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A bio-inspired synthesis of hybrid flavonoids from 2-hydroxychalcone driven by visible light†

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A bio-inspired synthesis of hybrid flavonoids from 2-hydroxylchalcone is described. Under the irradiation of 24 W CFL, 2-hydroxychalcone reacts with various nucleophiles to deliver structurally diverse hybrid flavonoids in good to excellent yields in the presence of a catalytic Brønsted acid. Moreover, moderate enantioselectivities could be obtained using a catalytic chiral phosphoric acid *via* counter anion directed addition. Based on mechanistic studies, the reaction is proposed to proceed *via* tandem double-bond isomerization/dehydrated cyclization of 2-hydroxychalcone to form a transient flavylium cation, which is *in situ* captured by nucleophiles to afford hybrid flavonoids.

Nature elegantly utilizes hybridization of different natural products to construct structurally diverse natural products by merging different biosynthetic pathways.[1] Inspired by nature's strategy, hybridization of natural products also provides new opportunities for the development of medicinal and agrichemical molecules.[2] Hybrid flavonoids[3] (Fig. 1, *e.g.* yuremamine[4] and diinsininol[5] A) are widely present in natural and pharmaceutical molecules, and exhibit wide biological activities including antitumor, antioxidant, antibacterial and anti-inflammatory properties. According to the biosynthetic pathway of flavonoids (Fig. 1, pathway 1),[6] hybrid flavonoids (*e.g.* diinsininol[5b]) may be biogenetically generated *via* nucleophilic addition of flavanone **IV** to anthocyanidin salt **II**, which is derived from flavanol **III** catalyzed by anthocyanidin synthase. Flavanol **III** is in turn produced from chalcone **2** through a series of enzyme-promoted transformations. However, an alternative biosynthetic pathway has also been widely accepted, in which sunlight plays a pivotal role (Fig. 1, pathway 2),[7] In this context, the photochemical interconversion of 2-hydroxychone **1** and flavylium salt **II** has been fully established, which reveals the equilibrium between those flavonoids in solution under the irradiation of UV or sunlight. As shown in Fig. 1, this process is initiated with the *E*/*Z* isomerization to deliver *Z*-enone **I**, which is transferred to flavylium cation **II** *via* dehydrative cyclization in the presence of Brønsted acid. The *in situ* capture of this flavylium cation has been proposed to constitute the key step for the biosynthesis of some type of hybrid flavonoids.[7f]

Synthesis of hybrid flavonoids *via* nucleophilic addition to flavylium cation has been extensively explored,[8] which relies on the high electrophilicity on the C4 of flavylium cation.[9] However, those protocols usually need base to act as

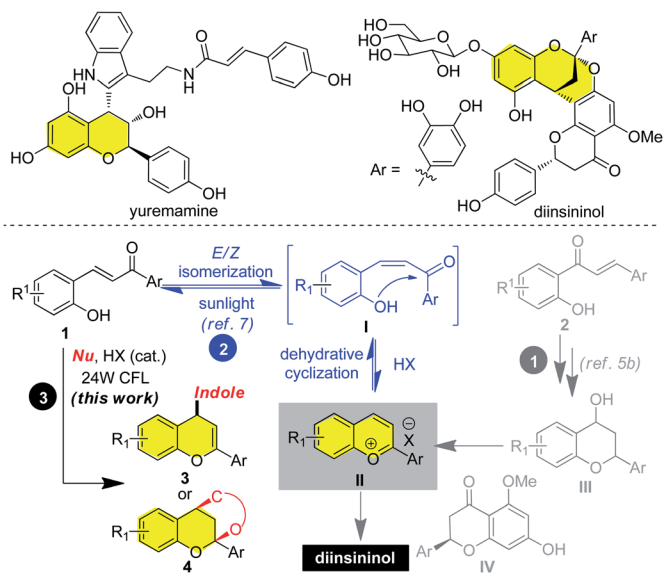

Fig. 1 Previous protocols for the synthesis of hybrid flavonoids and a bio-inspired synthesis of hybrid flavonoids form 2-hydrxoychalcone.

