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Recyclable cinchona alkaloid catalyzed asymmetric Michael addition reaction

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ABSTRACT

A highly enantioselective and diastereoselective Michael addition reaction of α-fluoro-β-ketoesters with maleimides is catalyzed by fluorous cinchona alkaloid to afford two adjacent chiral centers. The catalyst attached with a perfluoroalkyl tag can be recovered by fluorous solid-phase extraction (F-SPE).

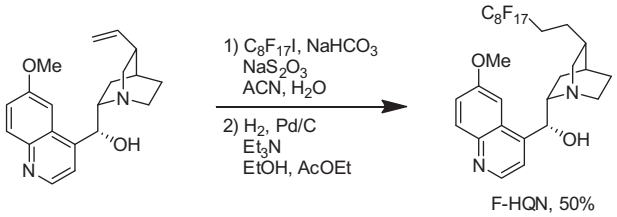
Introduction

Organocatalysis is becoming an increasingly important tool for asymmetric synthesis.[1] Compared to metal catalysis, organocatalysis has advantages of being free from toxic heavy metal, mild reaction condition, and easy structure modification. However, high catalyst loading (up to 20 mol %) and difficulty for catalyst recovery are the major drawbacks of organocatalysis,[2] which make organocatalyst recycling highly desirable. A great deal of attention has been focused on the development of supported organocatalysts with polymers,[3] ionic liquids,[4] and fluorous tags.[5] The perfluorinated alkyl chain-attached catalyst can be easily recovered by fluorous solid-phase extraction (F-SPE)[6] or by precipitation with fluorophobic solvents such as hexane and water. Since the first fluorous catalyst was reported in 2001,[7] many new fluorous organocatalysts have been developed and successfully applied in a range of asymmetric transformations.[5,8]

Because of strong carbon–fluorine bond, small covalent radius, and high electronegativity, fluorinated organic molecules could generate significant influence on reactivity, metabolic stability, and bioavailability of the compounds.[9,10] Organofluorine compounds have been developed as pharmaceutical and agricultural products such as fluoxetine (antidepressant),[11] atorvastatin (cholesterol-reducer),[12] and ciprofloxacin (antibacterial).[13] There is a strong demand for the development of new fluorine-containing building blocks.

The construction of chiral quaternary carbons is a challenging task in organic synthesis.[14] Creation of fluorinated chiral quaternary carbon center is even more difficult and only a handful of examples which mainly rely on metal catalysis can be found in the literature.[15] Introduced in this Letter is a cinchona alkaloid-based recyclable organocatalyst for asymmetric Michael addition. Reactions of α-fluoro-β-ketoesters with maleimides afford Michael addition product with a fluorine-containing chiral quaternary carbon adjacent to another chiral carbon.[16]

The synthesis of fluorous hydroquinine (F-HQN) was accomplished by a radical addition of perfluoroalkyliodide to quinine followed by the reduction of iodide by hydrogenation (Scheme 1).[7a] The screening of organocatalysts was carried out using ethyl 2-fluoro-3-oxo-3-phenylpropanoate and *N*-ethyl maleimide as substrates. In addition to F-HQN, other cinchona alkaloids, proline, and related organocatalysts were also evaluated (Table 1). Compared to free quinine, F-HQN has almost the same yield and enantioselectivity which means the fluorous tag has a minimal impact on



Scheme 1. Synthesis of F-HQN.

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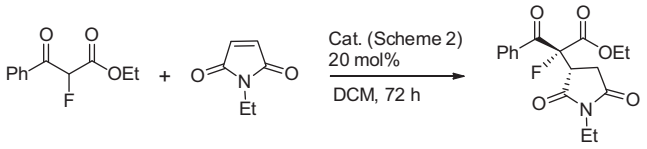
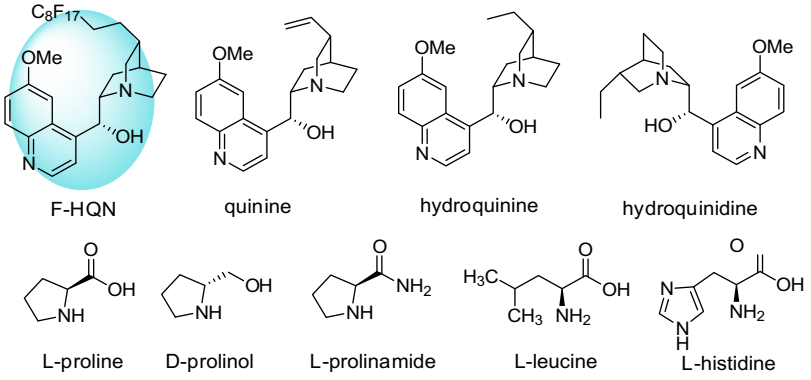
Table 1
Catalyst screening for the Michael addition reaction



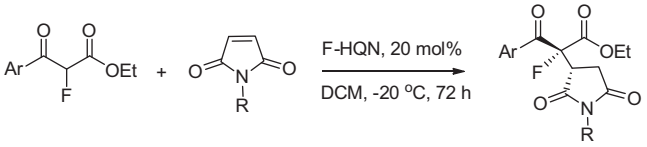
Entry	Cat.	T (°C)	Yield[a] (%)	dr[b]	ee[c] (%)
1	F-HQN	25	93	>20:1	77
2	Quinine	25	94	>20:1	80
3	Hydroquinine	25	50	>20:1	77
4	Hydroquinidine	25	95	>20:1	−85
5	L-Proline	25	—	—	—
6	D-Prolinol	25	—	—	—
7	L-Prolinamide	25	10	>20:1	19
8	L-Leucine	25	—	—	—
9	L-Histidine	25	—	—	—
10	F-HQN	0	92	>20:1	77
11	F-HQN	−10	88	>20:1	82
12	F-HQN	−20	85	>20:1	87

[a] Yield of isolated product.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.



