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One-pot fluorination and asymmetric Michael addition promoted by recyclable fluorous organocatalysts†

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A novel one-pot fluorination and asymmetric Michael addition reaction sequence promoted by recyclable fluorous bifunctional cinchona alkaloid–thiourea organocatalysts is introduced for the synthesis of α-fluoro-β-ketoesters bearing two chiral centers.

Asymmetric fluorination is an active topic in medicinal and agricultural chemistry.[1,2] Generation of α-fluorinated carbonyl compounds with two adjacent stereogenic centers is highly demanded in the synthesis of biologically active molecules such as histone deacetylase inhibitor **I**,[3] progestational and antiinflammatory agent **II**,[4] antiobesity and anticoronary agent **III**,[5] antimalarial candidate **IV**,[6] acaricide and insecticide **V**,[7] and plant growth regulatory activator **VI** (Fig. 1).[8] Synthesis of a fluorinated quaternary stereocenter next to a tertiary stereocenter can be accomplished by organocatalytic Michael addition of α-fluorinated β-ketoesters with Michael acceptors such as nitroalkenes, chalcones, α,β-unsaturated aldehydes, and *N*-alkyl maleimides. Pyrrolidine derivatives,[9] guanidines,[10] cinchona alkaloids,[11] bifunctional cinchona alkaloid–thioureas,[12] and bifunctional amine–thioureas[13] have been developed as organocatalysts for such a transformation.

As part of our continuous effort on the development of recyclable fluorous organocatalyts[14] for asymmetric synthesis,[15] we recently developed one-pot fluorination and Michael addition reactions.[16] We also reported asymmetric fluorination reactions promoted by fluorous cinchona alkaloid ester.[17] Introduced in this paper is a step economic one-pot fluorination and asymmetric Michael addition sequence promoted by recyclable fluorous catalysts. To the best of our knowledge, no such a one-pot transformation has been reported in literature for asymmetric synthesis.

Catalysts used to explore the one-pot fluorination and Michael addition reactions are shown in Fig. 2 which include cinchona alkaloids **c-1** to **c-4**,[18] bifunctional cinchona alkaloid-thioureas **c-5** to **c-7**,[19] pyrrolidine derivative **c-8**, and bifunctional amine-thiourea **c-9**.[14b] Among them, five are fluorous bearing a perfluorinated alkyl chain such as C_6F_{13} or C_8F_{17}. Selectfluor™ (F-TEDA-BF_4) was used as a fluorine source and an equimolar amount of β-ketoester **1a** and nitroalkene **2a** were used for the one-pot synthesis. Under the reaction condition of using 20 mol% of catalyst at 0 °C for 48 h, all the reactions generated target product **3a** except with catalysts **c-9** (Table 1, entries 1–9). The reaction with bifunctional cinchona alkaloid-thiourea catalysts **c-5**, **c-6** and **c-7** gave product in high yield (93–96%), good diastereoselectivity (5 : 1 to 6 : 1 dr), and enantioselectivity (80–82% ee). These results obtained from our one-pot reactions are similar to those from the Michael additions of α-fluorinated β-ketoesters reported in literature.[12b] Bifunctional pyrrolidine-thiourea catalyst **c-9** has the best diastereoselectivity (10 : 1 dr) but low yield and enantioselectivity. Since fluorous catalysts **c-5** and **c-6** are epimers, only **c-5** was used for further investigation. It was found that the reaction carried out under −20 °C for 48 h using 1 : 1 MeCN–MePh as a solvent was the best condition which gave product **3a** in 95% ee and 9 : 1 dr. The configuration of **3a** was determined by comparing the chiral HPLC analytical data with the literature data.[12b]

Electrophilic fluorination of **1a** could occur without a catalyst to afford racemic α-fluoro-β-ketoester **4a**.[16] Resulting compound **4a** bearing a more acidic α-proton facilitated the Michael addition to

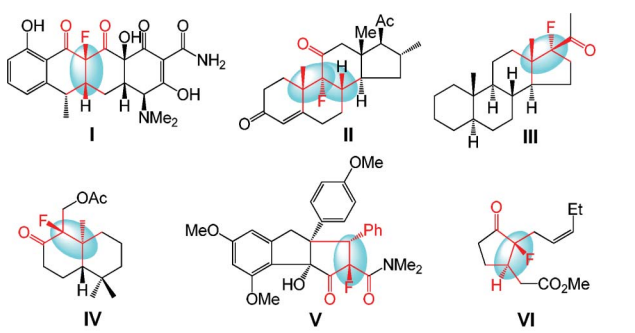

Fig. 1 Biologically interested α-fluorinated carbonyl compounds.

