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A recyclable fluororous organocatalyst for Diels-Alder reactions

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Abstract

Chiral fluororous imidazolidinone catalyst **2** provides consistently high enantioselectivities in Diels-Alder reactions of dienes and α , β -unsaturated aldehydes. The catalyst can be readily separated from the reaction products by fluororous solid-phase extraction, and recovered in excellent purity for direct reuse.

Over the past decade, much interest has been devoted to the development of highly efficient organocatalysts for a variety of reactions, and the pace of growth in this field of chemistry has been breathtaking.^{1–3} However, the need for high loading and separation of the organocatalyst from the product are still the issues need to be addressed in this area.^{4,5}

Fluororous organocatalysts are of high interest because they are soluble in common reaction solvents, yet they can be easily separated from the reaction mixture for subsequent reuse.^{6,7} Recently, enantioselective Michael additions have been achieved with fluororous pyrrolidine derivatives as recyclable catalysts.⁸

Chiral imidazolidinone **1** (Scheme 1) is a well-known enantioselective catalyst for many different chemical transformations^{2c} such as Diels-Alder,^{9a,9b} Michael addition,^{10a} 1,3-dipolar addition,^{10b} and Friedel-Crafts alkylation reactions.^{10c} Although polymer-supported chiral imidazolidinones have been known for several years,^{11,12} there is no reported fluororous variant to date. Described in this paper is a recyclable fluororous imidazolidinone organocatalyst which has comparable yields and enantioselectivities to the standard organocatalyst. It can be recovered by fluororous solid-phase extraction (F-SPE)⁶ and has significant better yield and purity than that of standard catalyst recovered by acid-base extraction.

The only structural difference between the fluororous catalyst **2** and the original imidazolidinone **1** is that the fluororous tag¹³ (p -C₈F₁₇CH₂CH₂-C₆H₄-) is attached to the *N*-methyl group. Since the single fluororous tag is away from the functional group for catalysis,⁹ it was hypothesized that this design would not affect the activity of the catalyst.

A simple three-step synthesis for the fluororous chiral imidazolidinone **2** is shown in Scheme 2.¹⁴ *N*-Fmoc-amide **3** was obtained by an amide coupling reaction of Fmoc-Phe-OH with a fluororous amine. Subsequent de-protection with piperidine gave aminoamide **4**. Treatment of **4** with excess amount of acetone in DMF with microwave irradiation gave the fluororous

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organocatalyst **2**. The overall yield of the three-step synthesis was 66%. Fluorous compound **2** is a stable white solid, and it was kept on bench for weeks without sign of decomposition.

A typical Diels-Alder reaction of acrolein and cyclohexadiene was conducted using either standard imidazolidinone **1** or its fluorous variant **2** as the catalyst (Table 1). We first carried out the Diels-Alder reaction with the normal imidazolidinone catalyst by following the literature procedures.⁹ Acrolein (100 μ L, 1.5 mmole) and cyclohexadiene (48 μ L, 0.5 mmole) were added into a solution of **1**-HCl salt (14 mg, 0.05 mmole) with 2 mL CH₃CN-H₂O (95:5, v:v). The mixture was stirred for 40 h at 25 °C. An acid-base extraction was utilized to separate the product and recover the organocatalyst.¹⁵ Thus, a 0.05M HCl aqueous solution was added to the reaction mixture. The solution was extracted with diethyl ether three times. The organic phases were combined, washed with aqueous NaHCO₃, dried and concentrated to give the product **5**. The acidic phase was neutralized and extracted with diethyl ether to provide 7.8 mg (65%) of recovered **1**. Although the product yield (82%) and ee (88.4%) were comparable to the reported data,⁹ the recovery of the organocatalyst **1** under the procedures described above was moderate and its purity was only 74% (Table 1, Entry 1). This purity is not sufficient for direct reuse of the recovered catalyst. Moreover, for some reactants (*e.g.* substance with -OH), the acid-base extraction approach might disturb the functional group in the final product.

The fluorous imidazolidinone **2** catalyzed reactions were then performed with wet solvents and under aerobic atmosphere, same to the reaction conditions described above without much effort of modification.¹⁶ After the reaction mixture was stirred for 40 h at room temperature, 0.1 g of MP-carbonate was added and the mixture was shaken for 30 min to free the amine **2**. After filtration, the solution was concentrated and then loaded onto a 0.5 g endcapped FluoroFlash[®] silica gel cartridge for F-SPE.¹⁴ The cartridge was first eluted with CH₃CN-H₂O (65:35) for product **5**, then with THF containing 1% Et₃N for fluorous catalyst **2**. Concentration of the THF fraction gave the fluorous catalyst **2** in good recovery (84%) and excellent purity (99%). The purity was assessed by GC and ¹H NMR analyses (Figure 1). The chiral GC of the major *Endo* products from both organic catalyst **1** and fluorous catalyst **2** are shown in Figure 2. While the yields, *endo:exo* ratios and high enantioselectivities of the product were comparable to those of the control experiment showing the similar catalytic activity of the two catalysts, the recovery of the fluorous catalyst **2** is much more efficient and its purity was good enough for direct reuse (Table 1, Entries 1 and 2).

