ORGANIC LETTERS

2011
Vol. 13, No. 5
876–879

A New Class of Structurally Rigid Tricyclic Chiral Secondary Amine Organocatalyst: Highly Enantioselective Organocatalytic Michael Addition of Aldehydes to Vinyl Sulfones

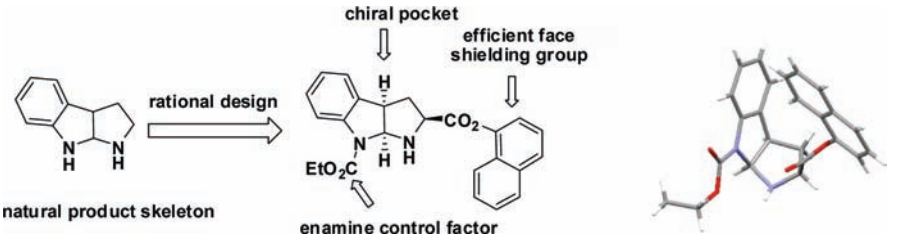
Jian Xiao,[†,‡] Yun-Peng Lu,[†] Yan-Ling Liu,[†] Poh-Shen Wong,[†] and Teck-Peng Loh*[,†]

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, and Dalian Institute of Chemical Physics, The Chinese Academy of Sciences, Dalian 116023, People's Republic of China

teckpeng@ntu.edu.sg

Received December 3, 2010

ABSTRACT



A new class of chiral secondary amine organocatalyst was rationally designed as an efficient catalyst to catalyze the elusive Michael addition of aldehydes to vinyl sulfones. High yield and excellent enantioselectivities could be obtained at room temperature without having to resort to high catalyst loading, anhydrous solvents, and low temperatures. Efficient control of enamine conformation and face shielding as well as the rigid nature of the tricyclic skeleton, with an inherent chiral pocket, provide a well-organized chiral environment to effect this elusive reaction efficiently.

In recent years, we have witnessed an exponential growth in the field of organocatalysis. This is due to the many advantages they can offer.[1] Among the organocatalysts, chiral secondary amines which involve enamine catalysis have been used widely in many different organic transformations to generate products in high optical purities. In addition to the widely employed naturally occurring

[†] Nanyang Technological University.
[‡] The Chinese Academy of Sciences.

(1) (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (b) Dalko, P. I., Ed. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (d) List, B. *Chem. Commun.* **2006**, 819. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (f) Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (g) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (h) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (i) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (j) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (k) Westermann, B.; Ayaz, M.; Berkel, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846. (l) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(2) For reviews, see: (a) List, B. *Synlett* **2001**, 1675. (b) List, B. *Tetrahedron* **2002**, *58*, 5573. (c) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (d) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (e) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904. For pioneering work using proline as catalyst, see: (f) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496. (g) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (h) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (i) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (j) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (k) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (l) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785.

10.1021/ol102933q © 2011 American Chemical Society
Published on Web 01/27/2011

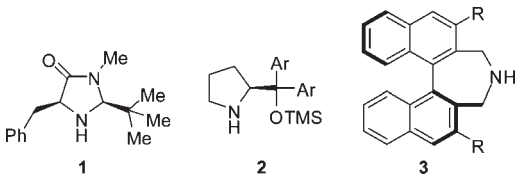
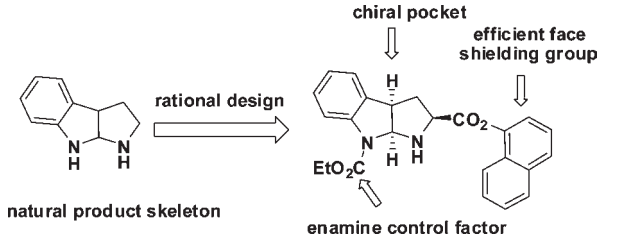


