42 ppm, an aromatic singlet peak at δ 7.47 ppm, and another singlet phenolic proton peak at δ=12.03 ppm. The structure of **3** was further confirmed by X-ray analysis of the structurally related compound **5**.

Table 1. Optimization of the reaction conditions for synthesis of **3** and **4**[a]



Entry	Catalyst (mol%)	Solvent	Condition	Yield (%)[b]	
				3	4
1	Cat. I (20)	Toluene	80 °C, 15 h	23	34
2	Cat. II (20)	Toluene	80 °C, 15 h	78	5
3	Cat. III (20)	Toluene	80 °C, 20 h	35	14
4	Cat. IV (10)	Toluene	80 °C, 20 h	65	9
5	Cat. V (20)	Toluene	80 °C, 20 h	0	68
6	Cat. VI (20)	Toluene	80 °C, 20 h	0	76
7	Cat. VII (20)	Toluene	80 °C, 20 h	0	55
8	Cat. II (20)	DMSO	80 °C, 30 h	25	12
9	Cat. II (20)	CH_3CN	80 °C, 20 h	65	9
10	Cat. II (20)	H_2O	80 °C, 20 h	51	14
11	Cat. II (20)	EtOH	80 °C, 12 h	82	6
12	Cat. II (10)	EtOH	80 °C, 12 h	85	trace
13	**Cat. II (10)**	**EtOH**	**60 °C, 22 h**	**91**	**0**
14	Cat. II (10)	EtOH	40 °C, 36 h	48	0
15	Cat. VI (20)	DMSO	100 °C, 15 h	0	65
16	Cat. VI (20)	CH_3CN	80 °C, 20 h	0	72
17	Cat. VI (20)	H_2O	100 °C, 36 h	0	54
18	**Cat. VI (20)**	**EtOH**	**80 °C, 15 h**	**0**	**85**
19	Cat. VI (10)	EtOH	80 °C, 30 h	0	65
20	Cat. VI (30)	EtOH	80 °C, 15 h	0	83

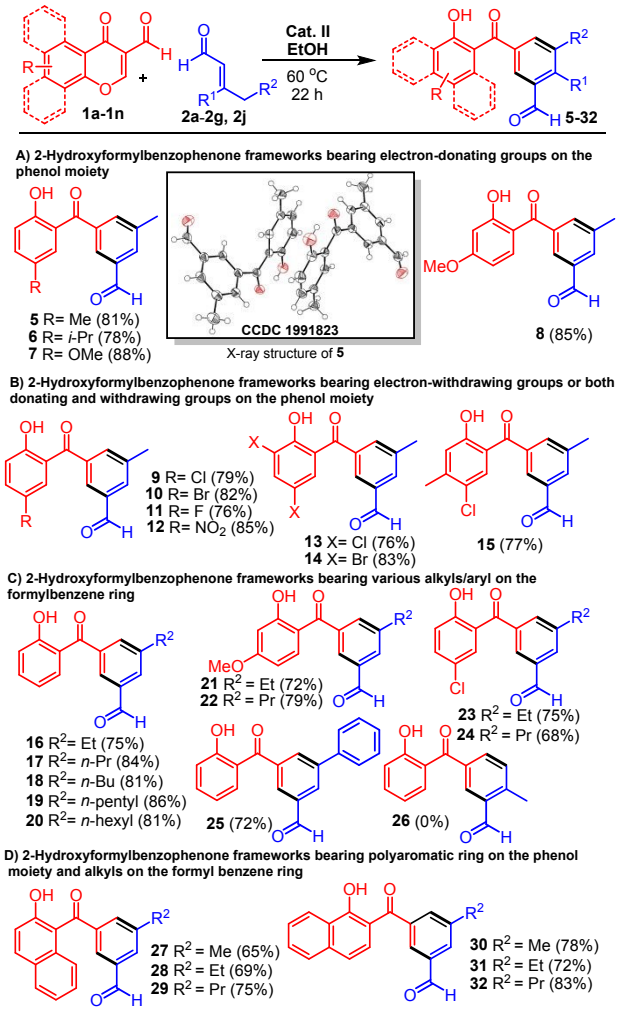


[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), catalyst, and solvent (5.0 mL).
[b]Yield of isolated product after column chromatography.

