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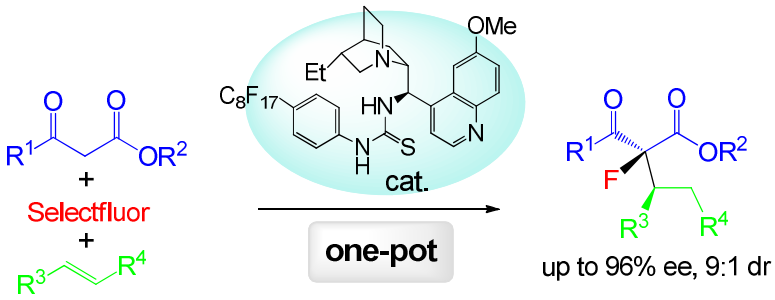

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One-pot fluorination and asymmetric Michael addition promoted by recyacable fluorous organocatalysts

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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.

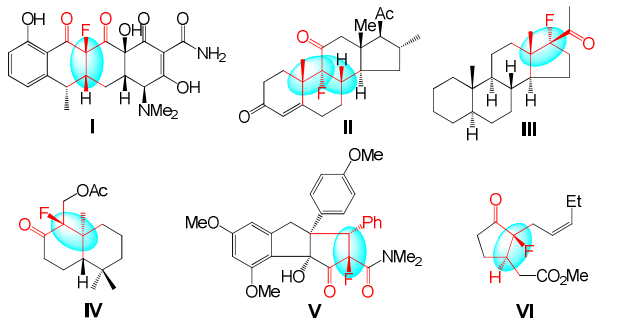

Fig. 1 Biologically interested α-fluorinated carbonyl compounds

As part of our continuous effort on the development of recyclable fluorous organocatalysts[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 diasteroselectivity (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]

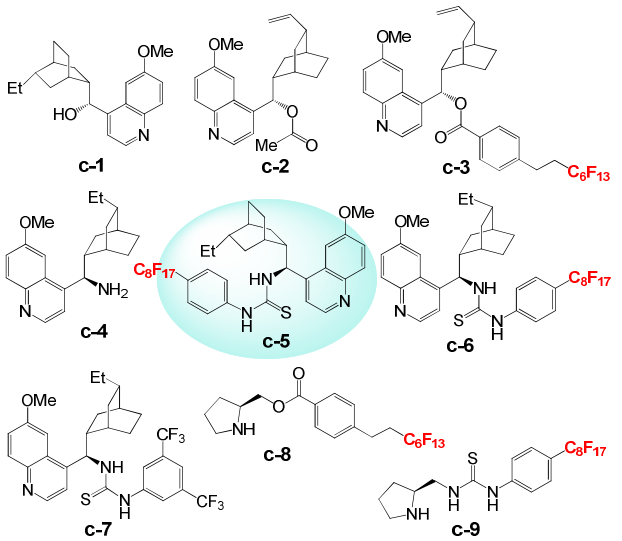

Fig. 2 Organocatalysts tested for one-pot reaction

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

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† Electronic Supplementary Information (ESI) available: Experimental section and characterization data. See DOI: 10.1039/b000000x/

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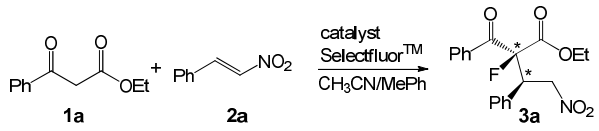
addition to generate product **3a** with two stereogenic centers. To confirm the mechanism of the cascade reaction, the reaction of **1a** and **2a** under the optimized condition was monitored by LC-MS analysis. Analytical results of the reaction mixtures at different reaction time are shown in Fig. 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 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**.

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



	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 condition: 0.1 mmol of **1a**, 0.1 mmol of Selectfluor™, 0.1 mmol of **2a**, 20 mol% of 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.

