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An efficient, recoverable fluorous organocatalyst for accelerating the DABCO-promoted Morita–Baylis–Hillman reaction

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Abstract

A convenient method for Morita–Baylis–Hillman reaction of arylaldehydes with methyl acrylate has been developed by using fluorous-tag organocatalyst 1-[4-(perfluorooctyl)phenyl]-3-phenylthiourea and DABCO at room temperature. The fluorous organocatalyst could be recovered from the reaction mixture by fluorous solid-phase extraction (F-SPE) with excellent purity for direct reuse.

Keywords: Organocatalyst; Morita–Baylis–Hillman reaction; Fluorous solid phase extraction (F-SPE)

Recently, organocatalysis has emerged as a competitive, eco-friendly catalysis method compared with the traditional metal-based catalysis [1]. In addition, organocatalysis has become powerful tool in the construction of biological substances and therapeutic agents [2]. Some potential disadvantages, however, have gradually appeared with its wide application. One problem is that high organocatalyst loading is required to finish the desired transformations; the other one is the high cost of some expensive materials for preparing complex organocatalyst. In order to overcome these limitations, an alternative strategy is needed to design the recyclable and reusable organocatalyst.

In recent years, fluorous technology has been reported as a new and powerful protocol to recover and reuse the catalyst [3]. The first example of application of solid–liquid separations based on fluorous silica gel was reported by Curran's group in 1997 [4]. Later, this new technology has been applied to the development of recoverable organocalyst for Michael reaction [5]. Meanwhile, we envisioned that the important concept could be also empolyed in designing recyclable thiourea organocatalyst. In our previous work, Schreiner thiourea of *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea **1** (Scheme 1) had been synthesized for activating C=N of imines [6]. Inspired by fluorous tag idea, we have designed a kind of fluorous thiourea organocatalyst **2** (Scheme 1) bearing $C_8F_{17}^-$ group. Besides, we have found that fluorous thiourea organocatalyst of $C_8F_{17}^-$ group could have better activity than other thiourea derivative organocatalyst in the direct reductive amination of aldehydes [7]. So we are furtherly extending the fluorous catalyst **2** for the Morita–Baylis–Hillman reactions.

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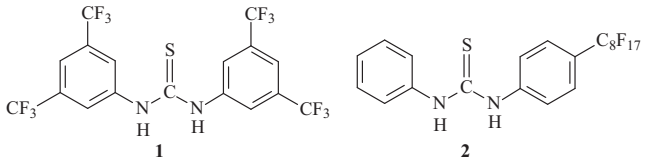


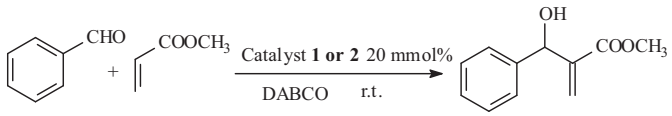
Scheme 1. Two kinds of thiourea-based organocatalyst.

The Morita–Baylis–Hillman reaction [8] is an organocatalytic one involving coupling of the α-position of activated alkenes with carbonyl electrophiles under the catalytic influence of a nucleophilic species. The corresponding adducts have been extensively used as intermediates in organic synthesis for a variety of applications. However, longer reaction time is required for the traditional MBH reaction of aromatic aldehydes. In 2004, Connon's group [9] first reported that the Schreiner thiourea could accelerate the DABCO-promoted MBH reaction of arylaldehyde with methyl acrylate. Therefore, we suppose that the thiourea organocatalyst bearing fluorous tag $C_8F_{17}^-$ could effectively accelerate the DABCO-promoted MBH reaction, and could be recovered by fluorous solid-phase extraction (F-SPE) technology.

Herein we report the recoverable thiourea catalyst **2** (Scheme 1) applying to the acceleration of the DABCO-promoted MBH reaction of arylaldehydes with methyl acrylate. Moreover, the strong electron-withdrawing effect of the fluorous tag in the *para* position enhances the acidity of the N–H of the thiourea and thus provides a stronger hydrogen-bonding interaction with the substrates.