With the optimized conditions in hand, we explored the substrate scope for the formation of 2-hydroxy-3-

formylbenzophenones by employing substituted 3-formylchromones **1a–1n** and α,β-unsaturated aldehydes **2a–2g,** and **2j** (Table 2) in the presence of Cat. **II**. Reactions of **1b–1e**, bearing electron-donating groups (Me, *i*-Pr, and OMe) at the 6- or 7-position on the chromone moiety, with **2a** proceeded smoothly, and the corresponding products **5–8** were obtained with 78–88% yields. Similarly, treatment of **1f–1h**, bearing electron-withdrawing halogen substituents (Cl, Br, and F) at the 6-position of the chromone moiety, with **2a** successfully generated products **9–11** with 76–82% yields. Moreover, the strong electron-withdrawing NO_2 group was well tolerated on the 3-formylchromone molecule; corresponding product **12** was obtained with 85% yield. Interestingly, disubstituted 3-formylchromones **1j** and **1k**, bearing two electron-withdrawing groups (6,8-dichloro or 6,8-dibromo), or **1l**, with both an electron-donating and an electron-withdrawing substituent (6-Cl and 7-Me) were also well tolerated, and corresponding products **13–15** were produced with 76–83% yields. In addition, treatment of **1a** with *trans*-2-hexenal (**2b**) or *trans*-2-heptenal (**2c**) proceeded smoothly to produce the desired products **16** and **17** with 75 and 84% yields. Reactions of **1a** with *trans*-2-octenal (**2d**), *trans*-2-nonenal (**2e**), or *trans*-2-decenal (**2f**), with long chains, afforded corresponding products **18–20** with 81–86% yields. Similarly, the reactions of substituted 3-formylchromone **1e** and **1f**, bearing substituents on the benzene ring, with **2b** or **2c** were performed, and corresponding products **21–24** were obtained with 68–79% yields. Moreover, the reaction of 3-formylchromone (**1a**) with (*E*)-4-phenylbut-2-enal (**2j**) bearing aromatic substituent afforded the desired product **25** in 72% yield. However, with 3-methyl-2-butenal (**2g**), desired product **26** was not obtained; instead, the starting materials were recovered. In addition, 4-oxo-4*H*-benzo[*h*]chromene-3-carbaldehyde (**1m**) and 1-oxo-1*H*-benzo[*f*]chromene-2-carbaldehyde (**1n**), bearing polyaromatic

Table 2. Formation of diverse 2-hydroxy-3'-formylbenzophenones **5–32** from substituted 3-formylchromones **1a–1n** and α,β-unsaturated aldehydes **2a–2g,** and **2j**[a]

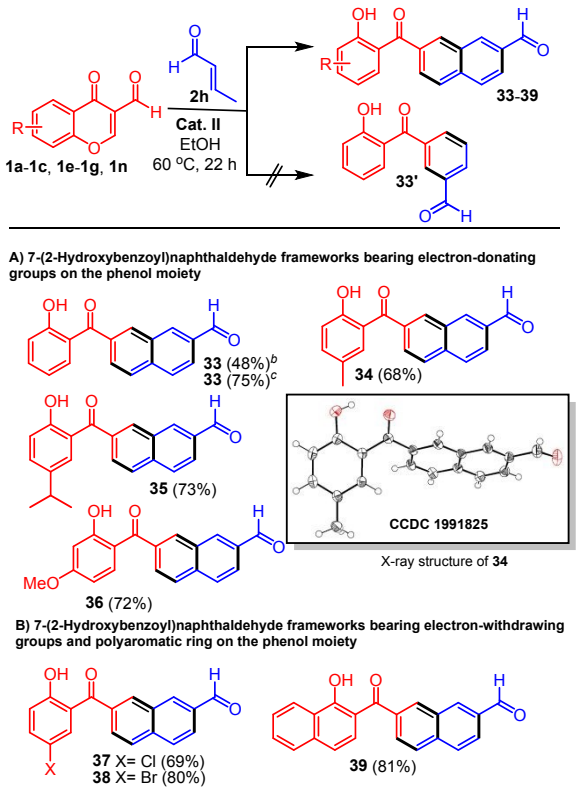


[a]Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), Cat. **II** (10 mol%) and EtOH (5.0 mL).

rings, were successfully combined with **2a**, **2b**, or **2c** to produce the corresponding angular compounds **27–29** (65–75%) and linear compounds **30–32** (72–83%).