To probe the scope of both diene and dienophile (α , β -unsaturated aldehydes) as the reaction components for the fluorous reactions and separations, four other Diels-Alder reactions were conducted (Table 2).¹⁶ We found that variation on olefin substituents did not decrease in yield, *endo:exo* ratios and enantioselectivity (Table 2, Entry 1, Me; Entry 4, Pr) comparing to the control experiments using standard imidazolidinone **1** (Table 2, Entry 2, M.; Entry 5, Pr). Meanwhile, similar stereoselectivity and yield were achieved using the recovered fluorous

organocatalyst **2** (Table 2, Entry 1, and Entry 3 with recovered **2**). The result confirms the quality of recovered fluororous imidazolidinone catalyst. Furthermore, the [4+2] cycloaddition between acrolein and two acyclic dienes also gave high yields and enantioselectivities (Table 2, Entries 6 and 7). Thus, the generality of the fluororous imidazolidinone **2** as an efficient recyclable organo-catalyst for Diels-Alder reactions has been clearly demonstrated

In addition, a Diels-Alder reaction between acrolein and cyclohexadiene with fluororous organocatalyst **2** was also carried out at gram scale (Table 2, Entry 8).¹⁶ The consistent results between the small scale reactions shown in Table 1 and the gram scale reaction is a good indicator that fluororous catalyst has good potential for scale up reactions.

In summary, a simple procedure for preparation of a chiral fluororous imidazolidinone catalyst **2** was developed. While the fluororous organocatalyst **2** provides consistently high enantioselectivities in Diels-Alder reactions of dienes and α,β -unsaturated aldehydes, the fluororous catalyst can readily be recovered from the reaction mixture by F-SPE with excellent purity. The recovered fluororous organocatalyst is ready for reuse.

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14. General procedure for the synthesis of fluororous chiral imidazolidinone **2**: (1) Amide coupling: A mixture of F-benzylamine (2.9 g, 5 mmole), Fmoc-amino acid (2.1 g, 5.5 mmole), HOBT (0.7 g, 5.5 mmole), DIC (0.65 g, 5.5 mmole) in 15 mL of CH₂Cl₂ was stirred at 25 °C for 1 h. The reaction mixture was concentrated, mixed with H₂O, and extracted with AcOEt. The organic layer was washed with aqueous NaHCO₃ and concentrated to give 4.5 g (98% yield) of **3**. This product was analyzed by LCMS: $m/z = 923$ [M+H]⁺. (2) Fmoc deprotection: Compound **3** (2.3 g, 2.5 mmol) in 20 mL of 1:4 piperidine/DMF was stirred at 25 °C for 1 h. The concentrated reaction mixture was mixed with 50 mL of H₂O, extracted with ether. Concentrated organic residue was triturated with hexanes to give desired product **4** as a white solid (1.4 g, 80%). This product was analyzed by GC; LCMS: $m/z = 701$ [M+H]⁺; ¹H NMR (270 MHz, CDCl₃): δ = 7.63 (m, 1H), 7.25 (m, 8H), 4.45 (d, 2H), 3.67 (dd, 1H), 3.32 (dd, 1H), 2.91 (m, 2H), 2.75 (m, 1H), 2.32 (m, 2H) and 1.50 (br, 3H); ¹³C NMR (270 MHz, CDCl₃): δ = 26.13, 32.99, 41.58, 42.81, 56.51, 102–125 (m, CF₂, CF₃) 126.91, 128.27, 128.65, 128.80, 129.41, 136.98, 137.91, 138.35, 174.20. (3) Cycloaddition: Compound **4** (0.5 g, 0.7 mmol) and 1.0 mL of acetone in 1.5 mL of DMF was irradiated under a single-mode microwave reactor at 250 w, 150 °C for 30 min. The reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography with hex:EtOAc (1:1) and then 100% EtOAc to give 0.44 g (85% yield) of **2** as a white solid. The product **2** was analyzed by GC; LCMS and HRMS: $m/z = 741.1710$ [M+H]⁺ (100%, calc. mass 741.1774), 594.1 [C₈F₁₇CH₂CH₂C₆H₅CH₂N=C(CH₃)₂]⁺ (24%); ¹H NMR (270 MHz, CDCl₃): δ = 7.30 (m, 5H), 7.12 (m, 4H), 4.65 (d, 1H), 4.08 (d, 1H), 3.89 (t, 1H), 3.17 (m, 2H), 2.88 (m, 2H), 2.34 (m, 2H) 1.71 (br, 1H) 1.22 (s, 3H) and 1.00 (s, 3H); ¹³C NMR (270 MHz, CDCl₃): δ = 26.09, 27.91, 32.85, 36.48, 43.24, 58.82, 104–125 (m, CF₂, CF₃) 126.91, 127.80, 128.29, 128.59, 129.90, 136.46, 136.64, 138.05, 174.16.
15. General procedure for the control experiments and the acid-base extraction: To a solution of **1**-HCl salt (14 mg, 0.05 mmole) with 2 mL CH₃CN-H₂O (95:5, v:v), acrolein (100 μL, 1.5 mmole) and cyclohexadiene (48 μL, 0.5 mmole) were added. The solution was stirred for 40 h at 25 °C. Then, 5 mL 0.05M HCl aqueous solution was added to the reaction mixture. The solution was extracted with 4 mL diethyl ether three times. The organic phases were combined, washed with aqueous NaHCO₃, dried over Na₂SO₄ and concentrated to give the product. The acidic phase was neutralized with aqueous NaHCO₃ and extracted with 4 mL diethyl ether three times. The combined ethyl ester layer was dried over Na₂SO₄. Free catalyst **1** (7.8 mg, 65%) was obtained from concentration of the ester layer with a purity of 74%.
16. General procedure for imidazolidinone-catalyzed Diels-Alder reaction: To a solution of **2** (37 mg, 0.05 mmole) and HCl (0.05 mmole) in 2 mL CH₃CN-H₂O (95:5, v:v), acrolein (100 μL, 1.5 mmole), and cyclohexadiene (48 μL, 0.5 mmole) was added. The solution was stirred for 40 h at 25 °C. Then, 0.1 g of MP-carbonate was added and the mixture was shaken for 0.5 h to free the amine **2**. After filtration, the solution was concentrated and then loaded onto a 0.5 g FluoroFlash[®] silica gel cartridge for F-SPE. It was first eluted with 4 mL CH₃CN-H₂O (65:35, v:v) to get the product **5**. After that, 4 mL THF with 1% Et₃N was used to elute the fluororous catalyst **2** out of the cartridge. Concentrated the THF fraction gave the fluororous catalyst **2** (31 mg) as a white solid in good recovery (84%), and excellent purity (99%). In case of the reactions with cyclopentadiene, 1.5 mmole diene and 0.5 mmole acrolein derivative was used. For the gram scale reaction, 555 mg (0.75 mmole) **1**, 1.5 mL acrolein (22 mmole), and 0.75 mL cyclohexadiene (7.5 mmole) were used, and the F-SPE was employed with a 10 g endcapped FluoroFlash[®] silica gel cartridge.

