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Highly Enantioselective Addition of Aliphatic Aldehydes to 2-Hydroxychalcone Enabled by Cooperative Organocatalysts

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Herein, we developed an enantioselective addition of aliphatic aldehydes to 2-hydroxychalcone promoted by cooperative organocatalysts, giving access to hybrid flavonoids in excellent enantioselectivities. This reaction took advantage of cycloisomerization of 2-hydroxychalcone to form a transient flavylium under the irradiation of 24W CFL, which was trapped by the *in situ* generated chiral enamine intermediate. The synergistic action of chiral phosphoric acid secured the excellent outcome of this reaction by ion-pairing with the transient flavylium.

Flavonoids are important plant pigment that widely distributed in nature,[1a] which display important biological activities including anti-inflammatory, antioxidant, anti-microbial, antiviral, as well as anticancer profiles.[1b] Hybrid flavonoids are a small family of flavonoids, possessing a flavonoids unit and another type of natural product units.[2] In this regard, Fissistigmatins are a novel type of sesquiterpene hybrid flavonoid isolated from *Fissistigma bracteolatum Chatt*. (Annonaceae) by Adam and co-workers (Figure 1).[3] Structurally, Fissistigmatins contain a flavonoid and sesquiterpene fragment, which is connected by a C4-C1'' bond. In this context, the enantioselective forging of the linker between those two fragments has posed formidable challenge.[2]

Despite of the great advances have been made in the synthesis of hybrid flavonoids from 2-hydroxychalcone or flavylium salts,[4] the catalytic asymmetric syntheses of this scaffold are scarcely reported.[5] In this context, Shi[5a] reported palladium catalyzed enantioselective addition of 2-hydroxyaryl boronic acid to 2-hydroxychalcone to construct bridged hybrid flavonoids. In 2010, Cozzi and co-workers[5b] reported an enantioselective nucleophilic addition of aldehyde to flavonium salt catalyzed by chiral imidazolidinone, delivering the hybrid flavonoids in moderate enantioselectivities and diastereoselectivities. More recently, Toste and colleagues[5c] reported the enantioselective nucleophilic addition of phenol or naphthol to flavylium salts by using chiral phosphoric acid as anionic phase transfer catalyst. Despite of those advances, a mild methodology for the enantioselective construction of the C4-C1'' linker remains highly desirable.

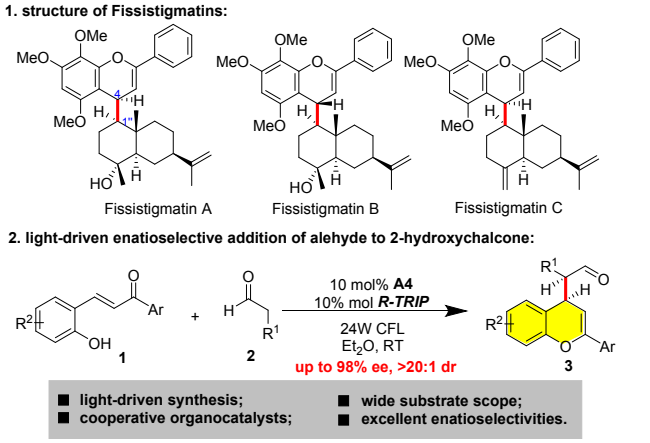

Figure 1. Structure of Fissistigmatins and enantioselective addition of aliphatic aldehydes to 2-hydroxychalcone.

With the blooming evolution of organocatalysts,[6] tremendous progresses have been witnessed by employing cooperative organocatalysts to realize enantioselective reactions that are otherwise difficulty achieved by using single organocatalyst.[7] Recently, we developed a bio-inspired synthesis of hybrid flavonoids from 2-hydroxychalcone driven by visible light.[8] The reaction took advantage the photocyclization of 2-hydroxychalcone under the irradiation of 24 W CFL via tandem *E* to *Z* isomerization/dehydrative cyclization process to generate a flavylium intermediate.[8,9] In line with our previous work, we discovered that the highly enantioselective addition of aliphatic aldehydes to 2-hydroxychalcone promoted by cooperative organocatalysts

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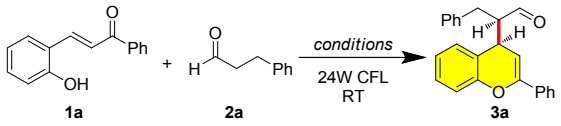
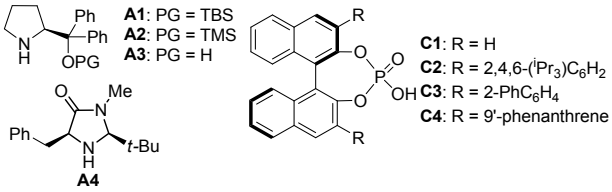
driven by visible-light, enabling enantioselective construction of the C4-C1'' linkage of Fissistigmatins. Herein, we would like to report our preliminary results.