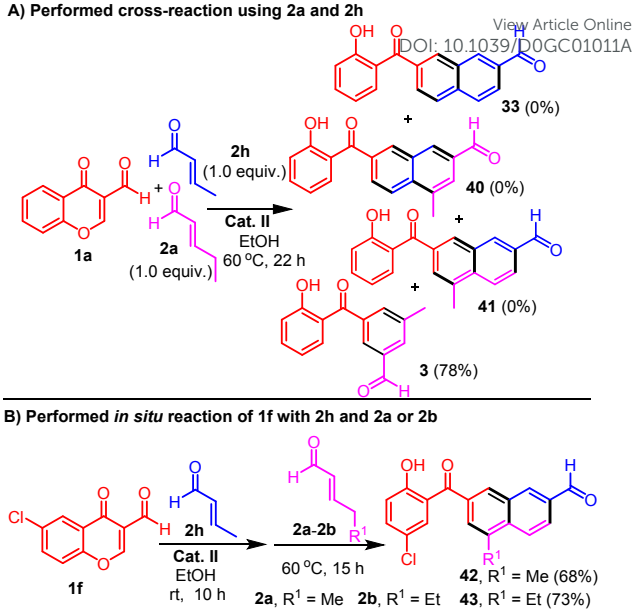
To explore the substrate scope of this protocol, further reactions with *trans*-crotonaldehyde (**2h**) as a substrate were then performed (Table 3). Surprisingly, treatment of **1a** with 1.2 equivalents of **2h** and Cat. **II** in ethanol at 60 °C for 22 h did not provide desired product **33'**; instead, compound **33** was unexpectedly produced in 48% yield. Importantly, with 2.4 equivalents of **2h**, the yield of **33** increased to 75%. A number of reactions were carried out with 3-formylchromones **1a–1c**, **1e–1g**, and **1n** and **2h** (2.4 equiv.) under the standard conditions, which resulted in the formation of synthetically useful 2-hydroxynaphthophenones **33–39**, bearing a formyl group, with 68–81% yields. The structures of the synthesized compounds were confirmed by analysis of their spectral data and X-ray analysis of **34**.

Table 3. Formation of diverse 7-(2′-hydroxybenzoyl)-2-naphthaldehydes **33–39** from substituted 3-formylchromones **1a–1c**, **1e–1g**, or **1n** and *trans*-crotonaldehyde (**2h**)[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (2.4 mmol), Cat. **II** (10 mol%) and EtOH (5.0 mL). [b]Reaction with 1.2 equiv. of **2h**. [c]Reaction with 2.4 equiv. of **2h**.

To provide 7-(2′-hydroxybenzoyl)-2-naphthaldehyde derivatives bearing alkyl substituents on the benzene ring, further experiments between 3-formylchromones **1a** or **1f** and α,β-unsaturated aldehydes **2a**, **2b**, or **2h** were performed (Scheme 3). Treatment of **1a** (1.0 mmol) with **2a** (1.0 mmol) and **2h** (1.0 mmol) under the standard reaction conditions provided only product **3** (78%), without the formation of the other possible products **33**, **40**, and **41**. This result showed the significant difference in chemoselectivity between the two different α,β-unsaturated aldehydes. Other reactions were attempted to form diverse products by sequential *in situ* reactions through the combination of two different α,β-unsaturated aldehydes. Treatment of **1f** (1.0 mmol) with **2h** (1.0 mmol) at room temperature for 10 h, followed by addition of **2a** (1.0 mmol) or **2b** (1.0 mmol) at 60 °C for 15 h provided products **42** or **43** with 68 and 73% yields, respectively.



Scheme 3. (a) Cross reaction of **1a** with **2a** and **2h**. (b) One pot construction of 7-(2′-hydroxybenzoyl)-2-naphthaldehydes **42** and **43**.