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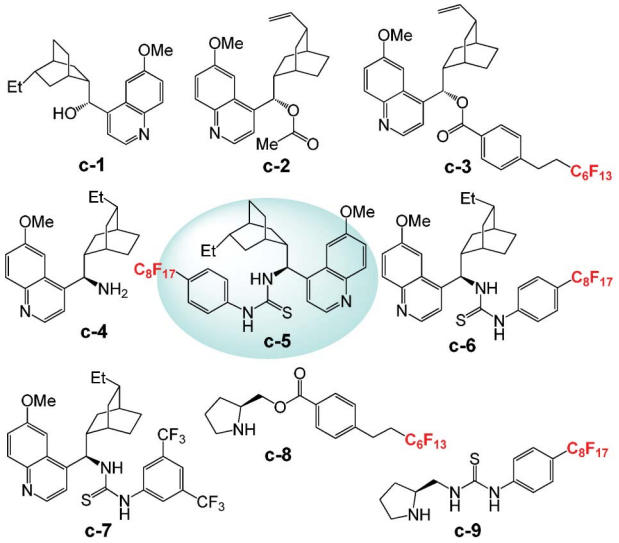
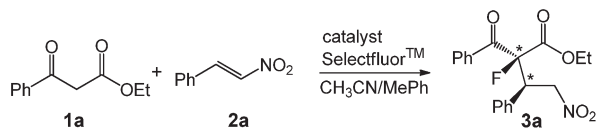


Fig. 2 Organocatalysts tested for one-pot reaction.

generate product **3a** with two stereogenic centers. To confirm the mechanism of the cascade reaction, the reaction of **1a** and **2a** under the optimized condition was monitored by LC-MS analysis. Analytical results of the reaction mixtures at different reaction time are shown in Fig. 3. The amount of racemic fluorinated compound **4a** was produced up to 30% in the first 6 h and then slowly decreased. The amount of product **3a** was steadily increased during the reaction process. Only a small amount of Michael addition product **5a** was detected in the reaction mixture. This

Table 1 Catalyst screening for one-pot fluorination and Michael addition[a]



	Cat.	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]	dr[d]
1	**c-1**	0	48	80	−58	3 : 1
2	**c-2**	0	48	36	42	3 : 1
3	**c-3**	0	48	31	46	4 : 1
4	**c-4**	0	48	86	−71	3 : 1
5	**c-5**	0	48	96	81	6 : 1
6	**c-6**	0	48	95	−80	6 : 1
7	**c-7**	0	48	93	−82	5 : 1
8	**c-8**	0	72	50	25	10 : 1
9	**c-9**	0	72	—	—	—
10[e]	**c-5**	25	24	71	36	1 : 1
11[f]	**c-5**	25	24	67	41	1 : 1
12[g]	**c-5**	25	24	94	58	2 : 1
13	**c-5**	25	24	97	66	2 : 1
14	**c-5**	−10	36	95	90	6 : 1
15	**c-5**	−20	48	92	95	9 : 1

[a] Reaction conditions: 0.1 mmol **1a**, 0.1 mmol Selectfluor™, 0.1 mmol **2a**, 20 mol% catalyst in 1 : 1 CH_3CN–MePh. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^1H NMR. [e] CH_3CN as solvent. [f] MePh as solvent. [g] CH_3CN/CF_3Ph as solvent.

