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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9287–9290

A recyclable fluorous organocatalyst for Diels–Alder reactions

Qianli Chu,[a] Wei Zhang[a,*] and Dennis P. Curran[b]

[a]*Fluorous Technologies, Inc., University of Pittsburgh Applied Research Center, 970 William Pitt Way, Pittsburgh, PA 15238, United States*
[b]*Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, United States*

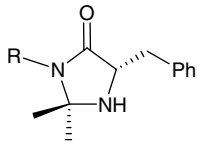
Received 25 September 2006; revised 17 October 2006; accepted 20 October 2006
Available online 13 November 2006

Abstract—Chiral fluorous 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 fluorous 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 that need to be addressed in this area.[4,5]

Fluorous 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 fluorous 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,b] 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 fluorous variant to date.



1. R = -CH_3

2. R = -$CH_2C_6H_4$-*p*-$CH_2CH_2C_8F_{17}$

Scheme 1. The chiral imidazolidinone **1** and its fluorous variant **2**.

* Corresponding author. Tel.: +1 412 826 3062; fax: +1 412 826 3053; e-mail: w.zhang@fluorous.com

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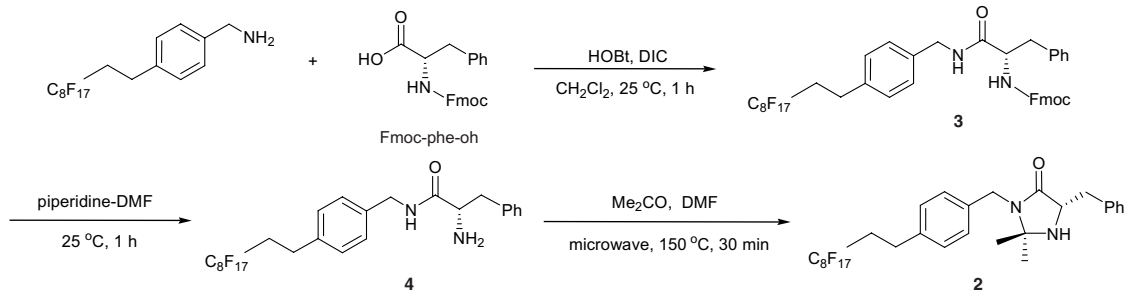
doi:10.1016/j.tetlet.2006.10.101

Described in this paper is a recyclable fluorous imidazolidinone organocatalyst which has comparable yields and enantioselectivities to the standard organocatalyst. It can be recovered by fluorous solid-phase extraction (F-SPE)[6e] and has significantly better recovery yield and purity than that of the standard catalyst recovered by acid–base extraction.

The only structural difference between the fluorous catalyst **2** and the original imidazolidinone **1** is that the fluorous tag[13] (*p*-$C_8F_{17}CH_2CH_2$–C_6H_4–) is attached to the *N*-methyl group. Since the single fluorous tag is away from the functional group for catalysis,[9] it was hypothesized that this design would not affect the activity of the catalyst.

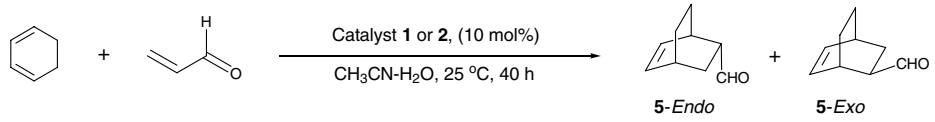
A simple three-step synthesis for the fluorous chiral imidazolidinone **2** is shown in Scheme 2.[14] *N*-Fmoc-amide **3** was obtained by an amide coupling reaction of Fmoc-Phe-OH with a fluorous amine. Subsequent de-protection with piperidine gave aminoamide **4**. Treatment of **4** with excess amount of acetone in DMF with microwave irradiation gave the fluorous 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 any 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 following the



Scheme 2. Synthesis of the fluorous chiral imidazolidinone **2**.

Table 1. The Diels–Alder reaction of acrolein and cyclohexadiene catalyzed by either the organic imidazolidinone **1** or its fluorous 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.

literature procedures.[9] Acrolein (100 μL, 1.5 mmol) and cyclohexadiene (48 μL, 0.5 mmol) were added into a solution of **1**·HCl salt (14 mg, 0.05 mmol) with 2 mL CH_3CN–H_2O (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 0.05 M 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 $NaHCO_3$, 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% (Table1, 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, similar 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 Fluoro*Flash*® silica gel cartridge for F-SPE.[14] The cartridge was first eluted with CH_3CN–H_2O (65:35) for product **5**, then with THF containing 1% Et_3N 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 ^{1}H NMR analyses (Fig. 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

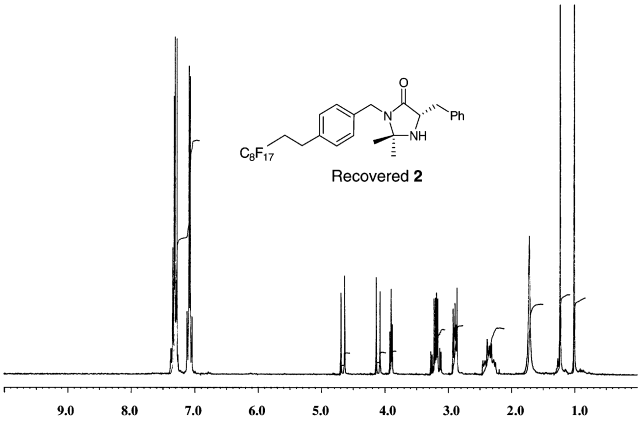


Figure 1. ^{1}H NMR spectrum of the fluorous chiral imidazolidinone **2** after recovery by F-SPE.