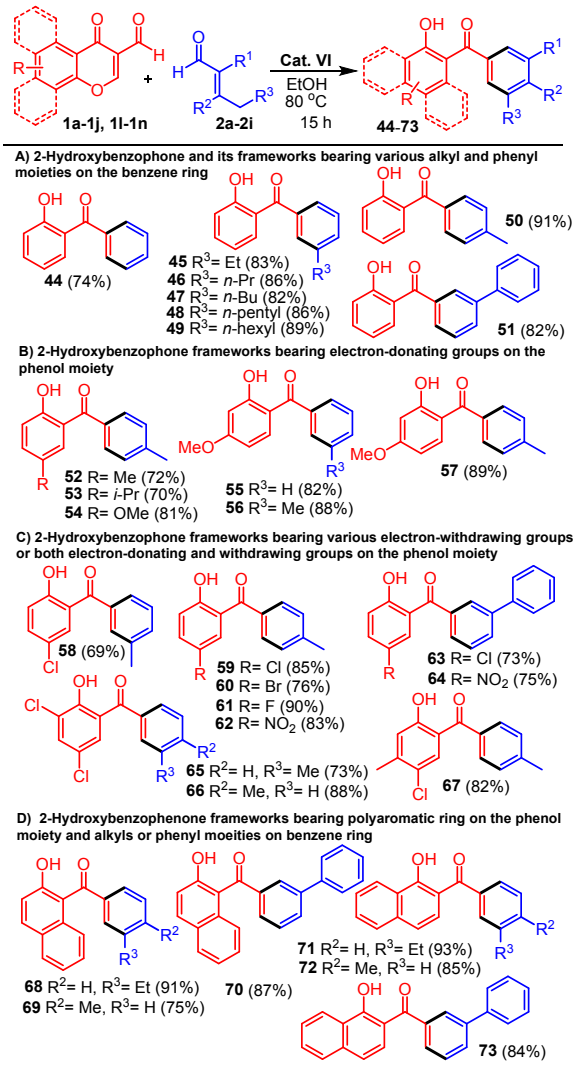
The scope of the reaction was further extended for the formation of diverse and functionalized 2-hydroxybenzophenones **44–73** without any formyl groups by employing the series of 3-formylchromones **1a–1j** and **1l–1n** with α,β-unsaturated aldehydes **2a–2i** in the presence of Cat. **VI** (Table 4). Treatment of **1a** with crotonaldehyde (**2h**) gave readily available 2-hydroxybenzophenone (**44**) with 74% yield. Combination of **1a** with **2b–2f** afforded the desired products **45–49** with 82–89% yields. Importantly, with 3-methyl-2-butenal (**2g**) and (*E*)-2-phenyl-2-butenal (**2i**), the desired products **50** and **51** were produced with 91 and 82% yields, respectively. The combination of **1b–1e**, bearing electron-donating groups, with **2a**, **2h**, or **2i** proceeded smoothly, and the corresponding products **52–57** were obtained with 70–89% yields. Treatment of **1f–1i**, bearing electron-withdrawing groups, with **2a**, **2g**, or **2i** was also successful, and products **58–64** were isolated with 69–90% yields. Reactions of **1j** or **1l**, bearing two substituents on the benzene ring, with **2a** or **2g** provided the corresponding products **65–67** with 73–88% yields. Furthermore, **1m** or **1n**, bearing polyaromatic rings, were successfully combined with **2b**, **2g**, or **2i** to afford products **68–73** (75–93%).

To explore the applicability of benzannulation reactions, we carried out the gram-scale reactions under standard reaction conditions (Scheme 4) and successfully isolated the desired products **3** and **4** in 76 and 81% yields, respectively (for details, see ESI).

To investigate the application of this protocol, the conversion of the synthesized compound **55** into biologically interesting molecules via C–H activation was next attempted (Scheme 5). Rh(III)-catalyzed direct C–H alkenylation of **55** with several acrylates, such as methyl, ethyl, phenyl, or benzyl acrylates (**3a–3d**) at 60 °C for 12 h produced the Heck type products **74–77** with 71–85% yields, respectively, and that

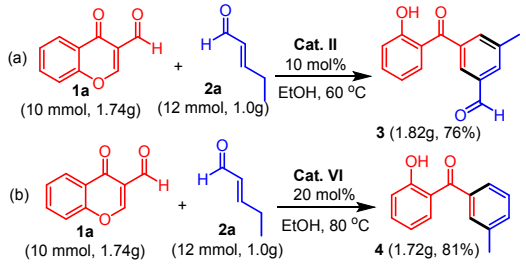
with styrene (**3e**) provided **78** with 92% yield. In addition, with *N*-phenyl maleimide (**3f**), addition product **79** was produced with 58% yield.

Table 4. Formation of diverse 2-hydroxybenzophenones **44–73** from substituted 3-formylchromones **1a–1j** or **1l–1n** and α,β-unsaturated aldehydes **2a–2i**[a]

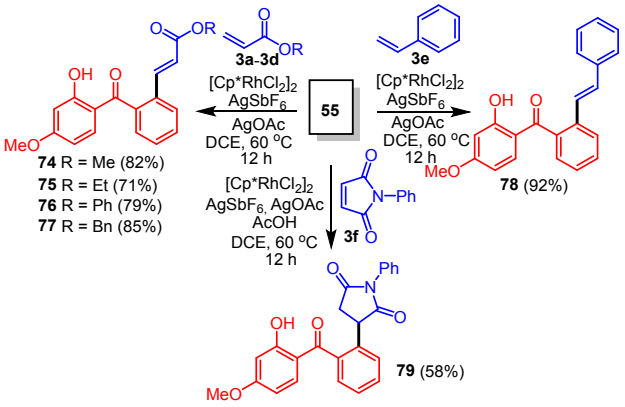


[a]Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), Cat. VI (20 mol%) and EtOH (5.0 mL).