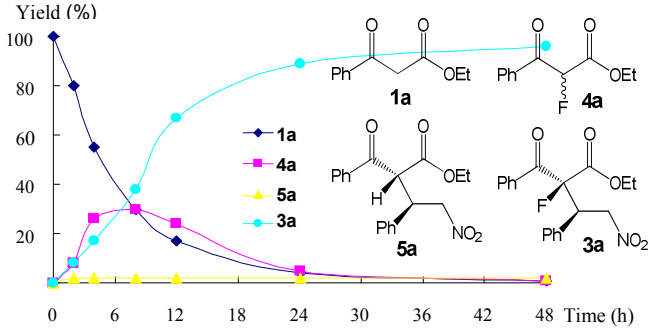
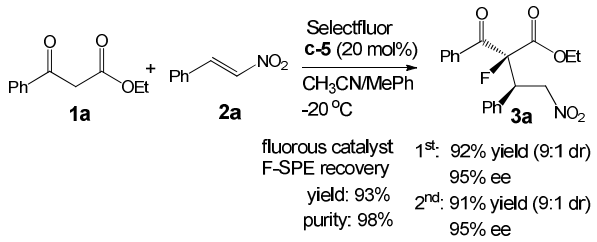


Fig. 3 Compound distribution of **c-5** catalyzed one-pot reaction

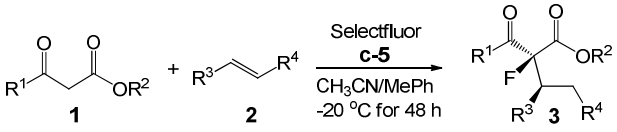
It was found that recyclable fluorous catalysts **c-5** and **c-6** performed as well as their non-fluorous counterpart **c-7**. Catalyst **c-5** was easily isolated from the reaction mixture by fluorous solid-phase extraction (F-SPE) with 80:20 MeOH/H_2O and thenMeOH on a Fluoro*Flash*® cartridge.[20] 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).



Scheme 1 Catalyst recycling for the one-pot reaction

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

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



	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 condition: 0.1 mmol of 1, 0.1 mmol of Selectfluor™, 0.1 mmol of **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% of Cs_2CO_3 were used; [b]Isolated yield; [c]Determined by chiral HPLC; [d]Determined by ^1H NMR.

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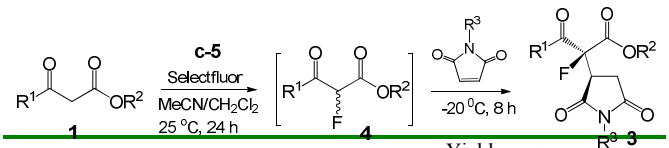
were still low (entries 10-11). Dibenzylideneacetone with two Michael acceptor sites gave the single Michael addition product **3l** in 8% ee (entry 12). We concluded that nitroalkenes constitute the best electrophiles to obtain high enantioselective Michael additions.

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 comparing to that shown in Table 2.

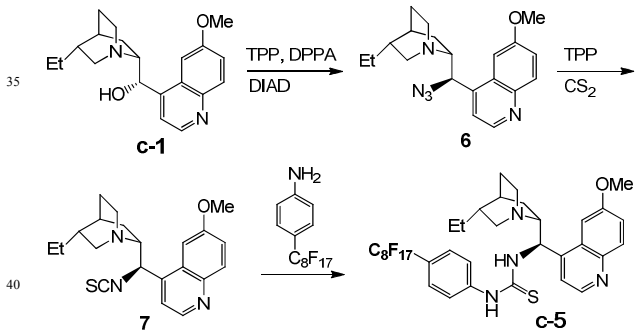
Table 3 One-pot fluorination and Michael addition with maleimides[a]



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 condition: 0.1 mmol of β-ketoester and 0.1 mmol of Selectfluor™ with 20 mol% of **c-5** in 1:1 CH_3CN/CH_2Cl_2 at 25 °C for 24 h, then add 0.1 mmol of 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 ^{1}H NMR.

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.



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

In summary, the fluorous bifunctional cinchona alkaloid-thiourea organocatalysts **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 can be readily applied to other asymmetric transformations such as Henry, Friedel-Crafts, Diels-Alder, and Morita-Baylis-Hillman reactions.[22]

This paper is dedicated to Professor Dennis P. Curran on the occasion of his 60th birthday. We thank the University of Massachusetts Boston, Centre for Green Chemistry for the support of this project. W.Y. acknowledges financial support from NUST Research Funding (2011ZDJH07), Jiangsu Provincial Natural Science Foundation of China for Key Projects (BK2010070), and National Natural Science Foundation of China (20902047).

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