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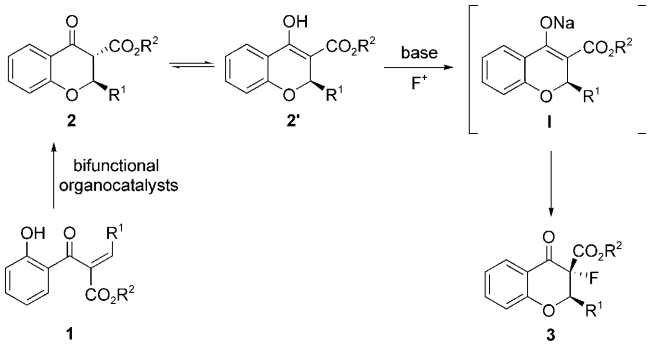
Asymmetric Synthesis of Fluorinated Flavanone Derivatives by an Organocatalytic Tandem Intramolecular Oxa-Michael Addition/Electrophilic Fluorination Reaction by Using Bifunctional Cinchona Alkaloids

Hai-Feng Wang,[a] Hai-Feng Cui,[a] Zhuo Chai,[a] Peng Li,[a] Chang-Wu Zheng,[a] Ying-Quan Yang,[b] and Gang Zhao*[a, b]

Flavanones are a large family of natural products with many important biological activities, such as antitumor and anti-inflammatory properties.[1,2] However, despite intensive research devoted to the synthesis of flavanone derivatives,[3] only a limited number of methods, particularly catalytic asymmetric methods, are available for the asymmetric synthesis of this class of compound.[4] Structurally, the asymmetric, intramolecular oxa-Michael addition reaction of a phenol to chalcone would provide an easy access to chiral flavanones due to the ready availability of the starting materials. However, it was not until 2007 that a breakthrough based on this strategy, by using an organocatalytic method, was accomplished, by Scheidt and co-workers,[4d] probably due to the low reactivity of the substrates. They addressed this challenge by utilizing an activated, unsaturated ketone, **1**, as the substrate and bifunctional chiral thioureas as catalysts (Scheme 1). Recently, Feng and co-workers[4g] reported a metal-catalyzed version of the same reaction employing chiral *N,N′*-dioxide nickel(II) complexes with excellent results. In view of these results, there is still the potential for the development of new organocatalysts to effect an asymmetric intramolecular oxa-Michael addition as a route to synthesize chiral flavanones.

On the other hand, the introduction of a fluorine atom into a compound often results in important changes in its biological activity, which can lead to potential applications in medicinal chemistry and the pharmaceutical industry.[5] One of the most challenging subjects in the field of synthetic fluorine chemistry is the enantioselective construction of the C–F bond at a stereogenic carbon center.[6] Since the first asymmetric fluorination reagents were reported by Differding and Lang [7a] in 1988 and the first catalytic enantioselective fluorination was disclosed by Hintermann and Togni[7b] in 2000, this intriguing field of catalytic asymmetric fluorination has been blooming.[8,9] Our group has developed a one-pot tandem reaction for the synthesis of fluorinated flavanones, from β-ketoesters and aldehydes, with excellent diastereoselectivities.[10] On the basis of these results, we envisaged that by using an appropriate bifunctional catalyst, an organocatalytic, asymmetric, intramolecular oxa-Michael addition of **1** would produce enantioenriched **2**, which could then be subjected to electrophilic fluorination to provide novel, chiral, fluorinated flavanone derivatives (Scheme 1). Herein, we report the details of this research.



Scheme 1. Organocatalyzed tandem intramolecular oxa-Michael addition/electrophilic fluorination reaction to access chiral fluorinated flavanones.