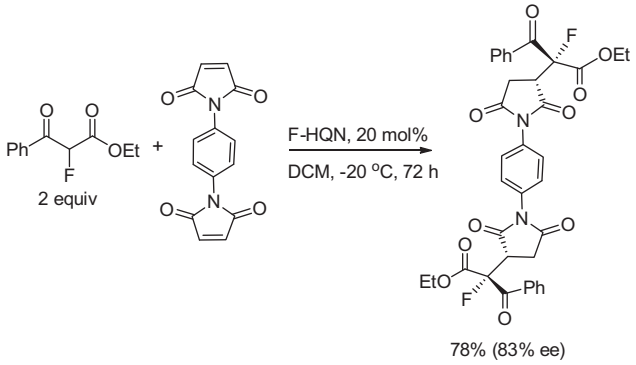
Scheme 2. Structures of screened catalysts.

Table 2
Scope of the Michael addition reaction

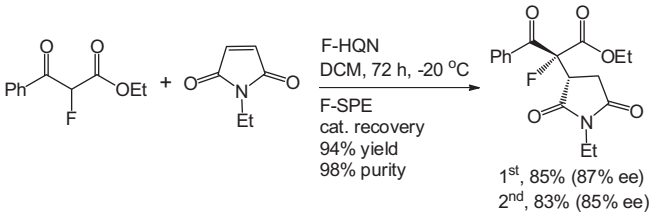


Entry	Ar	R	Yield (%)	dr[b]	ee[c] (%)
1	C_6H_5	Et	93	>20:1	82
2	C_6H_5	Me	98	>20:1	83
3	C_6H_5	Bn	90	>20:1	87
4	C_6H_5	Ph	75	>20:1	73
5	4-$NO_2C_6H_4$	Et	92	>20:1	80
6	4-$NO_2C_6H_4$	Ph	90	>20:1	75
7	4-$NO_2C_6H_4$	Bn	95	>20:1	85
8	4-ClC_6H_4	Me	90	>20:1	83
9	4-MeC_6H_4	Et	92	>20:1	84
10	4-MeC_6H_4	Bn	88	>20:1	85

[a] Yield of isolated product.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.



Scheme 3. Reaction of (1,4-phenylene)dimaleimide.



Scheme 4. Recovery of F-HQN.

the catalyst (entries 1 and 2). Hydroquinine (entry 3) gave the lowest yield among the four cinchona alkaloids. If L-proline or D-prolinol (entries 5 and 6) were used as the catalyst, the target product cannot be detected, but L-prolinamide gave 10% yield and 19% ee. Just like L-proline and D-prolinol, L-leucine and L-histidine (entries 8 and 9) did not give the desired product (Scheme 2). Accordingly, F-HQN was selected as the catalyst for further optimization. It was found that lower temperature (−20 °C) afforded relatively higher enantioselectivity (entry 12).

With the optimized reaction condition in hand, we turned our attention to explore the generality of the Michael addition reaction. As showed in Table 2, the F-HQN catalyzed reaction afforded adducts with excellent yield (up to 98%), enantioselectivity (up to 87%), and diastereoselectivity (>20:1) to afford two new adjacent stereogenic centers including the fluorinated quaternary carbon.[17] N-alkylated maleimides with methyl, ethyl, and benzyl could be tolerated. Moreover, *N*,*N*′-(1,4-phenylene)dimaleimide was also found to be a good substrate to give double Michael addition product in 78% yield and 83% ee (Scheme 3). The substitute groups on the aromatic rings of α-fluoro-β-ketoesters have a limited influence on the outcome of the products. Electron-withdrawing (entries 5–8), electron-donating (entries 9–10), and electron-neutral substrates (entries 1–4) all gave excellent results.

The efficiency of catalyst recovery was tested (Scheme 4). Upon the completion of reaction, a base was added to the reaction mixture. The organic phase was loaded onto a fluorous silica gel cartridge for F-SPE. It was found F-HQN was recovered in high yield (94%) and excellent purity (98%). The second-round reaction using the recovered catalyst gave similar product yield and ee.

In conclusion, we have developed a highly enantioselective and diastereoselective Michael addition reaction of α-fluoro-β-ketoesters with maleimides to afford products with a fluorinated quaternary carbon adjacent to another chiral carbon. This process is efficiently catalyzed by a recyclable fluorous cinchona alkaloid which can be recovered through F-SPE with high yield and purity.

Supplementary data

Supplementary data (reaction procedures and spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.094.

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