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

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Received 21 October 2009

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.

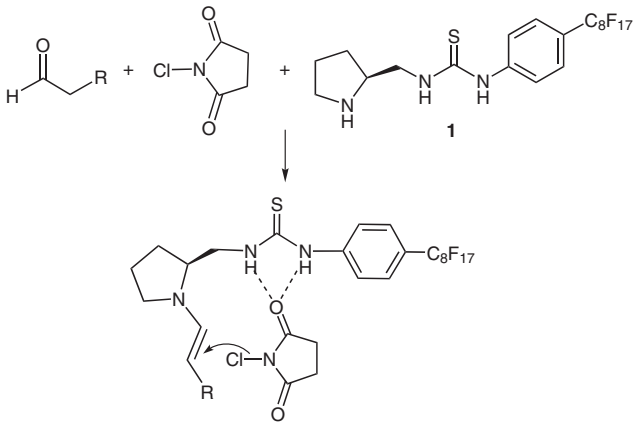
Key words: bifunctional organocatalyst, α-chlorination, α-chloroaldehyde, *N*-chlorosuccinimide (NCS), fluorous catalyst, fluorous solid-phase extraction (F-SPE)

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[3] have emerged as attractive tools in asymmetric reactions and have showed high enantioselectivity and recyclability in Michael addition reaction,[4] Diels–Alder reaction[5] as well as aldol reaction.[6] 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).[7]

Asymmetric chlorination is an important reaction because the chlorinated products are versatile synthetic intermediates in medicinal chemistry and material science.[8] Optically active α-chlorocarbonyls can be easily converted to various chiral building blocks.[9] In 2004, the enantioselective direct α-chlorination of unbranched aldehydes was independently reported by Jørgensen group[10] and MacMillan group[11] utilizing chiral secondary amine catalysts.

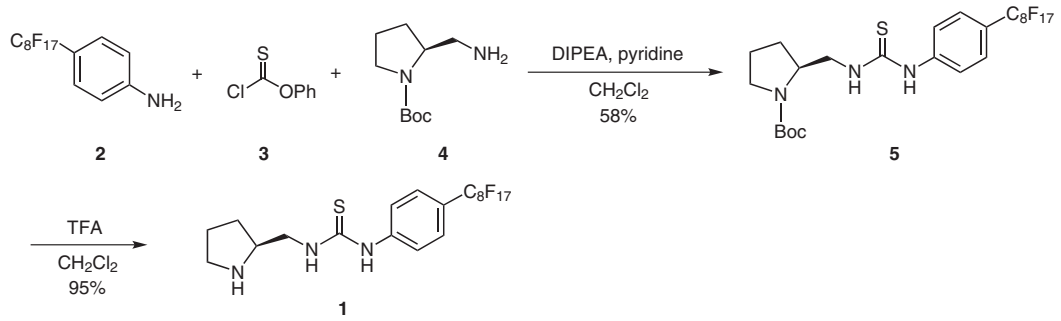
The use of hydrogen-bonding interactions has become a popular approach in recent years. In particular, thiourea-based bifunctional organocatalysts have found a broad scope of applications.[12,13] To the best of our knowledge, there is no literature describing the direct asymmetric α-chlorination of aldehydes with a thiourea-based bifunctional organocatalyst. According to the mechanism of the secondary amine-catalyzed asymmetric reactions and fluorous chemistry, we believe that a fluorous bifunctional catalyst **1** containing a secondary amine and a thiourea should be able to activate and facilitate the reaction process (Scheme 1). Moreover, the strong electron-withdrawing effect of the fluorous 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 fluorous tag can provide a handle for the catalyst recovery using F-SPE technique. Herein we wish to report the preparation of a novel recyclable fluorous (*S*)-pyrrolidine–thiourea bifunctional organocatalyst **1** and its application in direct α-chlorination of aldehydes using NCS as the chlorine source.



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

The *N*-Boc fluorous (*S*)-pyrrolidine-thiourea catalyst **5** 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**)[14] following Berkessel's method.[15] Subsequent removal of the Boc group in TFA–CH_2Cl_2 at 25 °C afforded the catalyst **1** as yellow solid in 55% yield (Scheme 2).

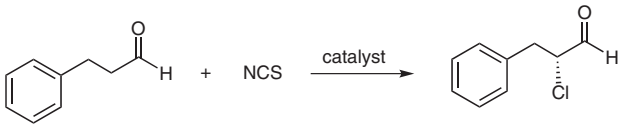
SYNLETT 2010, No. 3, pp 0433–0436
Advanced online publication: 18.01.2010
DOI: 10.1055/s-0029-1219198; Art ID: S12209ST



Scheme 2 Preparation of fluorous (*S*)-pyrrolidine–thiourea bifunctional organocatalyst **1**

We first carried out a model reaction involving hydrocinnamaldehyde, NCS, and fluorous bifunctional catalyst **1** to optimize the reaction conditions. 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 CH_2Cl_2, $CHCl_3$, or DCE as a solvent, while the best ee (85%) was found in CH_2Cl_2.

Table 1 Organocatalyst-Promoted α-Chlorination of Hydrocinnamaldehyde with NCS[a]



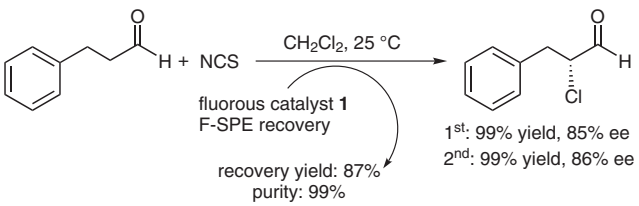
Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1** (10)	CH_2Cl_2	3	99	85
2	**1** (10)	$CHCl_3$	3	99	78
3	**1** (10)	DCE	3	99	82
4	**1** (10)	MeOH	<1 min	99[d]	0
5	**1** (10)	THF	3	47	29
6	**1** (5)	CH_2Cl_2	3	71	85
7	–	CH_2Cl_2	24	<5	0
8	L-proline (10)	CH_2Cl_2	3	99	18
9	L-prolinamide (10)	CH_2Cl_2	3	99	76
10	thiourea (10)	CH_2Cl_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] The ee was determined by chiral HPLC after reduction to the corresponding alcohol.
[d] Acetalization of aldehyde.