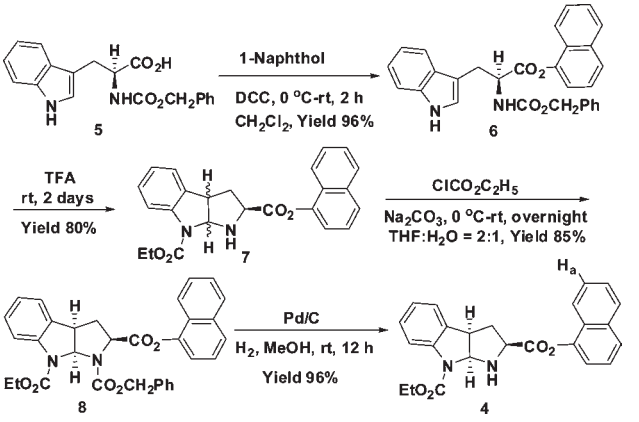
Figure 1. Typical chiral secondary amine organocatalysts **1**−**3**.

proline,[2] chemists have also rationally designed several other impressive chiral secondary amines as organocatalysts. Representative examples are MacMillan's imidazolidinones catalyst **1**,[3] Hayashi and Jørgensen's α,α-diarylprolinol ether catalyst **2**[4] and Maruoka's binaphthyl-based chiral secondary amine catalyst **3**,[5] which were found to induce high enantioselectivities in a large number of reactions that proline failed (Figure 1). Despite these significant progresses, there are still many limitations such as high catalytic loading, low temperature, low enantioselectivity and reactivity in many other reactions which could not be resolved using existing organocatalysts. Therefore, there is a tremendous amount of effort directed at the design of more efficient organocatalysts.[1] Toward solving some of these limitations, we rationally designed a new class of

Scheme 1. Rationally Designed New Class of Chiral Secondary Amine Organocatalyst **4** with a Chiral Pocket



Scheme 2. Synthesis of Chiral Organocatalyst **4**



chiral secondary amine **4** (Scheme 1) based on the naturally occurring hexahydropyrrolo[2,3-b]indole skeleton,[6] which has been identified as a new privileged chiral skeleton for asymmetric catalysis in our group.[7] In our new design of **4**, in addition to the intrinsic chiral pocket brought about by the conformation of the tricyclic skeleton, the ethyl carbamate group serves to control the conformation of the enamine while the bulky naphthyl group efficiently shields the top face of the pocket. It is anticipated that the unique rigid tricyclic structure, together with the inherent hydrophobic pocket, will bestow upon catalyst **4** more promising and superior properties as compared to other chiral secondary amine catalysts. In this paper, we report a new class of organocatalyst **4** with high potential as demonstrated in the highly enantioselective organocatalytic Michael reaction of aldehydes to vinyl sulfones.

Catalyst **4** could be easily prepared in four steps from **5** as shown in Scheme 2. DCC coupling of **5** with 1-naphthol furnished **6**, which was treated with TFA to afford an *endo* and *exo* mixture of **7**. Reaction of **7** with ethyl chloroformate in the presence of sodium carbonate, followed by hydrogenation, gave the desired catalyst **4** in good yield. The unique structure and stereochemistry of **4** has been unambiguously confirmed by X-ray crystallography. X-ray crystallographic analysis indicates that there is a face tilted-T orientation of the naphthyl and phenyl rings with H_a lying 2.77 Å perpendicularly under the face of the phenyl ring with an inter-ring angle of 77° (Figure 2). This

(3) (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (b) Jang, H.-Y.; Hong, J.-B.; MacMillan, D.W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (c) Kim, H.; MacMillan, D.W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (d) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

(4) For reviews, see: (a) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922. For the pioneering work, see: (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (d) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (e) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjasgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (f) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

(5) For reviews, see: (a) Maruoka, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 917. (b) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465. For selected examples, see: (c) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055. (d) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem. Asian J.* **2006**, *1*, 210. (e) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738. (f) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (g) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1838.

(6) For reviews of natural products containing hexahydropyrrolo [2,3-*b*]indole, see: (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (b) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem.*−*Eur. J.* **2011**, DOI: 10.1002/chem.201001451. For cinchona alkaloids-derived catalysts, see: (c) Tian, S. K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Kacprzak, K.; Gawroński, J. *Synthesis* **2001**, 961. For the pioneering work using natural product nornicotine as a catalyst, see: (e) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220. (f) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Chem. Commun.* **2007**, 4952. (g) Rogers, C. J.; Dickerson, T. J.; Brogan, A. P.; Janda, K. D. *J. Org. Chem.* **2005**, *70*, 3705. (h) Dickerson, T. J.; Lovell, T.; Meijler, M. M.; Noodleman, L.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 6603. (i) Rogers, C. J.; Dickerson, T. J.; Janda, K. D. *Tetrahedron* **2006**, *62*, 352.