To elucidate the reaction mechanism via intermediates, control experiments for the formation of products **4**, **9**, **33**, and intermediate **80** were next attempted (Scheme 6). First, reaction of **2a** with Cat. **II** in DMSO-d_6 provided intermediate **II**, which could not be isolated by column chromatography. However, this crude intermediate **II** was confirmed by ^{1}H NMR and HRMS of the crude mixture (See ESI). The reaction of intermediate **II** with **1f** provided corresponding intermediate **80** in 54% yield (Scheme 6a). When **1f** was also treated with **2a** in the presence of Cat. **II** in ethanol at room temperature for 10 h, intermediate **80** was isolated with 91% yield, without any formation of an aromatic ring (Scheme 6b). Intermediate **80** was successfully converted into aromatic compound **9** with 82% yield under the standard conditions (Scheme 6c). These results showed that compounds **II** and **80** are the intermediates for the formation of **9** of the 2-hydroxy-3-formylbenzophenone series. Furthermore, reaction of **2a** with Cat. **VI** in refluxing benzene for 3 h afforded intermediate **VII**, which was confirmed by ^{1}H NMR and HRMS of the crude mixture (see ESI). The reaction of intermediate **VII** with **1a** in ethanol at 80 °C for 2 h provided compound **4** in 80% yield (Scheme 6d). The possibility of the formation of products *via* [4+2] cycloaddition starting from **2a** was also investigated by employing 1,4-naphthoquinone (**81**). Treatment of **81** with **2a** in the presence of Cat. **VI** in ethanol at 80 °C for 10 h provided **82** with 76% yield through a formal [4+2] cycloaddition and air oxidation (Scheme 6e). In the case of [3+3+4] cycloaddition, the reaction of **33'** with **2h** in the presence of Cat. **II** did not provide the desired product **33**, which showed that compound **33'** was not an intermediate for the formation of **33** (Scheme 6f).

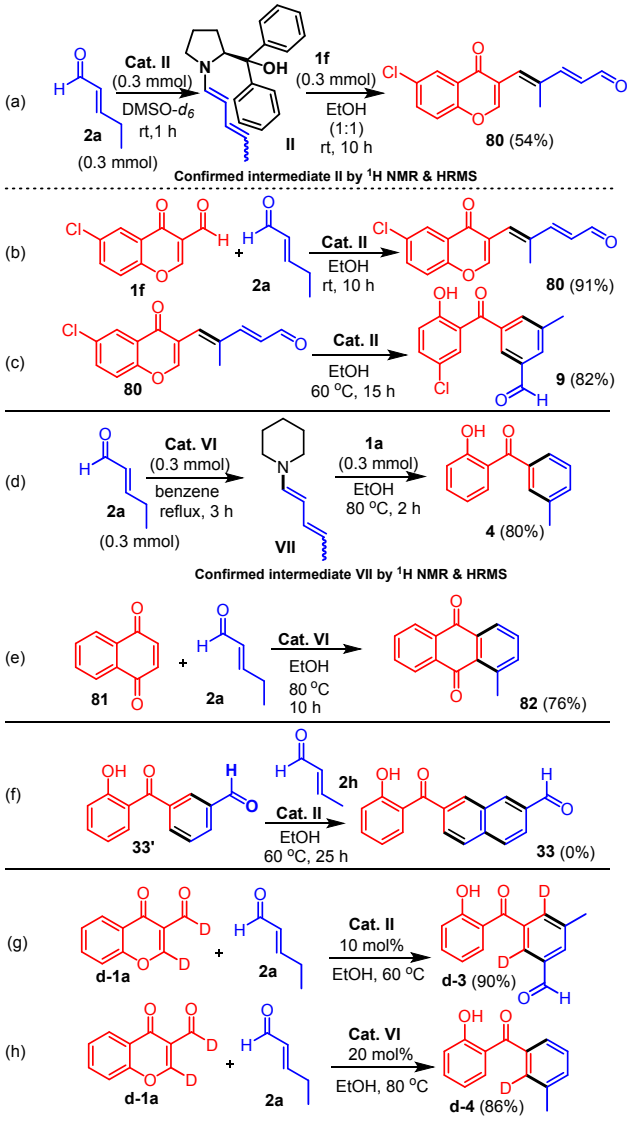


Scheme 4. Gram scale synthesis of **3** and **4**.



