DOI: 10.1002/adsc.201000214

Enantioselective Aldol Reaction using Recyclable Montmorillonite-Entrapped *N*-(2-Thiophenesulfonyl)prolinamide

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Received: March 18, 2010; Revised: May 10, 2010; Published online: June 30, 2010

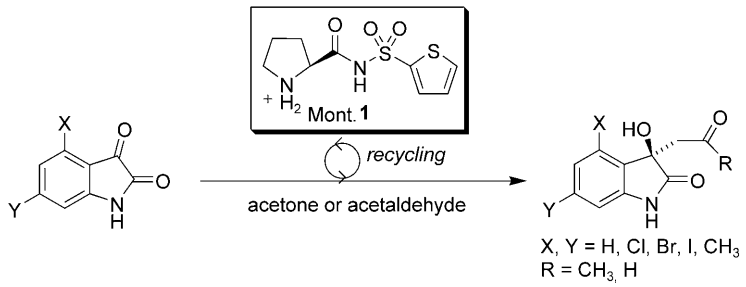
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000214.

Abstract: *N*-(2-Thiophenesulfonyl)prolinamide could be easily introduced into Montmorillonite by a simple ion-exchange reaction. The asymmetric aldol reactions between various isatins with acetone or acetaldehyde using a heterogeneous Montmorillonite-entrapped organocatalyst afforded products with high enantioselectivity. The catalyst was readily reusable without significant loss of catalytic activity or enantioselectivity.

Keywords: aldol reaction; enantioselectivity; heteroarenesulfonyl group; Montmorillonite; organocatalysis

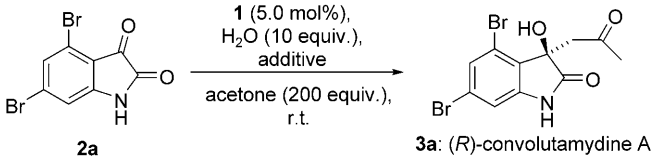
The enantioselective aldol reaction using organocatalysts is recognized as one of the most powerful carbon-carbon bond-forming reactions,[1] so the organocatalytic asymmetric aldol reaction to ketones as electrophiles has been intensively investigated,[2] as it provides efficient access to chiral tertiary alcohols. In particular, the utilization of isatin as an electrophile has attracted much attention because the reaction affords chiral 3-hydroxy-2-oxyindole derivatives, which are an important structure motif in biologically active compounds.[3] However, organocatalytic aldol reactions to ketones generally need a high catalyst loading of organocatalysts (normally 10–50 mol%) in which turnover numbers (TONs) are 2–10. Therefore, the design and development of highly active organocatalysts aimed at lowering catalyst loading and an appropriate catalyst recovery technique for organocatalysts have proved to be a significant challenge task and only limited success has been achieved.[4] Recently, we have reported that *N*-(2-thiophenesulfonyl)prolinamide acted as a highly efficient organocatalyst for the reaction of acetone or aldehydes with isatin derivatives.[5] This organocatalyst is now commercially available, but it is rather expensive.[6] Therefore, the recovery and reuse of this expensive organocatalyst is important from a cost and environmental standpoint. Although recovery and reuse of organocatalysts using polymer supports,[7] ionic liquid supports,[8] and fluorous chemistry[9] have been developed, these anchored organocatalysts have some disadvantages, including multi-step syntheses and deactivation of the inherent catalysis. Recently, Kaneda and co-workers have reported a pioneering work for the entrapment of MacMillan's organocatalyst on Montmorillonite using a cation exchange method, which allows facile separation from the reaction mixture and reuse of the entrapped catalyst.[10] However, to the best of our knowledge, there is no report on Montmorillonite-entrapped organocatalysts for the asymmetric aldol reaction. Herein our ongoing interest was extended to a recyclable organocatalyst on Montmorillonite for the asymmetric aldol reaction to isatins and the development of an efficient synthetic method (Scheme 1).

The Montmorillonite-entrapped *N*-(2-thiophenesulfonyl)prolinamide **1** was prepared by Kaneda's method.[10] The catalytic ability of the organocatalyst entrapped in Montmorillonite was examined in the synthesis of convolutamydine A[11] as an asymmetric aldol reaction to isatins. The reaction of 4,6-dibromoisatin **2a** with acetone using 5 mol% of Montmorillonite-entrapped *N*-(2-thiophenesulfonyl)prolinamide **1** in the presence of 10 equivalents of H_2O at room temperature afforded (*R*)-convolutamydine A **3a** in 99% yield with 84% *ee* (Table 1, entry 1). Although the addition of TsOH or CF_3SO_3H inhibited the reaction, the addition of carboxylic acids as a Brønsted acid improved the enantioselectivity of the reaction (entries 2–6). The addition of 10 mol% TFA afforded **3a** in 99% yield with 93% *ee* (entry 6).[12] The reaction using *N*-(2-thiophenesulfonyl)prolinamide as a homogeneous organocatalyst at room temperature afforded



Scheme 1. Recyclable catalyst for the asymmetric aldol reaction to isatins

Table 1. Enantioselective addition of acetone to 4,6-dibromoisatin in the presence of Montmorillonite-entrapped *N*-(2-thiophenesulfonyl)prolinamide **1**.