(7) (a) Xiao, J.; Xu, F. X.; Lu, Y. P.; Loh, T. P. *Org. Lett.* **2010**, *12*, 1220. (b) Xiao, J.; Wong, Z. Z.; Lu, Y. P.; Loh, T. P. *Adv. Synth. Catal.* **2010**, *352*, 1107. (c) Xiao, J.; Liu, Y. L.; Loh, T. P. *Synlett* **2010**, 2029. (d) Xiao, J.; Loh, T. P. *Org. Lett.* **2009**, *11*, 2876. (e) Xiao, J.; Loh, T. P. *Synlett* **2007**, 815. (f) Xiao, J.; Loh, T. P. *Tetrahedron Lett.* **2008**, *49*, 7184. For a discussion of "privileged" chiral catalyst, see: (g) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

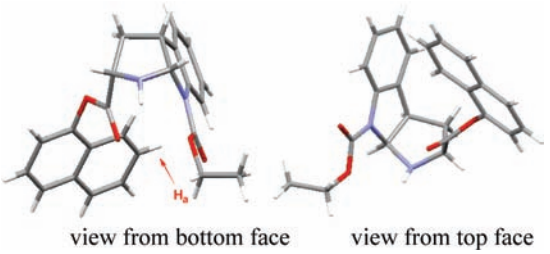


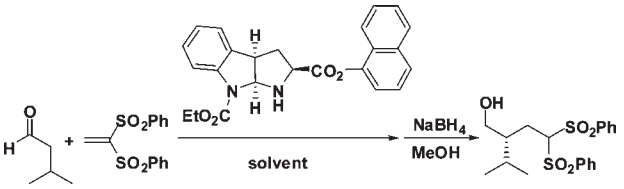
Figure 2. Crystal structure of organocatalyst **4**.

preferred conformation is primarily driven by the relief of torsional strain, further enhanced by attractive edge-to-face $\pi-\pi$ interactions.[8]

As a representative example, we focus on the asymmetric Michael addition of aldehydes to vinyl sulfones. If successful, this method will provide facile access to various optically pure sulfones, which are featured widely in many bioactive molecules,[9] and after desulfonylation, a wide range of optically pure aldehydes will be obtained, which offer an alternative solution to the problematic asymmetric alkylation of aldehydes.[10] Despite its apparent importance in organic synthesis, the highly enantioselective Michael addition of aldehydes to vinyl sulfones still remains a great challenge.[11] Only limited examples afford high enantioselectivities and most of them suffered from using high catalyst loading (up to 25 mol %), low temperature (−60 to 0 °C) and anhydrous solvents, which limit their applicability to organic synthesis.

At the onset, the Michael addition of isovaleraldehyde to vinyl sulfone was chosen as the testing ground. To our delight, the desired product could be obtained in 53% yield and 98% *ee* in the presence of 10 mol % catalyst **4** at room

Table 1. Evaluation of **4** as a Catalyst for the Asymmetric Michael Addition of Isovaleraldehyde to Vinyl Sulfone[a]



entry	loading (mol %)	solvent	yield (%)[b]	*ee* (%)[c]
1	10	MeOH	10	39
2	10	THF	42	–
3	10	$CHCl_3$	<10	–
4	10	MeCN	16	–
5	10	CH_2Cl_2	53	98
6	10	CH_2Cl_2[d]	<10	–
7	10	CH_2Cl_2	66	99
8	5	CH_2Cl_2[e]	63	99
9	5	CH_2Cl_2	99	99
10	5	CH_2Cl_2[f]	71	95
11	5	CH_2Cl_2[g]	<10	–
12	2	CH_2Cl_2	51	97

[a] Reactions were conducted with 3 equiv of aldehyde, 1 equiv of vinyl sulfone at room temperature in the presence of catalyst. [b] Isolated yield. [c] *ee* was determined by chiral HPLC on a chiral stationary phase. [d] 3-NO_2PhCO_2H (10 mol %) was added. [e] Aldehyde (4 equiv) was used. [f] Aldehyde (2 equiv) was used. [g] Anhydrous CH_2Cl_2 was used or molecular sieves (4 Å) was added.

