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Enantioselective α -Chlorination of Aldehydes with Recyclable Fluorous (*S*)-Pyrrolidine-Thiourea Bifunctional Organocatalyst

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Abstract

A novel fluorous (*S*)-pyrrolidine-thiourea bifunctional organocatalyst is prepared. The catalyst shows good activity and enantioselectivity for direct α -chlorination of aldehydes using *N*-chlorosuccinimide (NCS) as the chlorine source. It can be recovered from the reaction mixture by fluorous solid-phase extraction with excellent purity for direct reuse.

Keywords

bifunctional organocatalyst; fluorous catalyst; fluorous solid-phase extraction; α -chlorination; *N*-chlorosuccinimide (NCS)

Currently, there is much interest in organocatalysts due to low toxicity, operational simplicity, efficiency and good stereoselectivity compared to traditional metal-based catalysts.¹ However, the need for high catalyst loading (up to 20 mol%) and difficult to recover the catalyst are still the issues to be addressed. Recyclable organocatalysts such as solid-supported catalysts have been developed,² the activity may be effected due to the heterogeneous catalysis environment.

Recently, fluorous organocatalysts have emerged as attractive tools in asymmetric reactions and have showed high enantioselectivity and recyclability in Michael addition reaction,³ Diels-Alder reaction⁴ as well as Adol reaction.⁵ Compared to recyclable heterogeneous organocatalysts, the fluorous organocatalysts are soluble in common reaction solvents, yet they can be easily separated and recovered from the reaction mixture by fluorous solid-phase extraction (F-SPE).

Asymmetric chlorination is an important reaction because the chlorinated products are versatile synthetic intermediates in medicinal chemistry and material science.⁶ Optically active α -chlorocarbonyls can be easily converted to various chiral building blocks.⁷ In 2004, the enantioselective direct α -chlorination of unbranched aldehydes was independently reported by Jørgensen group⁸ and MacMillan group⁹ utilizing chiral secondary amine catalysts.

The use of hydrogen bonding interactions has become a popular approach in recent years. In particular, thiourea-based bifunctional organocatalysts have found a board scope of applications.^{10,11} To the best of our knowledge, there is no literature describing the direct asymmetric α -chlorination of aldehydes with a thiourea-based bifunctional organocatalyst. According to the mechanism of the secondary amine-catalyzed asymmetric reactions and fluororous chemistry, we believe that a fluororous bifunctional catalyst **1** containing a secondary amine and a thiourea should be able to activate and facilitate the reaction process (Figure 1). Moreover, the strong electron-withdrawing effect of the fluororous tag in the *para* position enhances the acidity of the NH proton of the thiourea and thus provides a stronger hydrogen-bonding interaction with the substrate. The fluororous tag can provide a handle for the catalyst recovery using F-SPE technique. Herein we wish to report the preparation of a novel recyclable fluororous (*S*)-pyrrolidine-thiourea bifunctional organocatalyst **1** and its application in direct α -chlorination of aldehydes using NCS as the chlorine source.

The *N*-Boc fluororous (*S*)-pyrrolidine-thiourea catalyst **1** was prepared via the condensation of 4-(perfluorooctyl)aniline **2** with phenyl chlorothioformate **3** followed by the substitution of phenol by (*S*)-*tert*-butyl 2-(aminomethyl) pyrrolidine-1-carboxylate **4**¹² following Berkessel's method.¹³ Subsequent de-Boc in TFA/CH₂Cl₂ at 25°C afforded the catalyst **1** as yellow solid in 55% yield (Scheme 1).

We first carried out a model reaction involving hydrocinnamaldehyde, NCS, and fluororous bifunctional catalyst **1** to optimize the reaction condition. As seen from Table 1, the solvent had a pronounced effect on both yield and ee (entries 1–5). Excellent yields were obtained when employing CH₂Cl₂, CHCl₃ or DCE as a solvent, while the best ee (85%) was found in CH₂Cl₂. THF was less efficient, affording the product in 29% ee. To our surprise, acetalization of aldehyde was found to be very quick (< 1 min) when the reaction was conducted in methanol. This may be due to the *in situ* formation of HCl from NCS, which was accelerated by thiourea part of the catalyst.¹⁴ The effect of catalyst loading was also evaluated. In the absence of catalyst, trace yield was obtained after 24 h. When 5 mol% of catalyst was used, the reaction was accelerated and afforded the product in 71% yield and 85% ee, while 10 mol% of catalyst was found to be most efficient. Other secondary amine catalysts such as *L*-proline and *L*-prolinamide were also utilized for the same reaction. Both catalysts promoted the reaction effectively, but lower ee values, 18 and 76%, were obtained respectively. In order to prove whether the thiourea part in the catalyst can facilitate the reaction, the reaction was conducted using thiourea as catalyst. The result indicated that thiourea could promote the reaction to provide the product in 52% yield after 12 h (entry 10).