Cinchona alkaloids and their derivatives were selected as catalysts to be investigated due to their easy availability and well-documented power as bifunctional organocatalysts in

[a] H.-F. Wang, H.-F. Cui, Z. Chai, P. Li, C.-W. Zheng, Prof. Dr. G. Zhao
Key Laboratory of Synthetic Chemistry of Natural Substances
Shanghai Institute of Organic Chemistry
345 LingLing Lu, Shanghai, 200032 (China)
Fax: (+86) 21-64166128
E-mail: zhaog@mail.sioc.ac.cn

[b] Y.-Q. Yang, Prof. Dr. G. Zhao
Department of Chemistry
University of Science and Technology of China
Hefei, Anhui 230026 (China)

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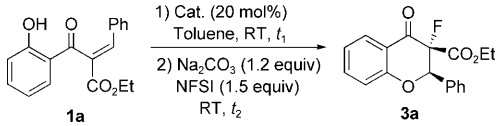
various asymmetric reactions.[11] As a model substrate, the activated α,β-unsaturated ketone **1a** first underwent an intramolecular oxa-Michael addition in the presence of a cinchona alkaloid followed by electrophilic fluorination with Na_2CO_3[12] and *N*-fluorobenzenesulfonimide (NFSI) to deliver the desired product **3a**. Table 1 summarizes the results of the catalyst evaluation. First, commercially available quinine (**4a**) and quinidine (**4b**) both provided encouraging results (Table 1, entries 1 and 2). Subsequent structural modifications on these two compounds led to the optimal catalyst **4m**, which gave the desired product in 99% yield and 92% enantiomeric excess (*ee*) (Table 1, entry 13). It is of note that several sterically more demanding catalysts, such as **4f**–**4i** (Scheme 2) all provided inferior results (Table 1, entries 6–9), which highlighted the uniqueness of this novel trifluoromethyl-group-containing catalyst **4m**. Interestingly, the organocatalysts also seemed to play a role in the electrophilic fluorination step because different reaction times were required for this step in each case. In all of the cases examined, only one diastereoisomer of the product **3a** was observed.

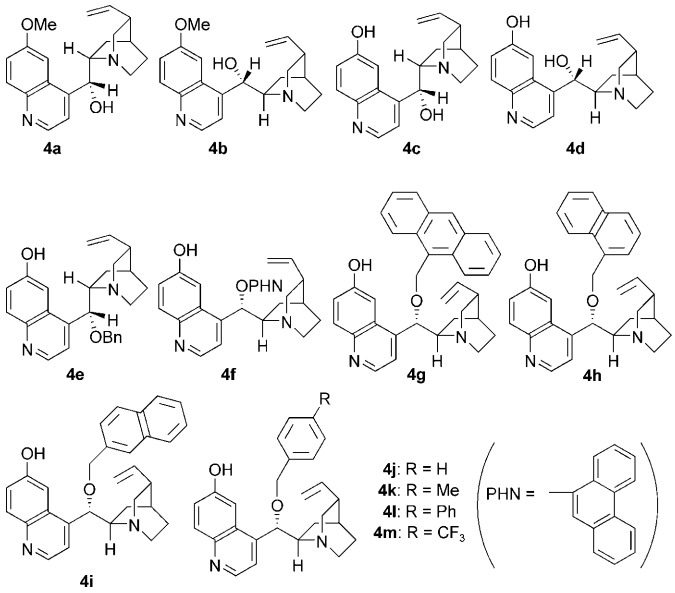
Table 1. Evaluation of different cinchona alkaloids as catalysts in the asymmetric synthesis of flavanones.[a]



Entry	Catalyst	t_1 [h]	t_2 [h]	Yield [%][b]	*ee* [%][c]
1	**4a**	72	17	83	−24
2	**4b**	72	17	76	16
3	**4c**	240	17	73	−57
4	**4d**	240	17	73	24
5	**4e**	84	3	89	−81
6	**4f**	156	17	83	42
7	**4g**	36	16	76	86
8	**4h**	10	12	70	83
9	**4i**	10	12	54	88
10	**4j**	12	4	99	81
11	**4k**	12	4.5	99	84
12	**4l**	11	12	80	85
13	**4m**	12	5	99	92

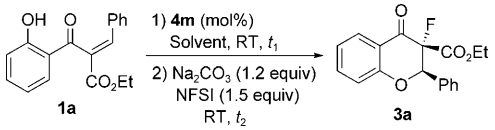
[a] Unless otherwise noted, the reaction was carried out with **1a** (0.1 mmol), catalyst **4** (0.02 mmol), and toluene (1.0 mL) at room temperature, then Na_2CO_3 (1.2 equiv) and NFSI (1.5 equiv) were added and the reaction was stirred for 3–17 h. [b] Yield of the isolated product after column chromatography on silica gel. [c] Determined by HPLC analysis on a chiral phase. Only a single diastereoisomer was observed by ^1H and ^{13}C NMR spectroscopy.