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.[16] The effect of catalyst loading was also evaluated. In the absence of catalyst, trace yield was obtained after 24 hours. 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 were obtained (18% and 76%, 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 hours (entry 10).

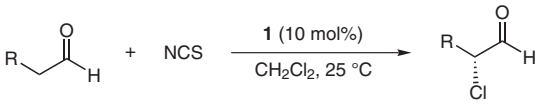
To demonstrate the scope of the reaction, a series of aldehydes were used for chlorination reactions. As revealed in Table 2, all the reactions proceeded efficiently to furnish the products in excellent yields (91–99%) and good enantioselectivities (85–95% ee). In all cases the reaction was found to proceed cleanly and no other byproducts, such as dichlorosubstitued aldehydes, were formed. The products listed in Table 2 are known compounds and their relative and absolute configurations were determined by comparison with the literature ^{1}H NMR and ^{13}C NMR data, and by chiral HPLC or GC analyses.

Finally, we performed the catalyst-recovery experiment using 0.5 mmol of aldehyde and 33 mg of catalyst **1** (Scheme 3). After completion of the reaction, the mixture was concentrated and then loaded onto a Fluoro*Flash*® silica gel cartridge for F-SPE.[17] 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 fluorous catalyst is stable and can be stored at room temperature for months without any sign of decomposition.



Scheme 3 Catalyst recycling experiment

Table 2 Enantioselective α-Chlorination: Substrate Scope[a]



Entry	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	Et	2	99	86
2	*i*-Pr	2	97	90
3	*n*-Pr	2	95	87
4	*t*-Bu	2	92	95
5	*n*-hexyl	3	96	92
6	*n*-nonyl	3	95	91
7	All	3	91	89
8	Bn	3	99	85[d]

[a] Reaction conditions: aldehyde (0.5 mmol), NCS (0.65 mmol), CH_2Cl_2 (1 mL).
[b] Measured by GC using benzyl methyl ether as internal standard.
[c] The ee was determined by chiral GC.
[d] The ee was determined by chiral HPLC after reduction to the corresponding alcohol.

In summary, a new fluorous (*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 Fluorous (*S*)-Pyrrolidine–Thiourea Bifunctional Organocatalyst

Phenyl chlorothioformate (**3**, 276 μL, 345 mg, 2 mmol) was added to a solution of 4-(heptadecafluorooctyl)aniline (**2**, 1.022 g, 2 mmol) and pyridine (178 μL, 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 μL, 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 × 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 (EtOAc–hexane = 5:1) to give the *N*-Boc-derivative **5** as a white amorphous solid (0.873 g, 58%).

The *N*-Boc derivative **5** (0.873 g, 1.16 mmol) was dissolved in a mixture of TFA and CH_2Cl_2 (1:1, 10 mL, v/v), and the solution was stirred for 2 h at 25 °C. The pH was adjusted to 8 with aq $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. Concentrated and purified by column chromatography (MeOH–EtOAc = 7:1) to give pyrrolidine–thiourea organocatalyst **1** as a light yellow solid (0.719 g, 95%); mp 117–119 °C; $[\alpha]_D^{20}$ +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, 2 H), 7.57–7.54 (d, *J* = 9 Hz, 2 H), 3.68–3.50 (m, 2 H), 3.48–3.41 (m, 1 H), 2.94–2.92 (m, 2 H), 2.00–1.71 (m, 3 H), 1.58–1.46 (m, 1 H). ^{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, 3 F), –110.23 (m, 2 F), –121.33 (m, 2 F), –121.83 (m, 6 F), –122.80 (m, 2 F), –126.21 (m, 2 F). ESI-HRMS: *m/z* calcd for $C_{20}H_{16}F_{17}N_3S$ $[M + H]^+$: 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 μL, 0.5 mmol) 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, then warmed to 25 °C, and stirred until the aldehyde was completely consumed as determined by GC analysis (ca. 2 h) using benzyl methyl ether as internal standard. After the completion of the reaction, the mixture was concentrated and then loaded onto a Fluoro*Flash*® silica gel cartridge (2 g) for F-SPE. The cartridge was first eluted with THF–H_2O (80:20, 10 mL) for the all the nonfluorous products, then with THF (5 mL) for the fluorous 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 H_2O 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 pentane–EtOAc (4:1) as eluent. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H, Ar), 4.26–4.18 (dm, *J* = 24 Hz, 1 H, CHCl), 3.84–3.64 (m, 2 H, OCH_2), 3.18–3.01 (m, 2 H, $PhCH_2$), 2.21 (t, *J* = 6.3 Hz, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): 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 hexane–*i*-PrOH (98:2) as eluent; t_R (min) = 11.38 (minor); 12.18 (major). The fluorous catalyst, in the THF fraction, was easily recovered by evaporating the solvent.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank Nanjing University of Science & Technology, University of Massachusetts Boston Joseph P. Healey grant and NIH GMS (1P50GM067082) for financial support.

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(17) Fluorous columns and products were purchased from Fluorous Technologies, Inc. D.P.C. owns an equity interest in this company.