To demonstrate the scope of the reaction, a series of aldehydes were used for chlorination reactions. As revealed in Table 2, all the reactions proceeded efficiently to furnish the products in excellent yields (91–99%) and good enantioselectivities (85–95% ee). In all cases the reaction was found to proceed cleanly and no other byproducts such as dichlorosubstituted aldehydes were formed.

Finally, we performed the catalyst recovery experiment using 0.5 mmol of aldehyde and 33 mg of catalyst **1** (Scheme 2). After completion of the reaction, the mixture was concentrated and then loaded onto a FluoroFlash[®] silica gel cartridge for F-SPE.¹⁵ It was found that the catalyst could be recovered in high yield (87%) with excellent purity (99%). The second round reaction using the recovered catalyst gave similar product yield and ee. Moreover, the fluororous catalyst is stable and can be stored at room temperature for months without any sign of decomposition.

In summary, a new fluororous (*S*)-pyrrolidine-thiourea bifunctional organocatalyst has been developed. The catalyst shows high activity and enantioselectivity in asymmetric α -chlorination of aldehydes using inexpensive NCS as a chlorination reagent. Also, the catalyst can be easily recovered by F-SPE with a good yield and high purity. Application of this catalyst for other asymmetric reactions are under investigation and will be reported in due course.

General procedure for the fluororous (*S*)-pyrrolidine-thiourea bifunctional organocatalyst

Phenyl chlorothioformate **3** (276 μ L, 345 mg, 2 mmol) was added to a solution of 4-(heptadecafluorooctyl)aniline **2** (1.022 g, 2 mmol) and pyridine (178 μ L, 174 mg, 2.2 mmol) in CH_2Cl_2 (10 mL) at 25°C. The mixture was stirred for 2 h, then added slowly to a solution of (*S*)-tert-butyl 2-(aminomethyl) pyrrolidine-1-carboxylate **4** (400.4 mg, 2 mmol) in CH_2Cl_2 (2 mL). *N,N*-Diisopropylethylamine (331 μ L, 259 mg, 2 mmol) was then added and the mixture was stirred for 30 min. Sat. aq. NaHCO_3 (20 mL) was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by flash chromatography (5:1 EtOAc/hexane) to give the *N*-Boc-derivative **5** as white amorphous solid (0.873 g, 58%).

The *N*-Boc-derivative **5** (0.873 g, 1.16 mmol) was dissolved in a mixture of 1:1 trifluoroacetic acid and dichloromethane (10 mL, v/v) and the solution was stirred for 2 h at 25 °C. The pH was adjusted to 8 with aqueous NaHCO_3 and the mixture was extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organic layers were dried over Na_2SO_4 . Concentrated and purified by column chromatography (7:1 MeOH/EtOAc) to give pyrrolidine-thiourea organocatalyst **1** as a light yellow solid (0.719 g, 95%); mp. 117–119 °C; $[\alpha]_{\text{D}}^{20} = +14.0$ (c = 0.865, CHCl_3); IR (neat): 3424.47, 3020.70, 1641.00, 1215.92, 1151.53, 742.08 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD) δ 7.72–7.69 (d, $J = 9$ Hz, 2H), 7.57–7.54 (d, $J = 9$ Hz, 2H), 3.68–3.50 (m, 2H), 3.48–3.41 (m, 1H), 2.94–2.92 (m, 2H), 2.00–1.71 (m, 3H), 1.58–1.46 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ = 182.84, 143.97, 132.37, 128.74, 127.29, 122.35–106.56 (m, CF_2, CF_3), 62.23, 47.31, 47.15, 30.38, 26.45; ^{19}F NMR (282.4 MHz, CD_3OD) δ –80.82 (m, 3F), –110.23 (m, 2F), –121.33 (m, 2F), –121.83 (m, 6F), –122.80 (m, 2F), –126.21 (m, 2F); HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{16}\text{F}_{17}\text{N}_3\text{S}[\text{M} + \text{H}]^+$: 654.0872, found: 654.0880.