1. Results and discussion

We first carried out a model reaction involving benzaldehyde, methyl acrylate, DABCO and fluorous thiourea catalyst **1** or **2** (Scheme 2) to optimize reaction conditions. As seen from Table 1, the yield obtained in the presence of catalysts **1** and **2**, was much higher than it was in the absence of catalyst (Table 1, entries 1–3). Meanwhile, the performace of catalyst **2** was better than catalyst **1**. In addition, the solvent had a pronounced effect on the yield (Table 1, entries 3–7, 9). Excellent yields were obtained when employing CH_3CN, DMSO or DMF as reaction solvent. This

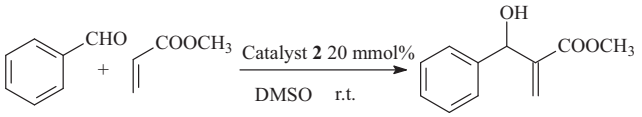


Scheme 2. The MBH reaction of benzaldehyde and methyl arcylate under different catalysts and solvents.

Table 1
Solvent effect and catalyst screening on the MBH reaction of benzaldehyde and methyl arcylate[a].

Entry	Catalyst **1** or **2**	DABCO (mol%)	Solvent	Time (h)	Yield (%)[b]
1	–	100	DMSO	24	31
2	**1**	100	DMSO	24	88
3	**2**	100	DMSO	24	91
4	**2**	100	CH_2Cl_2	32	45
5	**2**	100	THF	32	65
6	**2**	100	CH_3CN	24	85
7	**2**	100	DMF	24	88
8	**2**	100	No solvent	24	68
9	**2**	50	DMSO	24	85
10	**2**	20	DMSO	32	80
11	**2**	100	CH_3CN/H_2O (70/30)	24	74
12	**2**	100	$DMSO/H_2O$ (70/30)	24	76

[a] Reaction condition: benzaldehyde (2.0 mmol), methyl acrylate (6.0 mmol), catalyst **1** or **2** (20 mmol%), solvent (5.0 mL).
[b] Isolated yield from column chromatography.



Scheme 3. The MBH reaction of benzaldehyde and methyl arcylate under different bases.

demonstrated that solvents of higher dielectric constants afforded better yields and shorter time. Even the mild results could be obtained in the presence of few water in the solvent (Table 1, entries 11–12). And higher product yield was obtained when more amount of DABCO was employed.

Furthermore, various tertiary amine bases were screened in combination with catalyst **2** for the reaction (Scheme 3). The results of experiments were summarized in Table 2. DABCO was found to be more effective than other bases in our study. Moveover, it also could give good yield with DMAP (Table 2, entry 2). However, only moderate yields were obtained when using Et_3N or imidazole (Table 2 entries 1 and 3), and it should be noted that pyridine was almost totally inactive in this reaction (Table 2, entry 4). Meanwhile, as seen from Table 2, we found that the yield increased with the catalyst loading varying from 5 mol% to 20 mol%. And the yield was not increased when more amount of catalyst was employed.

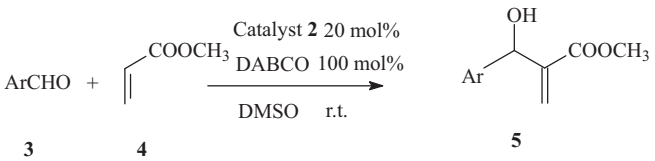
Under the optimized reaction conditions, we examined then the recovery of catalyst **2**. To establish the recovery strategy, fluorous solid phase extraction technique was used in our study. When the reaction was finished, catalyst **2** was recovered from the reaction mixtures by fluorous solid phase extraction. The catalyst **2** could be recovered with high recovery >93% in each cycle. Meanwhile, high yield 87–91% of the model reaction could be obtained mediated by recovered catalyst within three cycles. It showed that the catalyst **2** could be well recycled without the remarkabe loss of reaction activity.

Furthermore, we turned our interest to the reaction generality. A variety of aromatic aldehydes were examined under the optimal conditions (Scheme 4) [10]. The corresponding results were shown in Table 3. As seen from Table 3, the reaction proceeded smoothly to afford the corresponding adducts in good to excellent yields for aromatic aldehydes bearing electron-withdrawing substitutents (Table 3, entry 2). But for the aromatic aldehydes with electron-donating group, there were an obvious reduction in the yields (Table 3, entries 3–7). Heterocyclic aldehyde such as 2-furyaldehyde also showed moderate reactivity with yield 85% (Table 3, entry 9).

Table 2
The optimization of MBH reaction of benzaldehyde and methyl arcylate[a].

Entry	Base	Catalyst **2** (mol%)	Yield[b] (%)	Entry	Base	Catalyst **2** (mol%)	Yield[b] (%)
1	Et_3N	20	48	6	DABCO	20	91
2	DMAP	20	84	7	DABCO	10	80
3	Imidazole	20	58	8	DABCO	5	72
4	Pyridine	20	–[c]	9	DABCO	–	31
5	DABCO	30	92				

[a] Reaction condition: benzaldehyde (2.0 mmol), methyl acrylate (6.0 mmol), base (100 mol%), DMSO (5.0 mL), reaction time was 24 h, reaction temperature was 25 °C.
[b] Isolated yield from column chromatography.
[c] No reaction.