Next, we examined the influence of catalyst loading on the overall yield and enantioselectivity. Lowering the amount of **4m** from 20 to 15 mol% increased the *ee* value to 93% while maintaining the excellent yield (Table 2, entries 1 and 2). However, decreasing the amount of **4m** further to 10 or 5 mol% led to a drop in the yield, while similar *ee* values were obtained (Table 2, entries 3 and 4). As a compromise of both yield and enantioselectivity, a catalyst loading of 15 mol% was selected for the ensuing study. Lowering the reaction temperature to 0°C brought no improvement in enantioselectivity, but led to a decrease in the yield and a prolonged reaction time (Table 2, entry 5). Other arene solvents, such as xylene and $PhCF_3$, provided compa-



Scheme 2. Cinchona alkaloid catalysts used in this study.

Table 2. Screen of catalyst loading and solvents.[a]



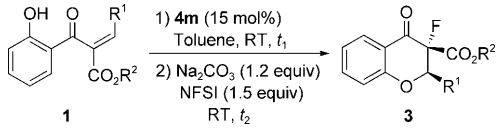
Entry	**4m** [mol%]	Solvent	t_1 [h]	t_2 [h]	Yield [%][b]	*ee* [%][c]
1	20	toluene	12	5	99	92
2	15	toluene	12	6	99	93
3	10	toluene	15	8	92	93
4	5	toluene	17	8	89	94
5[d]	15	toluene	72	10	92	93
6	15	xylene	9	12	99	93
7	15	$PhCF_3$	48	8	99	93
8	15	CH_2Cl_2	9	12	99	87
9	15	$CHCl_3$	10	12	99	87
10	15	CCl_4	10	48	70	91
11	15	$ClCH_2CH_2Cl$	9	8	89	86
12	15	MTBE	48	24	70	94
13	15	*n*-hexane	48	24	35	71
14	15	THF	48	8	99	89
15	15	Et_2O	48	24	51	95
16	15	EtOH	9	6	99	20
17	15	CH_3CN	8	6	96	62
18[e]	15	CH_3CN	8	8	96	60

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.1 mmol) and **4m** in solvent (1.0 mL) at room temperature for 8–48 h, then Na_2CO_3 (1.2 equiv) and NFSI (1.5 equiv) were added and the reaction was stirred for 5–48 h. [b] Yield of the isolated product after column chromatography on silica gel. [c] Determined by HPLC analysis on a chiral phase. Only a single diastereoisomer was observed by ^1H and ^{13}C NMR spectroscopy. [d] The reaction was carried out at 0°C. [e] Selectfluor was used instead of NFSI.

rable results in terms of yield and *ee* value, but with longer reaction times (Table 2, entries 6 and 7). Slightly lower *ee* values and yields were obtained with the use of chlorine-containing solvents, such as CH_2Cl_2, $CHCl_3$, CCl_4, and $ClCH_2CH_2Cl$ (Table 2, entries 8–11). Although higher *ee* values were obtained in Et_2O or methyl *tert*-butyl ether (MTBE), the yields were markedly diminished probably due to the poor solubility of NFSI in these two solvents (Table 2, entries 12 and 15). A similar reason may be invoked to explain the low yields in apolar CCl_4 and *n*-hexane (Table 2, entries 10 and 13). Additionally, Selectfluor, another commonly used electrophilic fluorinating reagent, was also tested (in CH_3CN for reasons of solubility) but did not give improved results (Table 2, entry 18). To summarize, the present tandem reaction was best performed with 15 mol% of **4m** in toluene at room temperature (Table 2, entry 2).