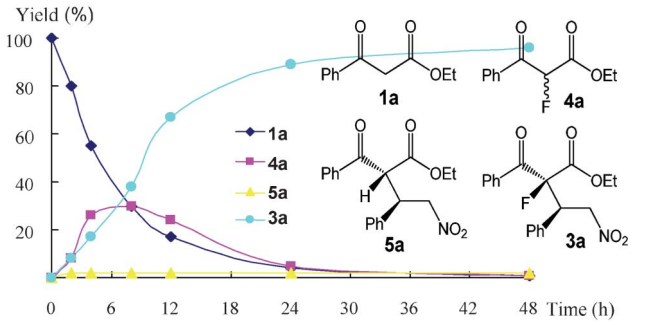
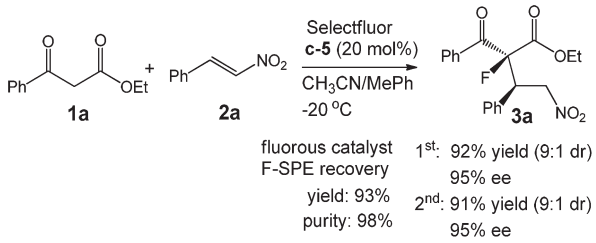


Fig. 3 Compound distribution of **c-5** catalyzed one-pot reaction.

experiment indicates that the facile fluorination occurred first to form racemic α-flourinated ketoester **4a** followed by **c-5** catalyzed asymmetric Michael addition to form **3a**.

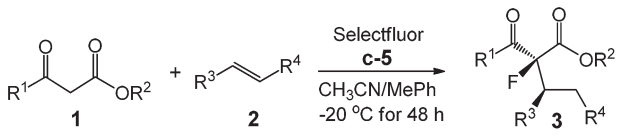
It was found that recyclable fluorous catalysts **c-5** and **c-6** performed as well as their non-fluorous counterpart **c-7**. Catalyst **c-5** was easily isolated from the reaction mixture by fluorous solid-phase extraction (F-SPE) with 80 : 20 MeOH/H_2O and then MeOH on a Fluoro*Flash*® cartridge.[20] The catalyst was recovered from the MeOH fraction in 93% yield and 98% purity. The reused catalyst has no significant change of product yield and selectivity (Scheme 1).

To explore the scope of catalyst **c-5**, a series of β-ketoesters **1** were reacted with Michael acceptors **2** such as nitroalkenes, chalcones, and α,β-unsaturated ketones/esters (Table 2). Reactions of ethyl benzoylacetates with nitrostyrenes gave excellent product yield and good to excellent enantioselectivity (entries 1–6). The substituents on the aromatic rings of β-ketoesters and nitrostyrenes gave the products with decreased diastereoselectivity. The reaction of methyl ketone afforded product **3g** in good yield but decreased enantio- and diastereoselectivities (entry 7). Furyl nitroalkene produced product **3h** in 96% yield with moderate enantio- and diastereoselectivities (62% ee and 3 : 1 dr). As a less reactive Michael acceptor, the reaction of chalcone and its derivatives were conducted using increased amounts of catalyst in the presence of $CsCO_3$. Even though the product yield and selectivity were still low (entries 10–11). Dibenzylideneacetone with two Michael acceptor sites gave the single Michael addition product **3l** in 8% ee (entry 12). We concluded that nitroalkenes constitute the best electrophiles to obtain high enantioselective Michael additions.



Scheme 1 Catalyst recycling for the one-pot reaction.

Table 2 One-pot fluorination and Michael addition catalysed by **c-5**[a]



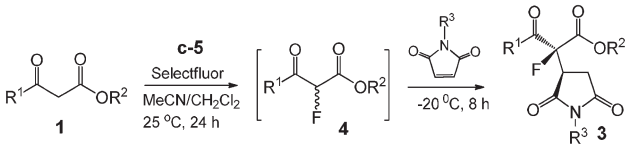
1 2 3

	R^1	R^2	R^3	R^4	3	Yield (%)[b]	ee (%)[c]	dr[d]
1	Ph	Et	Ph	NO_2	**3a**	92	95	9/1
2	Ph	Et	4-BrPh	NO_2	**3b**	96	96	5/1
3	Ph	Et	4-MePh	NO_2	**3c**	90	91	3/1
4	Ph	Et	3-BrPh	NO_2	**3d**	91	83	3/1
5	4-MePh	Et	Ph	NO_2	**3e**	94	85	4/1
6	Me	Me	Ph	NO_2	**3f**	87	57	2/1
7	Ph	Et	2-Furyl	NO_2	**3g**	96	62	3/1
8	Ph	Et	Ph	PhCO	**3h**	59	36	3/1
9	Ph	Et	Ph	4-MeOPhCO	**3i**	47	37	4/1
10	Ph	Et	4-NO_2Ph	PhCO	**3j**	71	20	2/1
11	Ph	Et	Ph	PhCH=CHCO	**3k**	42	8	4/1

[a] Reaction conditions: 0.1 mmol **1**, 0.1 mmol Selectfluor™, 0.1 mmol **2** and 20 mol% **c-5** in 1 : 1 CH_3CN–MePh at −20 °C for 48 h; in chalcone cases 50 mol% **c-5** and 20 mol% Cs_2CO_3 were used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^1H NMR.

