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Short communication

An efficient, recoverable fluorous organocatalyst for direct reductive amination of aldehydes

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ABSTRACT

A commercially available perfluorooctyl aniline and phenyl isothiocyanate were reacted under mild conditions to give 1-[4-(perfluorooctyl)phenyl]-3-phenylthiourea as an analogue of thiourea-based organocatalyst. This fluorous organocatalyst was successfully employed to direct reductive amination of aldehydes. It could be readily separated from reaction product by fluorous solid phase extraction for direct use.

1. Introduction

In the past decade, much interest has been devoted to the development of highly efficient organocatalysts for a variety of reactions [1]. However, the efficient separation of catalysts from reaction products becomes an increasingly important aim. The high loading levels of organocatalysts make them less atom economical. But the potential disadvantages can be offset by suitable protocol for recovery and reuse. Unfortunately, few atttempts have been made to devise general strategies to recover and reuse organocatalysts.

Recently, fluorous technology has emerged as a new and powerful protocol to recover and reuse the catalyst. In 1997, Curran's group reported the first example of application of solid–liquid separations based on fluorous silica gel [2]. They found that these separations were operationally convenient and were applicable to substances that contain only relatively few fluorine atoms such as light-fluorous reagent. This is a key finding since light-fluorous reagents and catalysts have chemical and physical properties that are similar to their non-fluorous counterparts. This new technology has been applied to the development of recoverable organocatalyst for Michael reaction [3]. We envisioned that the important concept could be also employed in designing recyclable thiourea organocatalyst. Recently we have synthesized Schreiner catalyst of N,N′-bis[3,5-bis(trifluoromethyl)phenyl] thiourea (**I** Scheme 1) [4]. Inspired by fluorous tag idea, we have designed a kind of fluorous thiourea organocatalyst (**II** Scheme 1) bearing C_8F_{17}–. So we supposed that fluorous thiourea organocatalyst of C_8F_{17}– could have better activity than other thiourea derivative organocatalyst.

The reductive amination presents one of the effective methods for the synthesis of various kinds of amine [5], in which the carbonyl component is treated with amine and reductant in "one-pot" fashion. Thus, many methods have been reported to accomplish this direct process [6–8]. Some classical methods [9] rely on the Brønsted acid and Lewis acid to facilitate formation of the intermediate imines and to activate C=N for preferential reduction in the presence of the carbonyl compound. Nevertheless, application of these methods to sensitive, acid-labile or polyfunctional substrates is limited. Many of these procedures seem not to be adaptable for asymmetric variants. It promotes the development of novel catalytic concepts for a mild direct reductive amination as an important research goal.

Therefore in our previous work, the direct reductive amination mediated by thiourea derivative catalyst, N,N′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea **I** through the formation of hydrogen bond between thiourea and carbonyl functionality has been reported [4]. We found that the catalytic reactivity of thiourea catalyst **I** was better than thiourea itself. But the recovery of catalyst **I** has not been examined in detail at that time.

Herein we introduce C_8F_{17}– into thiourea organocatalyst in order to facilitate the recovery of the catalyst, since we supposed that fluorous thiourea derivative can accelerate this process effectively. Meanwhile the fluorous catalyst can be recycled by

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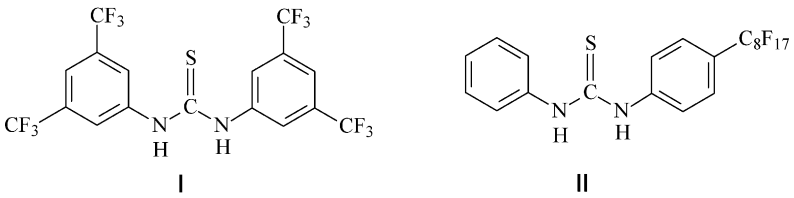
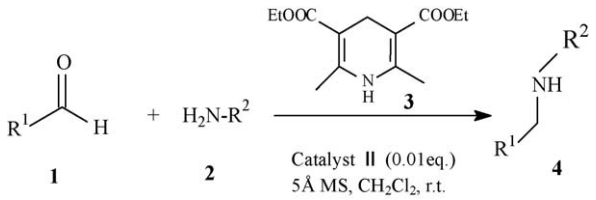


Scheme 1. Two kinds of thiourea-based organocatalyst.