Typical procedure for the α -chlorination of hydrocinnamaldehyde and recycling of the catalyst

Fluorous catalyst **1** (32.65 mg, 0.05 mmol, 10 mol%) was added to a stirred ice-cooled solution of hydrocinnamaldehyde (65.8 μ L, 0.5 mol) in CH_2Cl_2 (1.0 mL) followed by the addition of NCS (87 mg, 0.65 mmol). The reaction mixture was stirred for 1 h and then warmed to 25°C and stirred until the aldehyde was completely consumed as determined by GC analysis (~2 h) using benzyl methyl ether as internal standard. After the completion of the reaction, the mixture was concentrated and then loaded onto a FluoroFlash[®] silica gel cartridge (2 g) for F-SPE. The cartridge was first eluted with 80:20 THF- H_2O (10 mL) for the all the non-fluororous products, then with THF (5 mL) for the fluororous catalyst. The combined filtrates of THF- H_2O fraction were extracted with hexane, dried over Na_2SO_4 and concentrated to afford the pure 2-chloro hydrocinnamaldehyde in 99% yield. Then the aldehyde was diluted with MeOH (2 mL), followed by addition of NaBH_4 (100 mg, 2.6 mmol) in several portions. The mixture with stirred for 10 min, quenched with water and extracted with EtOAc. The organic layer was separated and dried over Na_2SO_4 . After

evaporating the solvent, the crude product was purified by Flash column with 4:1 pentane/EtOAc as eluent. ¹H NMR (300 MHz, CDCl₃): δ = 7.35-7.22 (m, 5H, Ar), 4.26-4.18 (dm, *J* = 24 Hz, 1H, CHCl), 3.84-3.64 (m, 2H, OCH₂), 3.18-3.01 (m, 2H, PhCH₂), 2.21 (t, *J* = 6.3 Hz, 1H, -OH); ¹³C NMR (75 MHz, CDCl₃) δ 137.05, 129.26, 128.52, 126.94, 65.81, 64.74, 40.65. The ee was determined by HPLC on a Daicel Chiralpak OD-H column with 98:2 hexane/*i*-PrOH as eluent. *R*_t (min): 11.38 (minor); 12.18 (major). The fluororous catalyst, in the THF fraction, was easily recovered by evaporating the solvent.

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Figure 1.
Plausible transition state of the chlorination reaction catalyzed by catalyst **1**.

Scheme 1.
Preparation of fluororous (*S*)-pyrrolidine-thiourea bifunctional organocatalyst **1**.

Scheme 2.
Catalyst recycling experiment.

Table 1

Organocatalysts Promoted α -Chlorination of Hydrocinnamaldehyde with NCS^a

entry	Catalyst (mol%)	solvent	Time (h)	Yield (%) ^b	ee (%) ^c
1	1 (10)	CH ₂ Cl ₂	3	99	85
2	1 (10)	CHCl ₃	3	99	78
3	1 (10)	DCE	3	99	82
4	1 (10)	MeOH	<1min	99 ^d	0
5	1 (10)	THF	3	47	29
6	1 (5)	CH ₂ Cl ₂	3	71	85
7	-	CH ₂ Cl ₂	24	<5	0
8	L-Proline (10)	CH ₂ Cl ₂	3	99	18
9	L-Prolinamide (10)	CH ₂ Cl ₂	3	99	76
10	Thiourea (10)	CH ₂ Cl ₂	12	52	0

^a reaction conditions: hydrocinnamaldehyde (0.5 mmol), NCS (0.65 mmol), solvent (1 mL), 25°C.

^b measured by GC using benzyl methyl ether as internal standard.

^c ee determined by chiral HPLC after reduction to the corresponding alcohol.

^d acetalization of aldehyde.

Table 2Enantioselective α -Chlorination: Substrate Scope^a

entry	R	Time (h)	Yield (%) ^b	ee (%) ^c
1	Et	2	99	86
2	<i>i</i> -Pr	2	97	90
3	<i>n</i> -Pr	2	95	87
4	<i>t</i> -Bu	2	92	95
5	<i>n</i> -Hexyl	3	96	92
6	<i>n</i> -nonyl	3	95	91
7	Allyl	3	91	89
8	CH ₂ Ph	3	99	85 ^d

^a reaction conditions: aldehyde (0.5 mmol), NCS (0.65 mmol), CH₂Cl₂ (1 mL).^b measured by GC using benzyl methyl ether as internal standard.^c ee determined by chiral GC.^d ee determined by chiral HPLC after reduction to the corresponding alcohol.