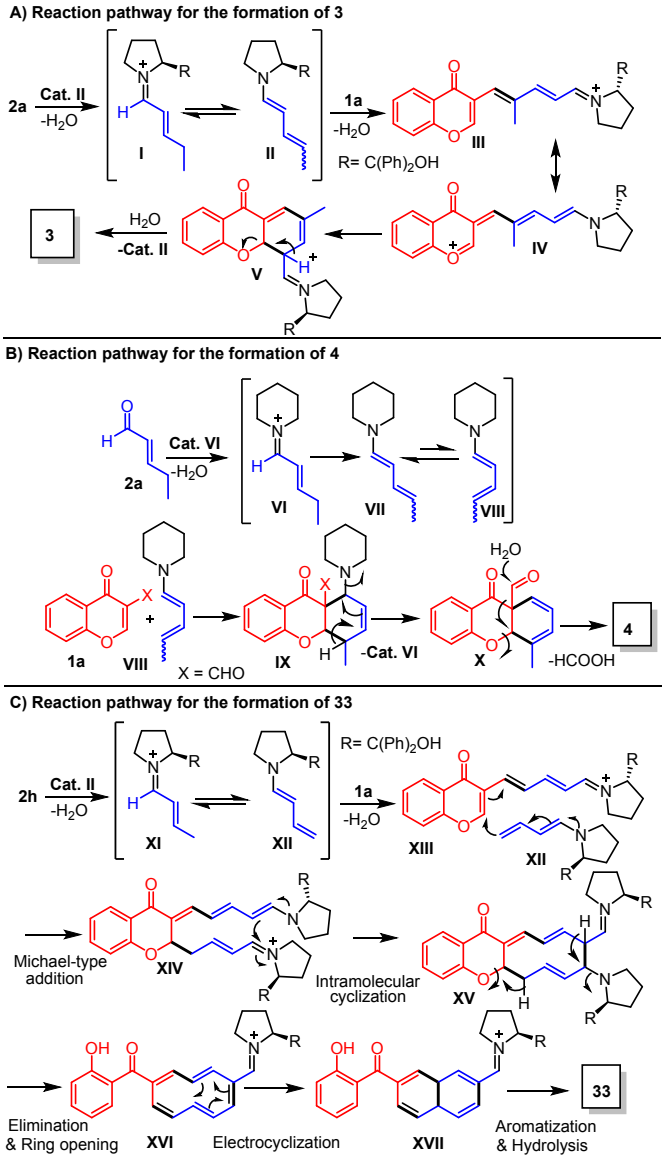
Scheme 5. Conversion of **55** to functionalized molecules **74-79.**

To confirm the mechanism of the products, we conducted further reactions with deuterated compound **d-1a** under standard reaction conditions (Schemes 6g and 6h). Treatment of **d-1a** with **2a** in the presence of Cat. **II**, provided the product **d-3** in 90% yield, retaining the two deuteriums derived from a formyl group and 2-position on **d-1a** (Scheme 6g). However, in the case of Cat. **VI**, mono-deuterated product **d-4** was obtained in 86% yield, retaining only one deuterium from 2-position (Scheme 6h). These control experiments indicated that Cat. **II** and Cat. **VI** chemoselectively produced the products **d-3** and **d-4** through [3+3] and [4+2] cycloadditions, respectively.



Scheme 6. Control experiments.

Based on the control experiments and the observed products, plausible mechanisms for **3**, **4**, and **33** are depicted in Scheme 7. For the formation of **3**, in the presence of Cat. **II**, **2a** first gives enamine intermediate **II**, *via* iminium ion **I** formation followed by deprotonation (Scheme 7A). Nucleophilic addition of intermediate **II** to **1a** gives another iminium ion intermediate **III** by removal of water. In the formation of enamine intermediate **II**, [4+2] cycloaddition did not proceed owing to steric hindrance by the bulky group on Cat. **II**. Instead, intermediate **III** gives intermediate **IV** through resonance structure formation; **IV** is cyclized to afford **V** by intramolecular cyclization. Ring opening through deprotonation and the subsequent hydrolysis finally give **3** with regeneration of Cat **II**. In this case, double cyclization products were not produced through further nucleophilic addition of intermediate **II** to intermediates **III** or **IV** because of steric hindrance of the methyl group on intermediates **III** and **IV**. In the formation of **4**, enamine intermediate **VIII** formed *via* **VI** and **VII** undergoes formal [4+2] cycloaddition with **1a** to give Diels–Alder adduct **IX** (Scheme 7B). Intermediate **IX** gives another intermediate **X** with regeneration of the catalyst through deprotonation. Intermediate **X** finally gives **4** through elimination of formic acid and ring opening. Importantly, after the reaction, the presence of formic acid was confirmed by GC-MS analysis of the crude reaction mixture, providing evidence of this reaction pathway (see ESI, Fig. S3, S4).