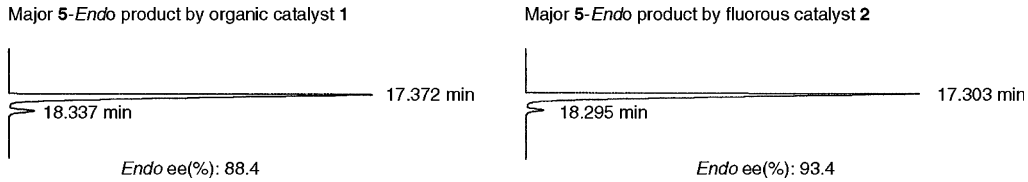


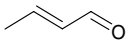
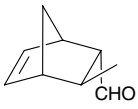
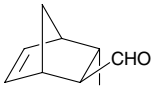
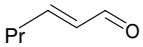
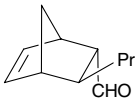
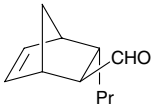
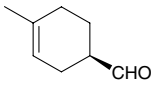
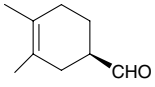
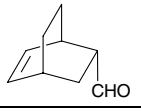
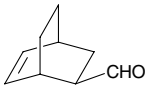
Figure 2. Chiral GC (Bodman Chiraldex Γ-TA column, 90 °C, 23 psi) chromatograms of the Diels–Alder products. Left: from organic imidazolidinone **1**; Right: from fluorous imidazolidinone **2**.

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) compared 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 fluorous 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 fluorous 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 fluorous 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 fluorous catalyst has good potential for scale up reactions.

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

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

Entry	Diene	Dienophile	Catalyst	Product (s)		Yield (%)	*endo*:*exo*	ee% of *endo* (*exo*)[a]	Recovery of catalyst **2**[b] (%)	Purity of recovered catalyst[c] (%)
				endo	*exo*					
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

[a] Determined by GC with Bodman Chiraldex Γ-TA column.
[b] Recovered by F-SPE.
[c] Determined by GC.
[d] Control reaction catalyzed by standard catalyst **1**.
[e] Reaction catalyzed by recovered fluorous catalyst **2**.
[f] Gram scale reaction.

Acknowledgement

This work was supported by the National Institute of General Medical Sciences SBIR Grants (2R44GM062717-02 and 2R44GM067326-02).

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13. www.fluorous.com. Professor Dennis P. Curran owns an equity interest in Fluorous Technologies, Inc.
14. General procedure for the synthesis of fluorous chiral imidazolidinone **2**: (1) Amide coupling: A mixture of F-benzylamine (2.9 g, 5 mmol), Fmoc-amino acid (2.1 g, 5.5 mmol), HOBT (0.7 g, 5.5 mmol), DIC (0.65 g, 5.5 mmol) in 15 mL of CH_2Cl_2 was stirred at 25 °C for 1 h. The reaction mixture was concentrated, mixed with H_2O, and extracted with AcOEt. The organic layer was washed with aqueous $NaHCO_3$ 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 H_2O, 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, $CDCl_3$): $\delta = 7.63$ (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); ^{13}C NMR: (270 MHz, $CDCl_3$): $\delta = 26.13$, 32.99, 41.58, 42.81, 56.51, 102–125 (m, CF_2, CF_3) 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%, calcd mass 741.1774), 594.1 $[C_8F_{17}CH_2CH_2C_6H_5CH_2N{=}C(CH_3)_2]^+$ (24%); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.30$ (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); ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 26.09$, 27.91, 32.85, 36.48, 43.24, 58.82, 104–125 (m, CF_2, CF_3) 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 mmol) with 2 mL CH_3CN–H_2O (95:5, v:v), acrolein (100 μL, 1.5 mmol) and cyclohexadiene (48 μL, 0.5 mmol) were added. The solution was stirred for 40 h at 25 °C. Then, 5 mL 0.05 M 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 $NaHCO_3$, dried over Na_2SO_4 and concentrated to give the product. The acidic phase was neutralized with aqueous $NaHCO_3$ and extracted with 4 mL diethyl ether three times. The combined ethyl ester layer was dried over Na_2SO_4. 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 mmol) and HCl (0.05 mmol) in 2 mL CH_3CN–H_2O (95:5, v:v), acrolein (100 μL, 1.5 mmol) and cyclohexadiene (48 μL, 0.5 mmol) were 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 Fluoro*Flash*® silica gel cartridge for F-SPE. It was first eluted with 4 mL CH_3CN–H_2O (65:35, v:v) to get the product **5**. After that, 4 mL THF with 1% Et_3N was used to elute the fluorous catalyst **2** out of the cartridge. The concentrated THF fraction gave the fluorous catalyst **2** (31 mg) as a white solid in good recovery (84%) and excellent purity (99%). In case of the reactions with cyclopentdiene, 1.5 mmol diene and 0.5 mmol acrolein derivative were used. For the gram scale reaction, 555 mg (0.75 mmol) **1**, 1.5 mL acrolein (22 mmol) and 0.75 mL cyclohexadiene (7.5 mmol) were used, and the F-SPE was conducted on a 10 g endcapped Fluoro*Flash*® silica gel cartridge.