Having established the optimal conditions for the intramolecular oxa-Michael addition/electrophilic fluorination cascade reaction, we next explored the scope of the reaction and representative results are listed in Table 3. For substrates with different R^1 substituents, excellent yields and high *ee* values were generally obtained irrespective of the electronic nature or positions of the substituents on the arene ring (Table 3, entries 2–15), except for the heterocyclic substrate **1p** (R^1 = furan-2-yl; Table 3, entry 16). Notably, the reactions of substrates with electron-donating substituents generally required longer reaction times than those with electron-withdrawing groups. The *ee* value of product **3d** could be increased to >99% after a single recrystallization (Table 3, entry 4). While changing the ester moiety (R^2) of substrate **1a** to a less bulky methyl group resulted in a slightly lower yield and *ee* value, the use of a more sterically demanding *tert*-butyl group improved the enantioselectivity to 96% *ee* and still with an excellent yield, although a longer reaction time was required (Table 3, entries 17 and 18). The cyclohexyl-substituted substrate **1s** with a *tert*-butyl ester group also afforded the desired product **3s** with high enantioselectivity and yield (Table 3, entry 19). When R^1 was an ethyl group, the reaction still proceeded efficiently to give the desired product in excellent yield, but a sharp decrease in enantioselectivity was observed, which may be attributable to its decreased steric hindrance (Table 3, entry 20). The absolute configuration of product **3d** was determined as 2*R*, 3*R* by X-ray crystallographic analysis (Figure 1).[13]

Table 3. Scope of the catalytic synthesis of chiral fluorinated flavanones.[a]



1 3

Entry	R^1, R^2, **1**	t_1 [h]	t_2 [h]	**3**	Yield [%][b]	*ee* [%][c]
1	C_6H_5, Et, **1a**	12	6	**3a**	99	93
2	*p*-FC_6H_4, Et, **1b**	12	7	**3b**	99	92
3	*p*-ClC_6H_4, Et, **1c**	12	7	**3c**	99	92
4[d]	*p*-BrC_6H_4, Et, **1d**	12	7	**3d**	>99	90 (>99)[e]
5	*p*-$NO_2C_6H_4$, Et, **1e**	12	7	**3e**	99	90
6	*p*-CNC_6H_4, Et, **1f**	12	7	**3f**	99	92
7	*p*-$CF_3C_6H_4$, Et, **1g**	12	7	**3g**	97	92
8	*o*-BrC_6H_4, Et, **1h**	12	7	**3h**	99	89
9	*m*-BrC_6H_4, Et, **1i**	12	7	**3i**	99	93
10	*p*-PhC_6H_4, Et, **1j**	15	12	**3j**	97	93
11	2-naphthyl, Et, **1k**	15	12	**3k**	96	92
12	*p*-MeC_6H_4, Et, **1l**	15	12	**3l**	95	91
13	*p*-$MeOC_6H_4$, Et, **1m**	15	12	**3m**	96	90
14	*p*-$BnOC_6H_4$, Et, **1n**	15	12	**3n**	98	90
15	3-BnO-4-MeO-C_6H_3, Et, **1o**	24	12	**3o**	89	92
16	furan-2-yl, Et, **1p**	72	12	**3p**	56	73
17	C_6H_5, Me, **1q**	15	12	**3q**	93	88
18	C_6H_5, *t*Bu, **1r**	24	6	**3r**	94	96
19	cyclohexyl, *t*Bu, **1s**	144	48	**3s**	86	88
20	Et, *t*Bu, **1t**	24	20	**3t**	93	17

[a] Unless otherwise noted, the reaction was carried out with **1** (0.1 mmol), **4m** (0.015 mmol), and toluene (1.0 mL) at room temperature for 12–144 h, then Na_2CO_3 (1.2 equiv) and NFSI (1.5 equiv) were added and the reaction was stirred for 6–48 h. [b] Yield of the isolated product after column chromatography on silica gel. [c] Determined by HPLC analysis on a chiral phase. Only a single diastereoisomer was observed by ^1H and ^{13}C NMR spectroscopy. The absolute configuration of **3d** was determined as 2*R*, 3*R* by X-ray crystallographic analysis, and the other products, **3a**–**3c** and **3e**–**3t**, were assigned by assuming that a similar catalytic mechanism was followed. [d] The reaction was carried out on a 0.2 mmol scale. [e] The enantioselectivity was determined after a single recrystallization.