Scheme 7. Plausible mechanistic pathways for the formation of **3**, **4**, and **33**.

The formation of product **33** can be explained as shown in Scheme 7C. The control experiment depicted in Scheme 6f showed that compound **33'** is not an intermediate for the formation of **33**. Thus, in the presence of Cat. **II**, **2h** gives enamine intermediate **XII** *via* **XI**, which reacts with **1a** to give intermediate **XIII**. Intermediate **XIII** undergoes further nucleophilic addition to furnish intermediate **XIV**. Intramolecular cyclization of **XIV** gives another intermediate **XV**, which undergoes subsequent regeneration of the catalyst and ring opening to give intermediate **XVI**. 6π-Electrocyclization of **XVI** will generate intermediate **XVII**, which

undergoes aromatization and hydrolysis to produce the final product **33**.

The chemoselectivity of compounds **3** and **4** is probably due to the intermedeates **II** and **VII** produced by the reaction of **2a** with Cat. **II** or Cat. **VI**. To justify chemoselectivity of two products **3** and **4**, we used a simple energy-minimization calculation of intermediates **II** and **VII** using MM2 of ChemBio3D. The energy minimized structures of **II** and **VII** were shown in supplementary information (See ESI, Fig. S5). Based on energy minimized structures, it is assumed that the access of a butadiene moiety to the enone of dienophile **1a** to give the Diels-Alder product is difficult due to steric hindrance and blocking by the phenyl rings (See ESI, Fig. S6a). For this reason, the product derived from Diels-Alder reaction did not proceed, instead compound **3** was isolated through condensation of **II** and **1a** followed by intramolecular cyclization and ring opening. In the case of **VII**, there is no steric hindrance to give compound **4** via Diels-Alder reaction (See ESI, Fig. S6b).

UV absorption studies

Benzophenones are highly utilized and valued scaffolds as active ingredients in sunscreen, as a result of their optical and chemical properties.[21] However, one of the most popular materials used widely as a sunscreen ingredient, oxybenzone, is known to cause allergic reactions and skin cancer;[21b] this has prompted the development and design of novel derivatives as new UVA/UVB filters that potentially provide better protection. To determine the feasibility and efficiency of the synthesized molecules as UV filters, the UV absorption properties of the synthetic compounds (**3**, **8**, **12**, **14**, **36**, **37**, **44**, **45**, **51**, **54**, **62**, **63** and **64**) were evaluated in comparison with the structurally related oxybenzone (OBZ; Fig. 1).

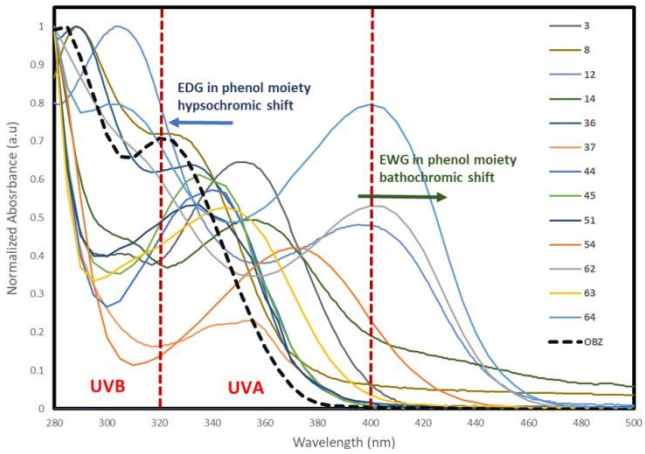


Fig. 1 Normalized absorbance of representative synthesized compounds from 280–500 nm with OBZ.

The UV protection properties were first evaluated by determining several important parameters of the UVA/UVB ratio and molar extinction coefficient based on λ_{max}, as shown in Table 5. The critical wavelength (λ_c) calculation and the UVA/UVB ratio are based on Diffey method.[22] The effective UVA and UVB attenuation values become more similar as the ratio comes closer to 1. In addition, the *in vitro* critical wavelength values in excess of 370 nm satisfy the classification requirements for extensive UVA/UVB protection.[23] We exclusively employed *in vitro* testing of sunscreens by using the known method based on spectrophotometric analysis of dilute solutions (see the ESI). With this information in hand, we have also calculated the *in vitro* sun protection factor (SPF) to further gauge the potential of our synthesized products relative to OBZ (Table 5).