Scheme 2. Direct reductive amination of aldehydes.

fluorous solid phase extraction. Furthermore the general application of this fluorous method to the synthesis of a variety type of amines is also described.

2. Results and discussion

In our experiments, we studied the direct reductive amination of aldehydes mediated by 1-[4-(perfluorooctyl)phenyl]-3-phenylthiourea **II** using Hantzsch 1,4-dihydropyridine **3** as reducing agent as shown in Scheme 2.

First of all, we began to explore the direct reductive amination of benzaldehyde and *p*-anisidine using Hantzsch 1,4-dihydropydine as a model reaction. As shown in Table 1 the catalytic activities of thiourea, N,N′-diphenyl thiourea, Schreiner thiourea catalyst **I** and fluorous thiourea catalyst **II** were examined comparatively. Obviously, fluorinated thiourea catalysts **I** and **II** were more active than non-fluorinated thiourea (entries 1–4). This is because thiourea catalyst with fluorinated ligand made double N–H bond more active than those of thiourea catalyst with non-fluorinated. And it was shown that f-tag thiourea **II** was more effective than Schreiner thiourea catalyst **I**. Under the same condition, reaction promoted by **II** occurred more rapidly (8 h) to give the product in excellent yield (94%) as shown in entry 4. In contrast, the use of the catalyst I for the same reaction time (8 h) resulted in the lower yield (82%). The result could be due to the electron-withdrawing effect of long fluorous chain, which was stronger than short fluorous chain. In addition, the catalyst **II** was so robust that catalyst loading could decrease to 0.01 equiv. in the entry 5.

To establish the recovery strategy of catalyst **II**, fluorous solid phase extraction technique was used in the research. In order to test this feature, **II** (0.1 equiv. employed to ensure the accuracy of evaluating catalyst recovery) was used to promote the direct reduction of benzaldehyde and *p*-anisidine. And then **II** was cleanly recovered from the reaction mixtures by fluorous solid phase extraction. In each run, the recovered catalyst retained its high activity with good recovery within three cycles (Table 2).

Having established the recoverable and reusable capacity of **II**, we next probed its use as an organocatalyst for wide range of direct reductive amination for different substrates (**4a–4k**) in Table 3. As shown in Table 3, the reaction proceeded smoothly with 0.01 equiv. of the catalyst and gave rise to good yields.

Electron-deficient (entry 3) and electron-rich (entry 4) aromatic aldehydes were both easily transformed into the products. Furthermore no reduction of nitro group (entry 3) was observed and free hydroxyl was tolerated (entry 5). In addition, electron-deficient aromatic aldehyde could obtain higher yield than electron-rich aromatic aldehyde.

From entry 6 to entry 10, a variety type of aromatic amines was easily reacted with aromatic aldehydes. It showed that the approach could be applied to various kinds of aromatic amine. Some relevant product yields were good (entries 6–8), and the other products yields were moderate (entries 9 and 10). Meanwhile, some functional groups such as nitro group and hydroxyl in the substrate of amines are also tolerated during the reaction process. In entry 11, aliphatic aldehyde could smoothly give reductive product in good yield too.

Table 1
Direct amination of benzaldehyde and *p*-anisidine under different conditions[a].