temperature in AR grade CH_2Cl_2 (Table 1, entry 5). However, for other organic solvents, the results were not satisfactory (Table 1, entries 1−4). The addition of acid was not beneficial to this reaction (Table 1, entry 6). It was found that excellent yield and enantioselectivity could be obtained with only 5 mol % **4** and 3 equiv of isovaleraldehyde (Table 1, entries 7−10). Interestingly, use of anhydrous solvent or addition of molecular sieves impede this reaction, which is different from the previous report (Table 1, entry 11). Catalyst **4** still shows high reactivity and retains the enantioselectivity even when the catalyst loading was decreased to 2 mol % (Table 1, entry 12).

Next, various substrates were examined and the reaction exhibited broad applicability in terms of the aldehyde substrate. The adducts were obtained in good yields and excellent enantioselectivities (up to 99% ee) in the presence of 5 mol % or 10 mol % of catalyst **4** (Table 2).[12] Further experimentation showed that when the naphthyl group was replaced by a methyl, phenyl and 2-(1-adamantyl)-4-methylphenyl group in catalyst **4**, the chiral product **10f** could be obtained in 81, 89, and 88% *ee*, respectively. Under the same conditions, however, MacMillan's imidazolidinones catalyst **1** gave the same product in low yield and low *ee*.[13]

(8) (a) Jennings, W. B.; Farrell, B. M.; Malone, J. F. *Acc. Chem. Res.* **2001**, *34*, 885. (b) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.

(9) For reviews, see: (a) El-Awa, A.; Noshi, M. N.; Jourdin, X. M.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315. (b) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793. (c) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107. (d) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547. For asymmetric organocatalysis with sulfones, see: (e) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixão, M. W.; Jøgensen, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2668. (f) Zhu, Q.; Lu, Y. *Aust. J. Chem.* **2009**, *62*, 951. (g) Alba, A. R.; Companyó, X.; Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018.

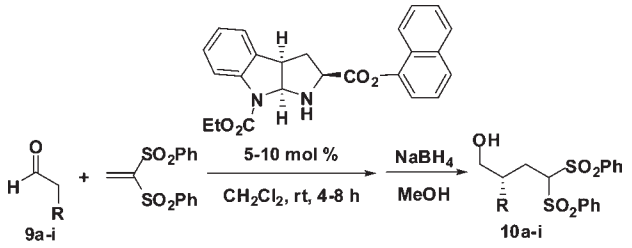
(10) (a) Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1360. (b) Alba, A.-N.; Viciano, M.; Rios, R. *ChemCatChem* **2009**, *1*, 437.

(11) (a) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361. (b) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559. (c) Quintard, A.; Bournaud, C.; Alexakis, A. *Chem.−Eur. J.* **2008**, *14*, 7504. (d) Mossé, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem.−Eur. J.* **2009**, *15*, 3204. (e) Landa, A.; Maestro, M.; Masdeu, C.; Puente, A.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem.−Eur. J.* **2009**, *15*, 1562. (f) Quintard, A.; Alexakis, A. *Chem.−Eur. J.* **2009**, *15*, 11109. (g) Zhu, Q.; Lu, Y. *Org. Lett.* **2008**, *10*, 4803. (h) Quintard, A.; Belot, S.; Marchal, E.; Alexakis, A. *Eur. J. Org. Chem.* **2010**, *5*, 927. For generation of quaternary carbon centers, see: (i) Alba, A.-N. R.; Companyo, X.; Valero, G.; Moyano, A.; Rios, R. *Chem. −Eur. J.* **2010**, *16*, 5354. (j) Zhu, Q.; Lu, Y. *Chem. Commun.* **2010**, 2235. (k) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097. (l) Moteki, S. A.; Xu, S.; Arimitsu, S.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, *17074*. For a tandem reaction, see: (m) Chua, P. J.; Tan, B.; Yang, L. M.; Zeng, X. F.; Zhu, D.; Zhong, G. F. *Chem. Commun.* **2010**, *46*, *7611*. For asymmetric Michael addition of aldehydes to vinyl sulfones in water, see ref 7c.