Table 5 Summary of optical properties of the representative synthesized compounds

Entry	λmax (nm)	ε(mol -1 cm-1 L)	λc (nm)	Broad spectrum	UVA/UV B Ratio	SPF
3	305 350	3212 4762	376	Y	1.09	6.33 ± 0.05
8	290 321	11912 8000	358	N	0.41	18.25 ± 0.20
12	304 395	10599 4762	386	Y	0.50	18.33 ± 0.19
14	355	4871	382	Y	0.85	6.12 ± 0.04
36	290 333	20263 12068	357	N	0.43	25.18 ± 0.22
37	352	5170	367	N	0.59	8.95 ± 0.07
44	340	8000	362	N	0.92	11.61 ± 0.13
45	335	10395	361	N	0.81	15.10 ± 0.14
51	330	8000	363	N	0.67	13.15 ± 0.15
54	370	5116	389	Y	1.55	4.50 ± 0.03
62	340 400	9959 8762	389	Y	0.60	25.08 ± 0.21
63	345	5224	371	Y	0.92	6.44 ± 0.08
64	302 400	9693 9034	391	Y	0.79	15.20 ± 0.17
OBZ	285 325	14336 9197	353	N	0.40	16.31 ± 0.15

Based on our results, compounds **12**, **36**, **62**, and **64** exhibit superior photoprotective properties in terms of molar absorptivity, broad spectrum absorption, UVA/UVB ratio, and SPF. The presence of additional π-bonds and functional groups in the benzophenone scaffold increases the UVA protection based on the λ_c value and UVA/UVB ratio. The UV absorption properties of the synthetic compounds are comparable to the standard sunscreen ingredient OBZ and are better in terms of the λ_c, broad-spectrum classification, and SPF values. Product **8**, structurally identical to OBZ, exhibits the same UV filtering capacity, as expected.

The mathematical method used to calculate SPF from the UV/Vis absorption is only treated as an initial screening procedure to determine which synthesized compounds exhibit good potential as UV protection agents. Further tests with more sophisticated equipment and methods are beyond the

scope of this work and are intended for future specialized works. In addition, these UV absorption parameters can be improved through combinations of ingredients in the sunscreen formulation, which generate possible synergies to improve performance, particularly when evaluated *in vivo*.

Conclusions

In conclusion, we have developed an eco-friendly organocatalyst-controlled methodology for the highly selective synthesis of polyfunctionalized 2-hydroxybenzophenone frameworks, such as 2-hydroxy-3'-formylbenzophenones, 7-(2'-hydroxybenzoyl)-2-naphthaldehydes, and 2-hydroxybenzophenones, via cascade benzannulation through individual [3+3] cycloadditions, [3+3+4] cycloadditions, and [4+2] cycloadditions, with readily available 3-formylchromones and α,β-unsaturated aldehydes as the starting materials. The novel protocol uses eco-benign, operationally simple, atom-economic, inexpensive, non-toxic, and readily available organocatalysts. The synthesized compounds were successfully employed for C−H alkenylation and alkylation reactions for the development of new and biologically interesting materials. The synthesized compounds showed superior photoprotective properties relative to the readily available sunscreen ingredient oxybenzone.

Conflicts of interest

There are no conflicts to declare.

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Graphical Abstract

Eco-friendly organocatalyst- and reagent-controlled selective construction of diverse and multifunctionalized 2-hydroxybenzophenone frameworks for potent UV-A/B filters by cascade benzannulation

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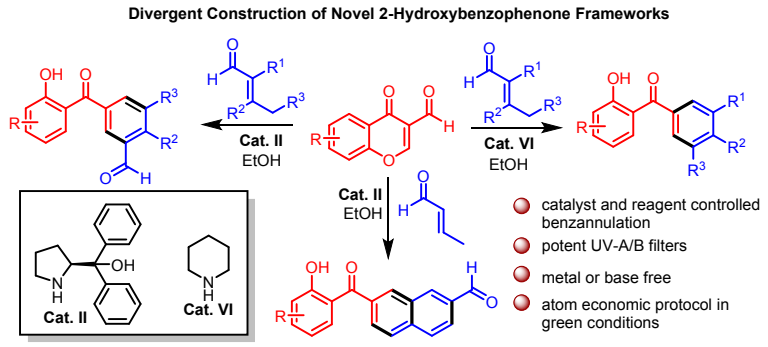

The organocatalyst- and reagent-controlled highly selective synthesis of diversely functionalized novel 2-hydroxybenzophenone frameworks for potent UV-A/B filters is developed