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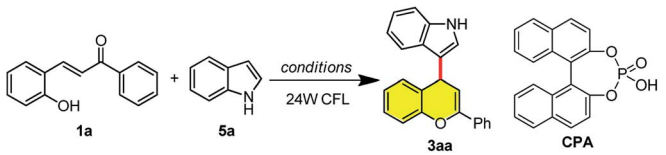
acid scavenger or heating in protic solvent. Furthermore, the flavylium cation is sensitive to light in solution.[7] The other commonly employed strategy is the tandem Michael addition/dehydrated cyclization of 2-hydroxylchalcone **1** to deliver flavonoids **3** or polycyclic flavonoids **4**.[10] Different catalysts such as I_2, TfOH and $NbCl_5$ have been discovered to be effective for promoting this reaction. However, this strategy is limited by its harsh reaction conditions (heating) or need of precious metal catalysts. Drawn inspiration from the light-driven biosynthetic pathway of hybrid flavonoids (Fig. 1, pathway 3),[6,7] we proposed that if a suitable nucleophile is exposed to 2-hydroxychalcone **1** in the presence of catalytic Brønsted acid under the irradiation of 24 CFL, hybrid flavonoids **3** or **4** could be biomimetically obtained *via* the *in situ* capture of the transient flavylium salt. Herein, we would like to describe our preliminary results on this bio-inspired synthesis of hybrid flavonoids driven by visible light.

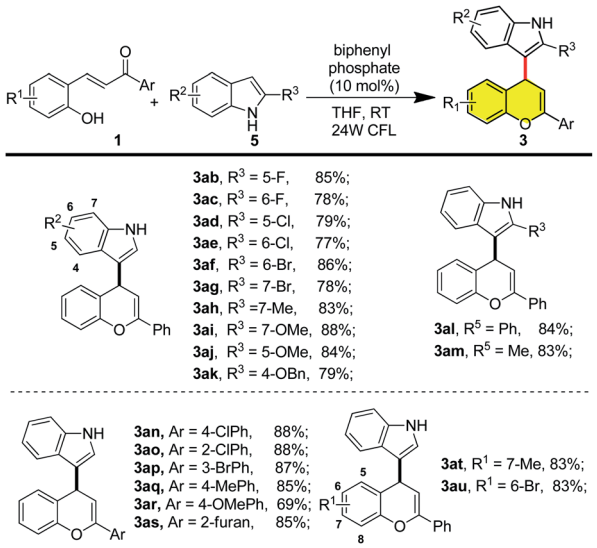
To verify our hypothesis, the reaction of hydroxyl chalcone **1a** with indole **5a** was initially examined to establish the optimal reaction conditions. To our delight, upon the irradiation of household 24 W compact fluorescent lamp (CFL) the desired flavonoid **3aa** could be obtained in 73% yield in the presence of phosphoric acid **CPA** (Table 1, entry 1). Subsequent survey of different kind of Brønsted acids showed that biphenyl phosphate was the most efficient promoter, affording desired product in 98% yield (Table 1, entry 2–6 and ESI†). In sharp contrast, when the reaction was run in the absence of Brønsted acid or in the dark (Table 1, entry 7 and 8), no product could be detected, indicating that the light-driven formation of flavylium from 2-hydroxychalcone might be involved. Subsequently, survey of solvents revealed that THF was the optimal solvent, which gave comparable yield and showed better solubility for 2-hydroxylchalcone **1a** (Table 1, entry 9 and ESI†).

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	**CPA**	MeCN	18	73
2	CSA	MeCN	18	42
3	HCl	MeCN	18	40
4	Biphenyl phosphate	MeCN	30	98
5	TsOH	MeCN	42	45
6	TFA	MeCN	42	43
7	—	MeCN	42	ND
8[c]	Biphenyl phosphate	MeCN	42	ND
9	Biphenyl phosphate	THF	19	98

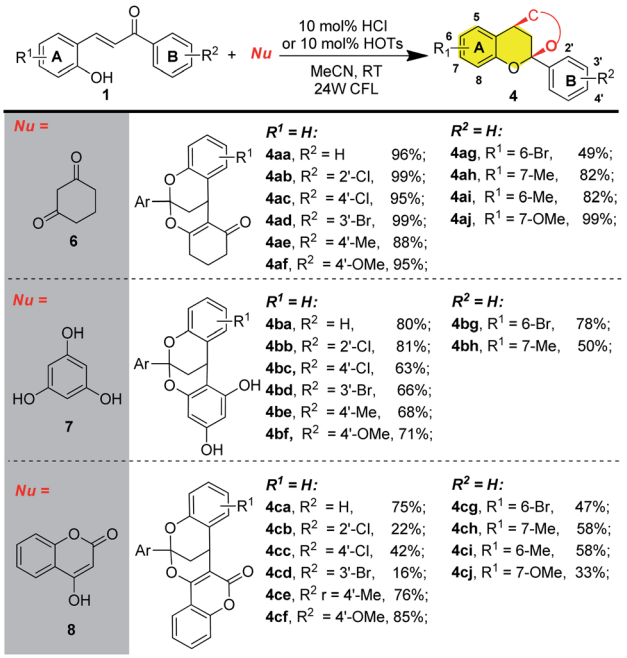
[a] Reaction conditions: to a mixture of hydroxyl chalcone **1a** (0.1 mmol) and indole (0.12 mmol) was added solvent (3 mL). The reaction mixture was stirred with irradiation by household 24 W compact fluorescent lamp (CFL). [b] Isolated yields. [c] The reaction was carried out in the dark.