2a **3a**: (*R*)-convolutamydine A

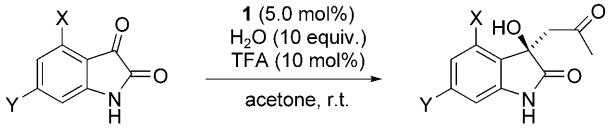
Entry	Additive (mol%)	Time [h]	Yield [%][a]	*ee* [%][b]
1	none	8	99	84
2	*p*-TolSO$_3$H (10)	72	42	91
3	CF$_3$SO$_3$H (10)	72	6	81
4	PhCO$_2$H (10)	10	99	89
5	CH$_3$CO$_2$H (10)	10	99	90
6	TFA (10)	20	99	93
7[c]	TFA (10)	48	94	95
8[d]	TFA (10)	168	86	91

[a] Yield of isolated **3a** after filtration and purification on silica gel.
[b] The *ee* was determined by HPLC analysis.
[c] The reaction was carried out at 0 °C.
[d] Catalyst loading is 2 mol%.

3a in 92% yield with 93% *ee*,[5a] therefore, the heterogeneous organocatalyst **1** did not lose its catalytic ability from the inherent homogeneous organocatalyst. Although the reactivity was lowered, the enantioselectivity was improved in the reaction performed at a lower temperature (entry 7). Furthermore, the catalyst loading of **1** can be reduced to 2 mol% without a significant loss of enantioselectivity (entry 8).

With these optimized conditions, the preparation of various convolutamydine A derivatives **3b–h** using 5 mol% of Montmorillonite-entrapped organocatalyst **1** is shown in Table 2. The reaction of *N*-Bn-protected dibromoisatin also afforded good enantioselectivity (entry 2). The reaction of substituted isatins such as 4,6-dichloro-, 4,6-diiode-, 4-bromo, 4-chloro, and 4-iodoisatins **2c–g** gave products **3c–g** in high yields with high enantioselectivity (entries 4–8), although the reaction of non-substituted isatin **2b** afforded product **3b** with low enantioselectivity (entry 3). Unfortunately, 4,6-dimethylisatin **2h** has low reactivity (entry 9).

Table 2. Enantioselective synthesis of convolutamydine A derivatives **3a–h**.



2a: X = Br, Y = Br **2e**: X = Br, Y = H
2b: X = H, Y = H **2f**: X = Cl, Y = H
2c: X = Cl, Y = Cl **2g**: X = I, Y = H
2d: X = I, Y = I **2h**: X = CH$_3$, Y = CH$_3$

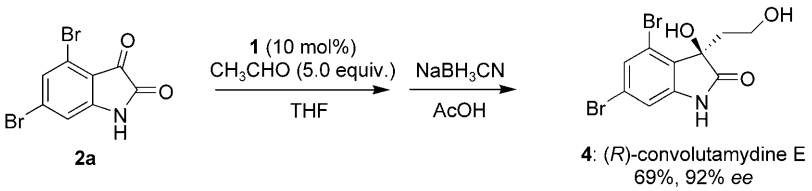
3a – h

Entry	Isatin	Reaction Time [h]	Yield [%][a]	*ee* [%][b]
1	**2a**	20	99	93
2[d]	**2a**[c]	30	95	96
3	**2b**	40	99	2
4[d]	**2c**	80	93	92
5	**2d**	24	96	96
6	**2e**	20	99	95
7	**2f**	20	98	91
8	**2g**	35	95	94
9	**2h**	50	Trace	-

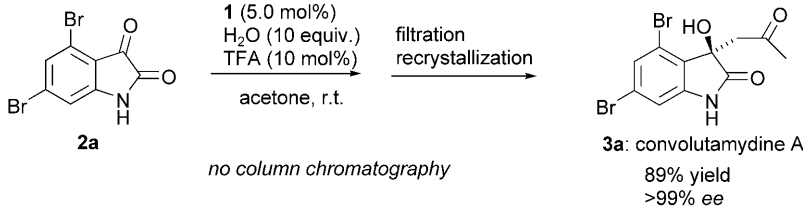
[a] Yield of isolated **3a–g** after filtration and purification on silica gel.
[b] The *ee* was determined by HPLC analysis.
[c] *N*-Benzylated **2a** was used.
[d] At 0 °C.

We next examined the reaction of 4,6-dibromoisatin **2a** with acetaldehyde in the presence of Montmorillonite-entrapped organocatalyst **1** (Scheme 2). The reaction was carried out using 10 mol% of **1** and 5 equivalents of acetaldehyde at room temperature. After the aldol reaction, the obtained intermediate aldehyde was reduced by NaBH$_3$CN in acetic acid to give (*R*)-convolutamydine E **4**[13,14] with high enantioselectivity.