Table 1. Optimization of the Reaction Conditions[a]

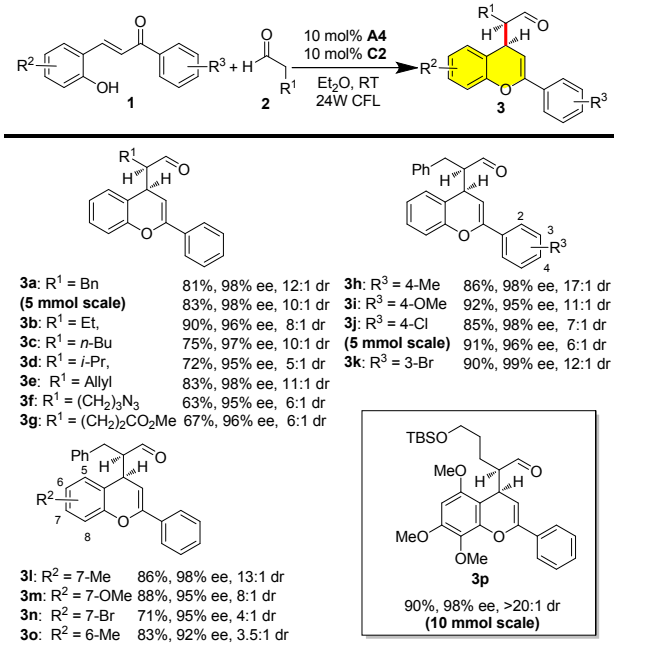


entry	amine (10 mol%)	additive (10 mol%)	yield (%)[b]	*ee* (%)[c] major, minor	*dr*
1	**A1**	TFA	59	79, 58	1:1
2	**A1**	**C1**	71	94, 83	2:1
3[d]	**A1**	**C1**	ND	NA	NA
4	**A1**	--	ND	NA	NA
5	--	**C1**	ND	NA	NA
6	**A1**	**C2**	74	95, 55	3:1
7	**A1**	**C3**	91	79, 20	2.5:1
8	**A1**	**C4**	74	68, -10	2 1
9	**A2**	**C2**	82	95, 91	2:1
10	**A3**	**C2**	29	-38, 12	2:1
11	**A4**	**C2**	81	98, 53	12:1
12	**A4**	(*S*)-**C2**	73	68, 41	3:1



[a] Reaction conditions: Reactions were performed with 2-hydroxylchalcone **1a** (0.1 mmol), hydrocinnamaldehyde **2a** (0.1 mmol), amine catalyst (10 mol %) and Brønsted acid (10 mol %) in Et_2O (1.0 mL) and irradiated by 24W CFL at RT for 24 h. [b] Isolated yields. [c] Determined by chiral HPLC on ChiralPak AD-H column. [d] Run in the dark.