Scheme 1 Substrate scope with regard to indole as nucleophile.

After establishing the optimal reaction conditions, the substrate scope was subsequently investigated. As shown in Scheme 1, electron-withdrawing group (*e.g.* F, Cl and Br) on the indole ring was compatible with the reaction conditions, providing corresponding products in good isolated yields (**3ab** to **3ag**). Indoles with electron-donating groups (*e.g.* Me, methoxy) were also well tolerated, affording **3ah** to **3ak** in good yields. Substituents (*e.g.* phenyl and methyl) on the C-2 of indole did not affect the outcomes of this reaction (**3al** and **3am**). Additionally, a variety of substituted 2-hydroxylchalcone was prepared and subjected to the standard reaction conditions. Satisfactorily, 2-hydroxylchalcones with electron-withdrawing groups (Cl, Br) and electron-donating group (Me, methoxy) could all be converted to hybrid flavonoids in good to excellent yields (**3an** to **3ar**, **3at** and **3au**). Heterocycle such as furan was also compatible with the reaction conditions to afford flavonoid **3as** in 85% yield.

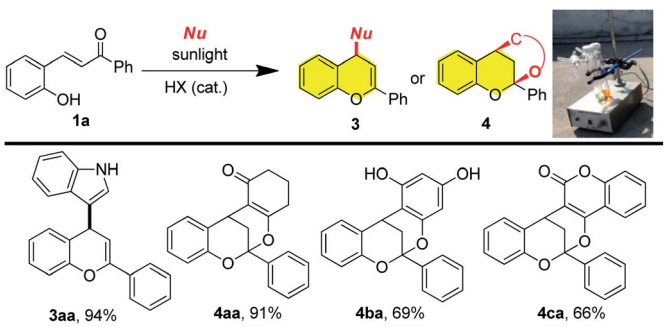
Furthermore, this protocol was also applicable to other type of bifunctional nucleophiles to give rise to polycyclic flavonoids resembling diinsininol. As listed in Scheme 2, cyclohexa-1,3-dione, phloroglucinol, 4-hydroxycoumarin could all engage in this type of reaction to give dioxabicyclo[3.3.1]nonane scaffold *via* tandem cycloisomerization/nucleophilic addition/cyclization process. For those substrates, employment of HCl (for cyclohexa-1,3-dione and 4-hydroxycoumarin) or TsOH (for phloroglucinol) was more beneficial (see ESI† for details). When cyclohexa-1,3-dione was employed as nucleophile, various substituents on the aromatic ring of 2-hydroxyl chalcone were well compatible excepting the Br on the aromatic ring A (**4ag**), delivering the desired product in good to excellent yields (Scheme 2, **4aa** to **4aj**). Phloroglucinol was also a suitable nucleophile for this reaction, generating polycyclic flavonoids in acceptable yields. Different type of substitutes were tolerated on the aromatic ring B of 2-hydryoxychalcone (Scheme 2, **4ba** to



Scheme 2 Substrate scope using bifunctional nucleophiles.

4bg), while the electron-donating groups on the aromatic ring A were unfavorable for this reaction, resulting in much lower yields (Scheme 2, **4bh**). Finally, 4-hydroxycoumarin was evaluated as the nucleophile to give access to coumarin hybrid flavonoids. For this specific substrate, the yields depended on the substituents on the aromatic rings of 2-hydryxoychalcone. Electron-withdrawing groups on the aromatic ring B of 2-hydryxoychalcone were detrimental for reactions (**4cb** to **4cd**), affording much lower isolated yields than those with electron-donating substituents (**4ce** and **4cf**) and substituents on the ring A were not well compatible with the reaction conditions (**4cg** to **4cj**).

To mimic the biosynthetic conditions, the sunlight-driven coupling of 2-hydroxychalcone with different nucleophiles was also carried out. As shown in Scheme 3, indole, cyclohexa-1,3-dione, phloroglucinol and 4-hydroxycoumarin could all engage in the tandem process under the irradiation of sunlight using the same reaction conditions shown in Scheme 1 or 2, providing

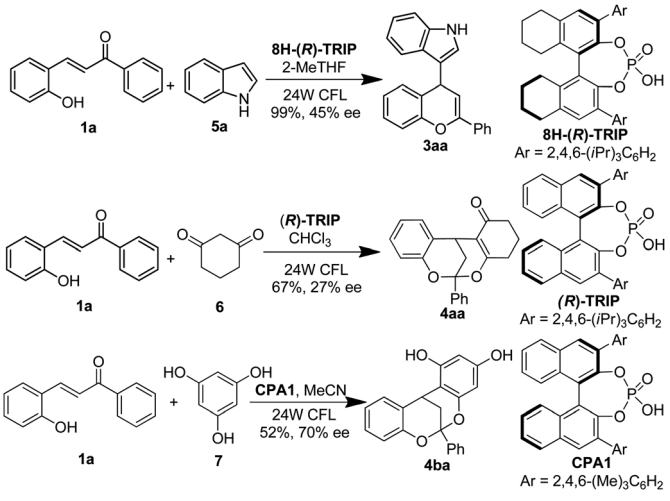


Scheme 3 Sunlight-driven synthesis of hybrid flavonoids.