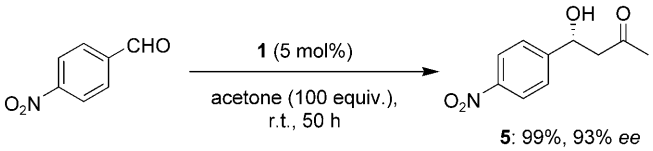
The Montmorillonite-entrapped organocatalyst **1** could be easily separated from the reaction mixture by simple filtration.[15] Therefore, we next examined a more efficient synthetic method for preparing convolutamydine A without column chromatography purification. After the aldol reaction between 4,6-dibromoisatin **2a** with acetone using Montmorillonite-entrapped organocatalyst **1**, simple filtration and recrystalli-



Scheme 2. Enantioselective synthesis of convolutamydine E.



Scheme 3. Efficient synthetic method for preparing convolutamydine A.



Scheme 4. Enantioselective reaction of *p*-nitrobenzaldehyde with acetone.

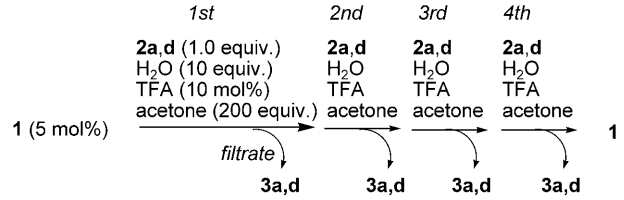
zation of crude mixture afforded **3a** in good yield as an enantiomerically pure product (Scheme 3).

We also examined the reaction of *p*-nitrobenzaldehyde with acetone in the presence of 5 mol% of Montmorillonite-entrapped organocatalyst **1** to give the product **5** in high yield with high enantioselectivity (Scheme 4).

The next important aspect was to examine the catalyst recovery and the possibility for catalyst reuse. After the aldol reaction with **2a**,**d**, catalyst **1** was easily separated and quantitatively recovered by simple filtration of the reaction mixture. The recovered catalyst retained its high activity and high levels of enantioselectivity (89–94% *ee*) even after four cycles despite some degree of activity loss observed in cycles 3 and 4 (Table 3).[16]

In conclusion, we developed an immobilization method for a chiral organocatalyst on Montmorillonite using a cation-exchange method. The Montmorillonite-entrapped *N*-(2-thiophenesulfonyl)prolinamide **1** did not lose its catalytic ability from the inherent homogeneous organocatalyst. To the best of our knowledge, this is the first report for recyclable organocatalysts for use in the aldol reaction with ketones. Furthermore, it was readily reusable without needing to regenerate the catalyst. The total turnover numbers (TONs) for the recyclable catalyst reached almost 80 with high enantioselectivity. Therefore Montmorillonite-entrapped *N*-(2-thiophenesulfonyl)prolinamide **1** acts as an environmentally friendly catalyst. Further studies focusing on the scope of this recyclable catalyst in asymmetric transformations are currently underway and will be reported in due course.

Table 3. Recycling of catalyst **1** by simple filtration.



Reuse	Time [h]	Yield [%][a]	*ee* [%][b]
1st (for **2a**)	20	99	93
2nd (for **2a**)	20	94	93
3rd (for **2a**)	24	95	91
4th (for **2a**)	40	89	89
1st (for **2d**)	24	96	96
2nd (for **2d**)	24	97	94
3rd (for **2d**)	48	78	94
4th (for **2d**)	80	51	92

[a] Yield of isolated **3a**,**d** after filtration and purification on silica gel.

[b] The *ee* was determined by the HPLC analysis.

Experimental Section

Preparation of 1

Na^+-Montmorillonite (300 mg), was added to *N*-(2-thiophenesulfonyl)prolinamide (50 mg) in water (20 mL) and the mixture was stirred at 50 °C for 2 h. The product was separated by filtration, washed with deionized water, and

dried under vacuum at room temperature to provide the Montmorillonite-entrapped *N*-(2-thiophenesulfonyl)prolinamide organocatalysts **1** as a white powder; yield: 325 mg.

Acknowledgements

This work was partly supported by a Grant-in-Aid for Young Scientists B (20750074) from JSPS and the Toyoaki Scholarship Foundation. We are grateful to Kunimine Industry Co. Ltd., Japan for a gift of Na^+-Montmorillonite.

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[15] We cannot detect *N*-(2-thiophenesulfonyl)prolinamide in the reaction mixture. Furthermore, catalyst **1** was removed by filtration after about 20% conversion of the product **3a**, and additional stirring of the filtrate did not give any products. This result implies that the organocatalyst did not dissolve in the reaction mixture.

[16] The reuse experiments were performed as follows: After the first aldol reaction of isatin using 5.4 mg of the Montmorillonite-entrapped organocatalyst, the Montmorillonite-entrapped organocatalyst was recovered by simple filtration, washed with acetone, and then subjected to the next aldol reaction.