Entry	Catalyst (equiv.)	Conditions	Yield[b]
1	Thiourea (1.0)	r.t. CH_2Cl_2 8 h	38%
2	N,N′-diphenyl thiourea (0.1)	r.t. CH_2Cl_2 8 h	65%
3	Schreiner thiourea **I** (0.1)	r.t. CH_2Cl_2 8 h	82%
4	Thiourea derivative **II** (0.1)	r.t. CH_2Cl_2 8 h	94%
5	Thiourea derivative **II** (0.01)	r.t. CH_2Cl_2 8 h	90%
6	None	50 °C, toluene, 24 h	Trace

[a] 2.0 mmol benzaldehyde, 2.2 mmol *p*-anisidine, 2.4 mmol Hantzsch 1,4-dihydropydine, 5 Å molecule sieve (activated) 1.0 g, solvent 10 ml.
[b] Isolated yield by column chromatography.

Table 2
Recycling and reuse of organocatalyst **II** in promoting the reaction of benzaldehyde and *p*-anisidine[a].

Cycle	*T*/h	Recovery[b]	Yield[c]
1	8	95%	94%
2	8	94%	93%
3	8	92%	93%

[a] 2.0 mmol benzaldehyde, 2.2 mmol *p*-anisidine, 2.4 mmol Hantzsch 1,4-dihydropydine, 5 Å molecule sieve (activated) 1.0 g, CH_2Cl_2 10 ml, catalyst **II** 0.20 mmol.
[b] Recovered by fluorous solid phase extraction.
[c] Isolated yield by column chromatography.

Table 3
Direct reduction reaction of substitute aldehyde and diverse aniline[a].

Entry	R^1	R^2	Product	Yield[b]
1	Ph	Ph	**4a**	77%
2	4-Cl-C_6H_4	Ph	**4b**	81%
3	4-NO_2-C_6H_4	Ph	**4c**	90%
4	4-MeO-C_6H_4	Ph	**4d**	70%
5	2-OH-C_6H_4	Ph	**4e**	75%
6	Ph	4-MeO-C_6H_4	**4f**	90%
7	Ph	4-OH-C_6H_4	**4g**	85%
8	4-NO_2-C_6H_4	4-MeO-C_6H_4	**4h**	95%
9	4-MeO-C_6H_4	4-MeO-C_6H_4	**4i**	75%
10	4-MeO-C_6H_4	4-NO_2-C_6H_4	**4j**	72%
11	Cyclohexyl	4-MeO-C_6H_4	**4k**	85%

[a] Aldehyde 2.0 mmol, amine 2.2 mmol, 2.4 mmol Hantzsch 1,4-dihydropydine, 5 Å molecule sieve (activated) 1.0 g, catalyst **II** 0.02 mmol, CH_2Cl_2 10 ml, reaction time was 8 h.
[b] Isolated yield by column chromatography.

3. Conclusions

In summary, we have developed an efficient and facial method for the direct reductive amination of aldehydes via the imine activation of hydrogen bond of recoverable fluorous thiourea catalyst. The protocol is mild and acid-free, together with the high chemoselectivity, which make a useful process for the synthesis of various kinds of amine.

4. Experimental

4.1. General

Reagents were obtained from commercial sources. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Advance RX300 spectrometer using TMS as an internal standard, chemical shift values were given in ppm. Mass spectra were obtained on a Sectorfield-MS. Elemental analyses were conducted using a Yanaco MT-3CHN elemental analyser. Melting points were uncorrected.

4.2. General procedure for synthesis of fluorous thiourea organocatalyst II

Phenyl isothiocyanate (0.55 mmol) was added dropwise to a solution of perfluorooctyl aniline (0.5 mmol) in THF (10 ml) at 40 °C. After addition, the mixture was strongly stirred at 40 °C under nitrogen atmosphere for 24 h. The bulk of solvent was removed in rotary evaporator under reduced pressure. The residue was added to cool diethyl ether 4 ml, then the mixtures was filtered at once. The filter was dried in vacuo at 40 °C for 12 h to obtain product (90% yield). Melting point 145–147 °C, ^{1}H-NMR (CD_3OD, 300 MHz) δ: 7.26–7.28 (m, 2H), 7.40–7.43 (d, J = 9.0 Hz, 2H), 7.48–7.52 (m, 1H), 7.60–7.63 (d, J = 9.0 Hz, 2H), 7.78–7.80 (d, J = 6.1 Hz, 2H), ^{13}C-NMR (CD_3OD, 75 MHz) δ: 112.3–119.6 (m, CF_2CF_3), 124.5, 125.3, 125.6, 125.9, 127.2, 128.9, 139.5, 142.8, 180.8. ^{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); MS (EI) m/z 647 (M^+).