(12) Epimerization of the aldehydes products was observed during the purification step; therefore, the corresponding aldehydes adducts were reduced to alcohols for determination of yield and ee.

(13) For instance, the product **10a** was obtained only in 30% yield and 31% ee in the presence of 10 mol % **1**.

Table 2. Asymmetric Michael Addition of Aldehydes to Vinyl Sulfone[a]



entry	R	product	yield (%)[b]	*ee* (%)[c]
1	CH_3	**10a**	82	92
2	CH_3	**10a**	59	96
3	C_2H_5	**10b**	66	93
4	C_2H_5	**10b**	71	94
5	C_3H_7	**10c**	56	94
6	C_3H_7	**10c**	88[d]	95
7	C_4H_9	**10d**	49	92
8	C_4H_9	**10d**	93	92
9	C_6H_{13}	**10e**	55	90
10	C_6H_{13}	**10e**	60	93
11	C_7H_{15}	**10f**	71	91
12	i-Pr	**10g**	99	99
13	$PhCH_2$	**10h**	95	93
14	$BnO(CH_2)_2$	**10i**	66	97

[a] Reactions were conducted with 0.1 mmol vinyl sulfone, 0.3 mmol aldehyde and 5 mol % (entries 1,3,5,7,9) or 10 mol % **4** (entries 2,4,6,8,10−14) at room temperature. [b] Yield of the isolated products. [c] *ee* was determined by HPLC analysis on chiral stationary phases after purification. [d] The stereochemistry has been assigned *R* configuration by X-ray crystallography, see the Supporting Information for details.

To probe the mechanism of this reaction, eight possible enamine geometries and the relative orientation of naphthalene were subjected to DFT calculation. The most stable conformation is *syn* enamine conformation **3A** with the naphthalene ring puckered in the chiral pocket, which is more favored by 2.64 kcal/mol than the second lower energy conformation **3B** with the naphthalene ring stretching out (Figure 3).[14] In addition to the relief of torsional strain, a weak hydrogen bond interaction between hydrogen in the naphthalene ring and the oxygen in the ester group was found to lock the naphthalene ring.

On the basis of the above analysis and the observed stereochemistry of the Michael product, we proposed a plausible transition state model **C**. In this transition state model, the ethyl carbamate group favors the enamine conformation **3A** and the bulky naphthyl group efficiently shields the *Si* face of the enamine to force the vinyl sulphone attack from the *Re* face to afford the product in *R* configuration (Figure 4).

(14) See Supporting Information for the calculation details.

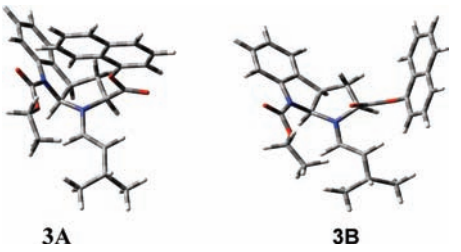


Figure 3. Lowest energy enamine conformation **3A** and **3B**.

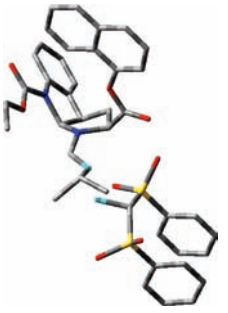


Figure 4. Proposed Transition State **C**.

In summary, we have developed a new class of chiral secondary amine organocatalyst **4** which can catalyze the elusive Michael addition of aldehydes to vinyl sulfones in good yields and excellent enantioselectivities. The desired chiral products could be obtained with high stereocontrol at room temperature without having to resort to high catalyst loading, anhydrous solvents and low temperatures. Efficient control of enamine conformation and face shielding as well as the rigid nature of the tricyclic skeleton, with an inherent chiral pocket provide a well-organized chiral environment to enable this elusive reaction to proceed smoothly. This chiral pocket directed asymmetric enamine catalysis opens new perspective and will find more application in asymmetric catalysis.

Acknowledgment. We thank Dr. Yongxin Li (Nanyang Technological University) for X-ray analyses. We gratefully acknowledge Nanyang Technological University and Ministry of Education Academic Research Fund Tier 2 (No. T207B1220RS) for the funding of this research.

Supporting Information Available. Additional experiment procedures, spectrum data for reactions products and 2 CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.