Scheme 4. The MBH reaction of different aromatic aldehydes and methyl arcylates.

Table 3
The MBH reaction of different aromatic aldehydes with methyl acrylate[a,b].

Entry	Ar	Time (h)	Product	Yield[c] (%)	Entry	Ar	Time (h)	Product	Yield[c] (%)
1	Ph-	24	**5a**	92	6	4-Cl-C_6H_4-	24	**5f**	82
2	4-NO_2-C_6H_4-	6	**5b**	96	7	4-Br-C_6H_4-	24	**5g**	83
3	4-CH_3-C_6H_4-	32	**5c**	76	8	2-Naphthyl-	24	**5h**	78
4	4-CH_3O-C_6H_4-	32	**5d**	72	9	2-Furyl-	24	**5i**	85
5	4-OH-C_6H_4-	32	**5e**	80					

[a] Reaction condition: arylaldehyde (2.0 mmol), methyl acrylate (6.0 mmol), DABCO (2.0 mmol), catalyst **2** (20 mol%), DMSO (5.0 mL), reaction temperature was 25 °C.
[b] Catalyst was recovered by fluorous solid phase extraction.
[c] Isolated yield from column chromatography.

2. Conclusions

In summary, a kind of fluorous tag thiourea organocatalyst 1-[4-(perfluorooctyl)phenyl]-3-phenylthiourea could effectively accelerate the DABCO-promoted Morita–Baylis–Hillman reaction of aromatic aldehydes with methyl acrylate. And the catalyst can be easily recovered by F-SPE for reuse. Application of this catalyst for other reactions are under investigation and will be reported in due course.

Acknowledgments

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References

[1] (a) P.I. Dalko, L. Moisan, Angew. Chem. Int. Ed. 43 (2004) 5138;
(b) B. List, Chem. Commun. (2006) 819;
(c) G. Guillena, D.J. Ramon, Tetrahedron: Asymmetry 17 (2006) 1465.
[2] (a) I.K. Mangion, D.W.C. MacMillan, J. Am. Chem. Soc. 127 (2005) 3696;
(b) R.M. Wilson, W.S. Jen, D.W.C. MacMillan, J. Am. Chem. Soc. 127 (2005) 11616.
[3] (a) D.P. Curran, Synlett 9 (2001) 1488;
(b) W. Zhang, D.P. Curran, Tetrahedron 62 (2006) 11837.
[4] D.P. Curran, S. Hadida, M. He, J. Org. Chem. 62 (1997) 6714.
[5] (a) L. Zu, H. Li, J. Wang, et al. Tetrahedron Lett. 47 (2006) 5131;
(b) L. Zu, J. Wang, H. Li, et al. Org. Lett. 8 (2006) 3077.
[6] Y.B. Huang, C. Cai, J. Chem. Res. 11 (2009) 686.
[7] Y.B. Huang, W.B. Yi, C. Cai, J. Fluorine Chem. 131 (2010) 879.
[8] (a) A.B. Baylis, M.E.D. Hillman, Ger. Pat. 2155113 (1972).;
(b) M.E.D. Hillman, A.B. Baylis, U.S. Pat. 3,743,669 (1973).
(c) K. Morita, Z. Suzuki, H. Hirose, Bull. Chem. Soc. Jpn. 41 (1968) 2815.
[9] D.J. Maher, S.J. Connon, Tetrahedron Lett. 45 (2004) 1301.
[10] General procedure for the MBH reaction and the recycle of catalyst by F-SPE: the mixture of benzaldehyde (2.0 mmol), fluorous thiourea catalyst **2** (0.4 mmol) and DABCO (2.0 mmol) in DMSO (5 mL) was added into methyl acrylate (6.0 mmol) at room temperature. The resulting mixture was stirred vigorously for 24 h. After finishing reaction, the crude product was evaporated by reduced pressure in order to remove excess methyl acrylate. 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 cartridge was eluted by pure methanol 15–20 mL so as to recover the catalyst. Meanwhile, the first elutant was evaporated to obtain the crude. The remains was purified by column chromatography on silica gel using mixtures of petroleum ether and ethyl acetate (70:30) as elutant to give the adducts **5a–5i** in pure form. All compounds were characterized by MS, ^{1}H NMR and ^{13}C NMR, and were compared with the authentic samples.