4.3. General procedure for the direct reductive amination of aldehyde

A mixture of aldehyde **1** (2.0 mmol), amine **2** (2.2 mmol), the Hantzsch 1,4-dihydropydine **3** (2.4 mmol), fluorous thiourea catalyst **II** (0.02 mmol) and MS 5 Å (1.0 g) were added into CH_2Cl_2 (10 ml). The reaction mixture was stirred at room temperature under nitrogen atmosphere. After 8 h, the crude product was filtrated and solvent was removed by reduced pressure. The residue was loaded onto a Fluoro*Flash*® silica gel cartridge (5 g), then eluted by methanol:water (75:25) 8–10 ml in order to separate non-fluorous organic components from the mixture. Then the first elutant was evaporated to remove solvent. The remains was purified by column chromatography on silica gel using mixtures of petroleum ether and ethyl acetate as elutant to give the product amines **4a–4k** in pure form.

N-benzyl-aniline (**compound 4a**): Ref. [10]. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.20 (s, 2H), 6.50–6.52 (d, J = 8.7 Hz, 2H), 6.59–6.63 (t, J = 7.4 Hz, 1H,), 7.04–7.09 (t, J = 7.4 Hz, 2H), 7.14–7.27 (m, 5H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 48.2, 112.8, 117.5, 127.1, 127.4, 128.5, 129.2, 139.4, 148.1. MS (EI) m/z 183 (M^+).

N-(**4-chlorobenzyl**)-**aniline** (**compound 4b**): mp 50–52 °C [51–52 °C Ref. [11]]. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.03 (s, 1H), 4.29 (s, 2H), 6.57–6.59 (d, J = 7.7 Hz, 2H), 6.71–6.73 (t, J = 7.8 Hz, 1H), 7.13–7.29 (m, 6H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 47.6, 112.8, 117.8, 128.7, 129.3, 133.0, 138.0, 147.8. MS (EI) m/z 218 (M^+).

N-(**4-nitrobenzyl**)-**aniline** (**compound 4c**): mp 67–69 °C [67–69 °C Ref. [11]]. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 4.26 (s, 1H), 4.77 (s, 2H), 6.57–6.58 (d, J = 7.7 Hz, 2H), 6.73–6.76 (t, J = 7.8 Hz, 1H), 7.15–7.20 (m, 6H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 47.5, 112.8, 118.1, 123.8, 127.6, 129.3, 147.3, 147.5, 157.3. MS (EI) m/z 228 (M^+).

N-(**4-methoxybenzyl**)-**aniline** (**compound 4d**): mp 63–65 °C [63–64 °C Ref. [11]]. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 3.80 (s, 3H), 3.94 (s, 1H), 4.25 (s, 2H), 6.22 (d, J = 7.7 Hz, 2H), 6.73 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.7 Hz, 2H), 6.62–7.38 (m, 4H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 47.8, 55.3, 112.8, 114.2, 117.5, 128.8, 129.2, 130.5, 148.2, 155.6. MS (EI) m/z 214 (M^+).

N-(**2-hydroxybenzyl**)-**aniline** (**compound 4e**): mp 110–112 °C [113–114 °C Ref. [11]]. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 3.94 (s, 1H), 4.40–4.41 (d, J = 4.9 Hz, 2H), 6.83–7.27 (m, 9H), 8.42 (s, 1H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 48.7, 115.9, 116.6, 120.0, 120.8, 122.9, 128.7, 129.2, 129.3, 147.2, 156.7. MS (EI) m/z 199 (M^+).