Initially, the reaction of 2-hydroxylchalcone **1a** with hydrocinnamaldehyde **2a** was optimized by varying the combination of chiral amine and Brønsted acid under the irradiation of 24W CFL (Table 1). To our delight, under the action of prolinol **A1** with TFA as additive the desired coupled product **3a** could be isolated in 59% yield and 79% *ee* with 1:1 *dr* (Table 1, entry 1). It is noteworthy that using chiral phosphoric acid **C1** as co-catalyst, the enantioselectivity was greatly improved to 94% *ee* albeit with 2:1 *dr* (Table 1, entry 2). In sharp contrast, when the reaction was performed in the dark (Table 1, entry 3) or in the absence of **C1** or **A1** (Table 1, entries 4 and 5), no product was isolated. Those results indicated the reaction proceed via the generation of a transient flavylium,[8] not by the direct Michael addition/dehydrated cyclization process.[4] Subsequent screening of different solvents revealed that Et_2O was the solvent of choice (see Supporting Information). To improve the diastereoselectivity, different chiral phosphoric acids and prolinol derivatives were thus evaluated (Table 1, entries 6-10). Unfortunately, none of them was beneficial for the stereoselectivity, excepting that **C2** afforded a slightly higher diastereoselectivity (3:1, Table 1, entry 6). To our delight, combining chiral imidazolidinone **A4** with **C2** gave excellent enantioselectivity (98% *ee*) and high diastereoselectivity (12:1) (Table 1, entry 11). Furthermore, the combination of (*S*)-**C2** with imidazolidinone **A4** was also tested to investigate whether stereodivergent synthesis of **3a** could be realized (Table 1, entry 12). However, only low enantioselectivity and diastereoselectivity was obtained, suggesting the mismatching of those two chiral organocatalysts.



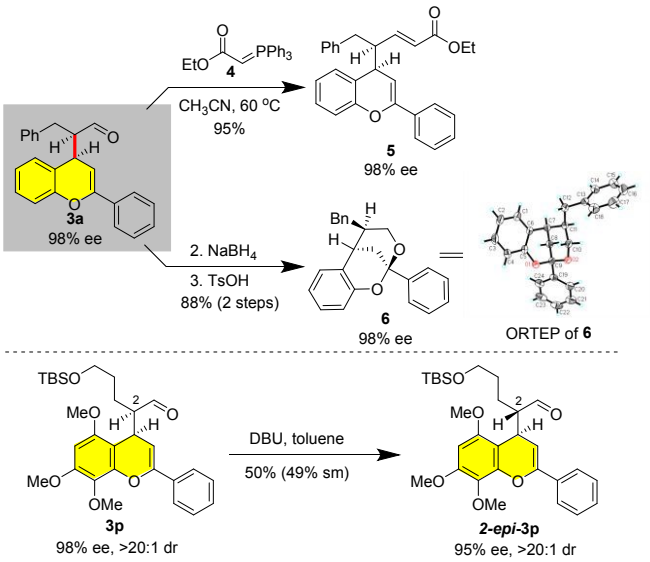
Scheme 1. Substrate scope.

Upon establishing the optimal reaction conditions, the substrate scope was then extensively examined (Scheme 1). Aliphatic aldehydes with different type of side chains (linear and branch) or functionalities (olefin, azide, and ester) were all well tolerated with the reaction conditions, delivering flavonoids **3a** to **3g** in excellent stereoselectivties (95%-98% *ee* and 5-12:1 *dr*). This reaction also showed good compatibility with substituents on both aromatic rings of 2-hydroxychalcone. As displayed in Scheme 1, electron-donating (Me, OMe) or electron withdrawing groups (Br, Cl) could be presented on both aromatic rings to afford corresponding flavonoids in excellent enantioselectivities and high diastereoselectivities (**3h** to **3o**). The reaction could be executed on gram scale, which gave comparable results (**3a** and **3j**). To our delight, flavonoid **3p** for the synthesis of Fissistigmatins could be prepared in gram scale from a TBS-protected aliphatic aldehyde in 90% yield with 98% *ee* and >20:1 *dr*.

To explore the synthetic potential and determine the stereochemistry of the coupled product, derivatizations of flavonoid **3a** were thus conducted. As depicted in Scheme 2, Wittig reaction of flavonoid **3a** with (carbethoxymethylene)triphenylphosphorane **4** afforded unsaturated ester **5** in 95% yield with 98% *ee*. Reduction of the aldehyde **3a** with $NaBH_4$ followed by treatment with TsOH to promote ketalization produced benzo[d][1,3]dioxocine **6** in 88%

yield for two steps. Fortunately, a crystal of **6** was obtained and the X-ray crystallographic analysis firmly established the absolute configuration.[10] Based on this result, the coupled product **3p** could be utilized for the asymmetric synthesis of Fissistigmatin A. However, the C2 stereochemistry of **3p** was opposite to the C1'' configuration of Fissistigmatin B.[3] Therefore, epimerization of **3p** was carried out. After some trials (see Supporting Information for details), we found that treatment of **3p** with DBU in toluene at 80 °C smoothly provided a separable **2-*epi*-3p** in 50% yield with 95% *ee* and 49% of **3p** was also recovered in 98% *ee*.