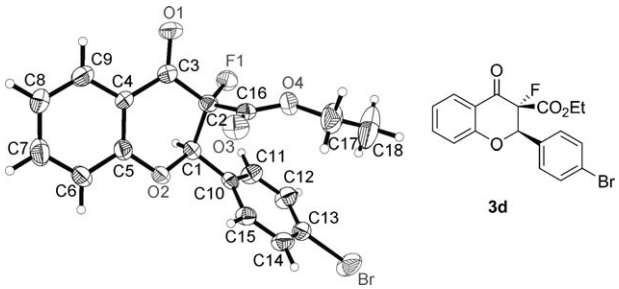
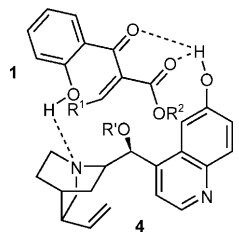


Figure 1. ORTEP structure of compound **3d**. Ellipsoids at 30% probability.

To propose a mechanism for the reaction, we assumed that the oxa-Michael addition was the enantiodiscriminating step and the stereocenter thus formed would govern the stereoselectivity of the electrophilic fluorination process as we have previously demonstrated.[10] Based on the experimental results and previous studies,[11] we proposed a transition-state model to explain the stereochemical outcome of the reaction (Scheme 3). The bifunctional catalyst may activate both the nucleophile and the electrophilic acceptor through a hydrogen-bonding interaction, directing the oxygen nucleophile to attack the *Re* face of the double bond to form the *R*-configured product.



Scheme 3. Proposed transition-state model for the oxa-Michael addition step.

In conclusion, we have developed a novel, organocatalytic, intramolecular oxa-Michael addition/electrophilic fluorination tandem reaction for the synthesis of a series of chiral monofluorinated flavanones. By using the new quinidine-derived bifunctional catalyst **4m**, high enantioselectivities (up to 96% *ee*) and excellent yields were obtained for most of the substrates under mild conditions. Further applications of the present reaction as well as the use of the bifunctional organocatalysts in other reactions are in progress in our laboratories.

Experimental Section

Typical procedure: A mixture of (*E*)-ethyl 2-(2-hydroxybenzoyl)-3-phenylacrylate **1a** (0.1 mmol) and catalyst **4m** (7 mg, 0.015 mmol) in toluene (1.0 mL) was stirred at room temperature for the appropriate time until **1a** was consumed (as monitored by TLC). Then Na_2CO_3 (12.7 mg, 0.12 mmol) and NFSI (47.3 mg, 0.15 mmol) were added and the mixture was stirred at room temperature for 6–12 h (as monitored by TLC). The reaction mixture was then concentrated and the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1:20, v/v) to give the desired products **3a** as a white solid (31.1 mg, 99%). $[\alpha]_D^{24} = -166.5$ ($c = 1.03$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.02$ (t, $J = 6.9$ Hz, 3H), 4.03–4.09 (m, 2H), 5.54 (d, $J = 8.4$ Hz, 1H), 7.13–7.19 (m, 2H), 7.38–7.52 (m, 5H), 7.62 (t, $J = 7.5$ Hz, 1H), 8.00 (d, $J = 7.5$ Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -175.30$ (d, $J = 7.9$ Hz, 1F). The *ee* value was determined by HPLC analysis by using a chiralcel OD column, hexane/2-propanol: 80:20, flow rate: 0.75 mL min^{-1}, t_R (minor) = 13.38 min, t_R (major) = 15.27 min.

Acknowledgements

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Keywords: asymmetric catalysis · cinchona alkaloids · domino reactions · fluorination · oxa-Michael addition

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[13] CCDC-734041 contains the supplementary crystallographic data for **3d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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