Figure 1.
 ^1H NMR spectrum of the fluorous chiral imidazolidinone **2** after recovery by F-SPE.

Figure 2. Chiral GC (Bodman Chiraldex Γ -TA column, 90 °C, 23 psi) chromatograms of the Diels-Alder products. Left: from organic imidazolidinone **1**; Right: from fluorous imidazolidinone **2**.

Scheme 1.

The chiral imidazolidinone **1** and its fluororous variant **2**.

Table 1

The Diels-Alder reaction of acrolein and cyclohexadiene catalyzed by either the organic imidazolidinone **1** or its fluororous variant **2**.

Entry	Catalyst	Yield (%)	5-Endo:Exo	ee% of 5-Endo ^a	Recovery of catalyst (%)	Purity of recovered catalyst ^b (%)
1	1	82	90.3 : 9.7	88.4	65 ^c	74
2	2	86	93.4 : 6.6	93.4	84 ^d	99

^a Determined by GC with Bodman Chiraldex Γ-TA column;

^b Determined by GC;

^c Recovered by acid-base extraction;

^d Recovered by F-SPE.

Table 2

Diels-Alder reactions of different dienophiles and dienes catalyzed by the chiral fluororous imidazolidinone **2** as well as two control experiments catalyzed by the standard organocatalyst **1**.

Entry	Diene	Dienophile	Catalyst	endo	exo	Product (s)	Yield (%)	Endo:Exo	ee% of Endo (Exo) ^a	Recovery of catalyst 2 ^b (%)	Purity of recovered catalyst ^c (%)
1			2				80	46:54	91.6 (81.6)	81	97
2			1				80 ^d	46:54	92.6 (80.0)	NA	NA
3			Recovered 2				78 ^e	46:54	91.2 (81.4)	80	97
4			2				89	47:53	93.0 (79.1)	81	98
5			1				86 ^d	47:53	93.0 (75.4)	NA	NA
6			2				78	NA	92.6	80	98
7			2				85	NA	88.5	82	98
8			2				83 ^f	92.1:7.8	92.2	86	97

^aDetermined by GC with Bodman Chiraldex Γ-TA column;

^bRecovered by F-SPE;

^cDetermined by GC;

^dControl reaction catalyzed by standard catalyst **1**;

^eReaction catalyzed by recovered fluororous catalyst **2**;

^fGram scale reaction.