Based on our previous work and observations in this study (Table 1), we proposed a putative reaction mechanism (Figure 2). The reaction consisted of three reaction processes: light-driven cycloisomerization, chiral phosphoric acid catalyzed dehydration and chiral imidazolidinone promoted nucleophilic addition. In the photochemistry process, under the irradiation of visible-light, *E* to *Z* isomerization of 2-hydroxychalcone **1** gave rise to *Z*-enone **7**, which spontaneously cyclized to give hemiketal **8**.[8,9] A transient chiral flavylium salt **9** was then generated via the dehydration hemiketal **8** in the phosphoric acid catalyzed process.[6g-h,8] Meanwhile, aldehyde **2** condensed with chiral amine **A4** to afford the enamine intermediate **10**.[6c,11] The attack of the latter to the chiral flavylium cation **9** delivered iminium **11**, which produced the coupled product **3** upon hydrolysis to regenerate **A4** and *R*-TRIP. As depicted the transition state **TS**, the ion-pairing and π-π stacking of the phosphate with the flavylium moiety made the *Si*-face of flavylium available for the nucleophilic attack. On the other hand, chiral *E*-enamine **10** favored the *Si*-face incoming of the electrophile. Consequently, the synergistic operation of those two chiral organocatalysts secured the formation of (*R*,*R*)-isomer in excellent enantioselectivities.



Scheme 2. Derivatization of the Coupled Products.

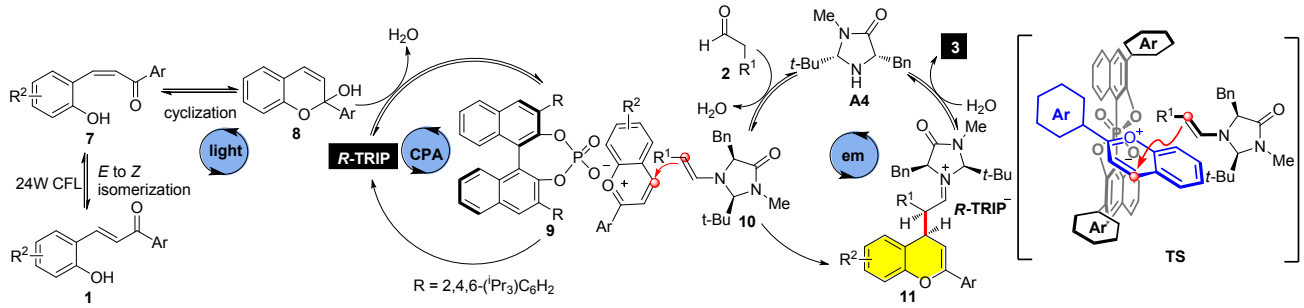


Figure 2. Proposed reaction mechanism.

In conclusion, by taking advantage of chiral phosphoric acid and chiral imidazolidinone as co-operative organocatalysts, direct coupling of 2-hydroxychalcone with aliphatic aldehydes was realized under the irradiation of visible-light. Excellent enantioselectivities were obtained by merging two different organocatalyzed processes, confirming the synergistic action of those two organocatalysts. The application of this protocol in the asymmetric synthesis of Fissistigmatins is currently pursued in our laboratory and the results will be reported in due course.

Conflicts of interest

There are no conflicts to declare

Acknowledgement

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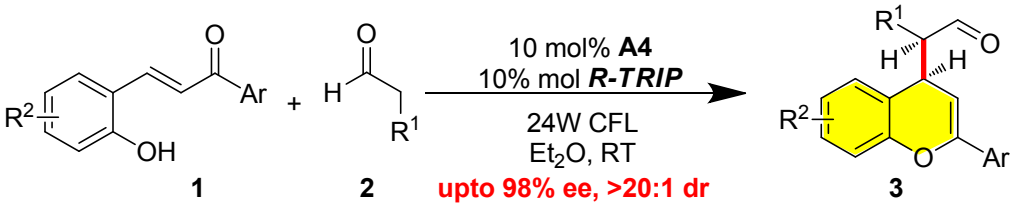

- **light-driven synthesis;**
- **cooperative organocatalysts;**
- **wide substrate scope;**
- **excellent enantioselectivities;**