Maleimides are reactive Michael acceptors.[21] One-pot reaction by mixing all the reaction components together afforded a low yield of expected product because of the competition of the direct Michael addition and the fluorination. A one-pot but two-step procedure was developed to address this issue. The Michael donor was first fluorinated with Selectfluor™ before the addition of the maleimide. Maleimides with different *N*-alkylation groups reacted with β-ketoester generated products in excellent yields (89–98%) with good ee (77–94%) and dr (>20 : 1) (Table 3). The diastereoselectivity is significantly improved compared to that shown in Table 2.

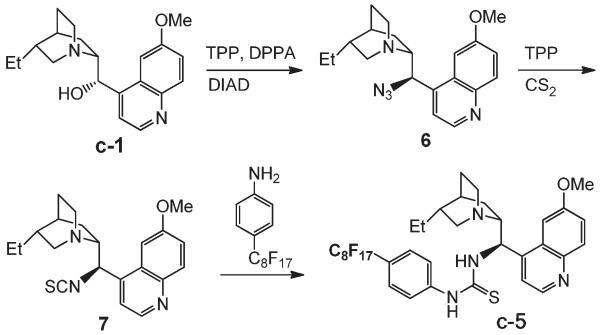
Table 3 One-pot fluorination and Michael addition with maleimides[a]



1 4 3

Entry	R^1	R^2	R^3	Pd	Yield (%)[b]	ee (%)[c]	dr[d]
1	Ph	Et	Et	**3l**	93	90	>20 : 1
2	Ph	Et	Me	**3m**	91	86	>20 : 1
3	Ph	Et	Ph	**3n**	90	87	>20 : 1
4	Ph	Et	$PhCH_2$	**3o**	96	91	>20 : 1
5	4-MePh	Et	Et	**3p**	92	77	>20 : 1
6	4-MePh	Et	$PhCH_2$	**3q**	95	91	>20 : 1
7	4-NO_2Ph	Et	Et	**3r**	98	80	>20 : 1
8	4-NO_2Ph	Et	$PhCH_2$	**3s**	96	94	>20 : 1

[a] Reaction conditions: 0.1 mmol β-ketoester and 0.1 mmol Selectfluor™ with 20 mol% **c-5** in 1 : 1 CH_3CN–CH_2Cl_2 at 25 °C for 24 h, then add 0.1 mmol maleimide at −20 °C for 8 h. [b] Isolated yield. [c] Determined by chiral HPLC and by comparing with the data in ref. 10. [d] Determined by ^1H NMR.



Scheme 2 Synthesis of fluorous catalyst **c-5**.

The synthesis of fluorous version bifunctional cinchona alkaloid–thioureas organocatalyst **c-5** was accomplished following the reported procedures (Scheme 2).[19b] Hydroquinidine **c-1** was converted to azide **6** by reacting with diphenyl phosphorazidate (DPPA) in the present of triphenyl phosphine (TPP) and diisopropyl azodicarboxylate (DIAD). The reaction of azide **6** with TPP and CS_2 afforded **7** which was then reacted with 4-perfluorooctylaniline under microwave heating to afford **c-5** in 27% overall yield after F-SPE purification.

In summary, the fluorous bifunctional cinchona alkaloid–thiourea organocatalyst **c-5** and its epimer **c-6** have been successfully employed in the one-pot fluorination and enantioselective Michael addition reactions for the synthesis of α-fluoro-β-ketoesters containing two stereogenic centers. The new bifunctional cinchona alkaloid-thiourea organocatalysts[22,23] can be readily applied to other asymmetric transformations such as Henry,[24] Friedel–Crafts,[25] Diels–Alder,[26] and Morita–Baylis–Hillman reactions.[27]

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