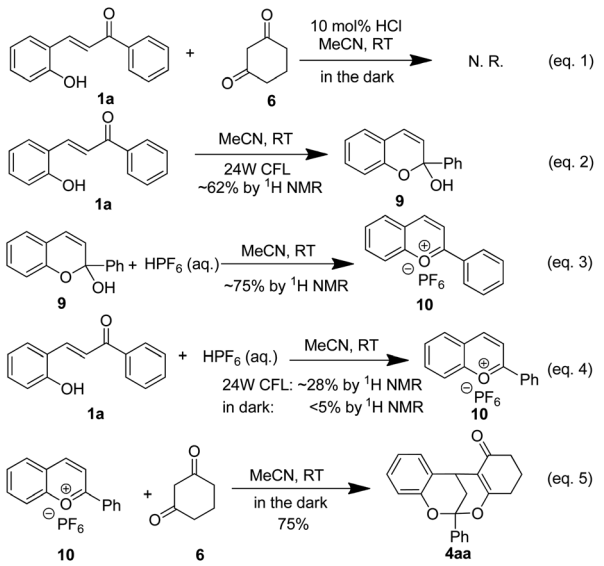
correspondent hybrid flavonoids **3aa** to **4ca** in comparable isolated yields with those using 24 W CFL as light source.

The enantioselective coupling of 2-hydroxychalcone was also explored using chiral phosphoric acid as organocatalyst *via* counter anion directed addition (Scheme 4).[11] To our delight, flavonoid **3aa** could be obtained in 99% yield with 45% ee employing catalytic 8*H*-(*R*)-TRIP. Additionally, the enantioselective coupling of cyclohexa-1,3-dione to 2-hydroxy chalcone **1a** could also be realized using (*R*)-TRIP as catalyst albeit in 67% yield with 27% ee. When phloroglucinol was employed reaction partner, flavonoid **4ba** could be obtained in 52% yield with 70% ee using **CPA1** as promoter (Scheme 4). Those initial results paved a new way for the enantioselective synthesis of hybrid flavonoids *via* counter-anion directed enantioselective addition.[11]

To gain in insights into the reaction pathway, a series of experimental were executed (Scheme 5). When the reaction was run in the dark, no product was detected with most of the starting material being recovered (Scheme 4, eqn (1)). The hemi-ketal **9** could be obtained in 62% yield when 2-hydroxylchalcone was irradiated by visible-light (Scheme 4, eqn (2)), which was in accordance with previous report.[7] Treatment hemi-ketal **9** with stoichiometric amount of HPF_6, flavylium salt **10** could be obtained in 62% yield (Scheme 4, eqn (3)). Additionally, when presence of stoichiometric amount of HPF_6, 2-hydroxyl chalcone could also be converted to flavylium salt **10** in 28% yield. The low yield was ascribed to the instability of flavylium cation (Scheme 4, eqn (4)). In sharp contrast, only trace of product could be observed when this reaction was run in the dark. We also found that addition of cyclohexa-1,3-dione **6** to flavylium **10** salt could smoothly proceeded in the dark, affording the flavonoid **4aa** in 75% yield (Scheme 4, eqn (5)). All these observations strongly supported the reaction proceeded through the tandem isomerization/cyclization/dehydration of 2-hydroxychalcone to produce a transient flavylium ion, which was *in situ* captured by the nucleophile to afford hybrid flavonoids (Fig. 1).



Scheme 4 Chiral phosphoric acid catalyzed enantioselective addition of nucleophile to 2-hydroxychalcone.



Scheme 5 Mechanistic studies.

Conclusions

In conclusion, a bio-inspired synthesis of hybrid flavonoids from 2-hydroxychalcone was developed. This protocol provided a facile entry to structurally diverse hybrid flavonoids under the irradiation of 24 W CFL. Based on the mechanistic studies, this reaction was proposed to proceed *via* the cascade double bond isomerization/dehydrated cyclization to afford a transient flavylium ion, which is *in situ* incepted by nucleophile. Furthermore, this protocol also provides novel strategy for the enantioselective synthesis of hybrid flavonoids.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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