N-benzyl-p-anisidine (**compound 4f**): mp 48–50 °C [48.6–48.9 °C, Ref. [8]]. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 3.73 (s, 3H), 4.28 (s, 2H), 6.60 (dt, J = 9.0, 3.0 Hz, 2H), 6.77 (dt, J = 9.0, 2.9 Hz, 2H), 7.25 (tt, J = 6.9, 2.1 Hz, 1H), 7.30–7.37 (m, 4H); ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 49.2, 55.8, 114.0, 114.8, 127.0, 127.4, 128.4, 139.5, 142.2, 152.0. MS (EI) m/z 213 (M^+).

N-benzyl-4-hydroxy-aniline (**compound 4g**): mp 88–90 °C [89–90 °C, Ref. [11]]. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 1.75 (s, 1H), 2.14 (s, 1H), 4.23 (s, 2H), 6.55 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 7.24–7.35 (m, 5H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 49.3, 114.4, 116.2, 127.2, 127.6, 128.6, 139.5, 142.3, 147.8. MS (EI) m/z 199 (M^+).

N-(**4-nitrobenzyl**)-**p-anisidine** (**compound 4h**): mp 97–99 °C [97.7–97.9 °C, Ref. [8]]. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 3.73 (s, 3H), 4.42 (s, 2H), 6.55 (dt, J = 9.0, 2.3 Hz, 2H), 6.75 (dt, J = 9.0, 2.3 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H,), 8.18 (dt, J = 8.8, 2.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 48.4, 55.6, 114.0, 114.7, 123.6, 127.5, 140.9, 146.8, 147.3, 152.3. MS (EI) m/z 258 (M^+).

N-(**4-methoxybenzyl**)-**p-anisidine** (**compound 4i**): mp 92–94 °C [91–93 °C, Ref. [10]], ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 3.73 (s, 6H), 4.32 (s, 2H), 6.32 (d, J = 8.7 Hz, 2H), 6.55 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 48.7, 55.3, 55.8, 114.0, 114.1, 114.9, 128.8, 131.6, 142.5, 152.2, 158.8. MS (EI) m/z 243 (M^+).

N-(**4-methoxybenzyl**)-**4-nitro-aniline** (**compound 4j**): mp 140–142 °C [140–141 °C, Ref. [10]], ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 3.81 (s, 3H), 4.35–4.36 (d, J = 5.5 Hz, 2H), 4.75–4.78 (m, 1H), 6.56–6.58 (d, J = 9.0 Hz, 2H), 6.89–6.91 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 8.07–8.09 (d, J = 9.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 47.2, 55.4, 111.3, 114.3, 126.4, 128.8, 129.3, 138.3, 153.0, 159.3. MS (EI) m/z 258 (M^+).

N-cyclohexylmethyl-p-anisidine (**compound 4k**): Ref. [8]. ^{1}H-NMR ($CDCl_3$ 300 MHz) δ: 0.92–1.02 (m, 2H), 1.12–1.30 (m, 3H), 1.56 (m, 1H), 1.66–1.82 (m, 5H), 2.90 (d, J = 6.6 Hz, 2H), 3.40 (brs, 1H), 3.74(s, 3H), 6.56 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$ 75 MHz) δ: 26.0, 26.6, 31.3, 37.6, 51.7, 55.9, 113.9, 114.9, 143.0, 151.8, MS (EI) m/z 219 (M^+).

4.4. General procedure for recovery of fluorous thiourea organocatalyst

After the residue was eluted by methanol: water (v/v = 75:25) at first for non-fluorous component, pure methanol was then added onto the fluorous gel column continuously for obtaining the elutant of fluorous thiourea catalyst **II**. When the bulk of solvent was removed and product was dried in vacuo at 50 °C for 8 h, the fluorous thiourea catalyst **II** could be recycled effectively. Furthermore, the recoverable organocatalyst could be used directly for the next run.

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