ORGANIC LETTERS

2008
Vol. 10, No. 12
2421−2424

Camphor Sulfonyl Hydrazines (CaSH) as Organocatalysts in Enantioselective Diels−Alder Reactions

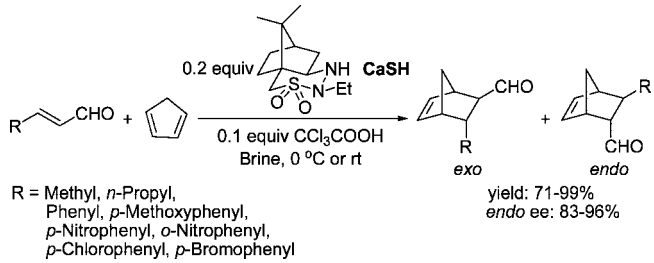
Hao He, Bao-Jian Pei, Ho-Hsuan Chou,[†] Tian Tian,[‡] Wing-Hong Chan, and Albert W. M. Lee*

Department of Chemistry, Hong Kong Baptist University, Kowloon Tong, Hong Kong SAR, China

alee@hkbu.edu.hk

Received March 13, 2008

ABSTRACT



Cyclic sulfonyl hydrazine was demonstrated for the first time as a new functionality for organocatalysis. A series of six-membered cyclic hydrazines derived from camphor sulfonic acid were synthesized. With trichloroacetic acid as cocatalyst, they are efficient organocatalysts for enantioselective Diels−Alder reactions with good chemical yields and up to 96% ee. The reactions took place in brine at 0 °C to room temperature.

Many of the biologically and pharmaceutically important molecules exist in chiral forms. In many cases, only one of the two possible chiral forms (enantiomers) of these molecules is active. Therefore, the challenge faced by synthetic chemists is how to prepare these useful molecules in pure enantiomeric forms by means of asymmetric synthesis. Various approaches such as chiral auxiliary and asymmetric catalysis have been used to realize asymmetric synthesis. The use of synthetic complexes of transition metals in asymmetric catalysis has been a very productive approach in the past decades.[1] In recent years, a new approach emerged. Asymmetric organocatalysis, the use of small chiral organic molecules to catalyze asymmetric transformations, has captured the attention of chemists around the world.[2,3] In this letter, we would like to report for the first time that sulfonyl hydrazine is a new functionality for effective organocatalysis. Moreover, brine is the reaction medium[4] for the hydrophobic effect.[5]

Camphor and its derivatives such as camphor sulfonic acid (CSA), which are readily available in optically pure forms for both of the enantiomers, are widely used synthons in asymmetric synthesis. The most noticeable example probably is the Oppolzer's sultam chiral auxiliary developed from CSA.[6] The preparation of the previously unknown camphor sulfonyl hydrazines (CaSH) from CSA via camphor sulfonyl chloride is outlined in Scheme 1.

Optically pure (+)-camphor sulfonyl chloride (**1**) readily prepared from CSA was cyclized with hydrazine monohydrate in the presence of a catalytic amount of acetic acid. After being reduced by sodium cyanoborohydride, the unsubstituted cyclic camphor sulfonyl hydrazine (CaSH) **4** could be obtained in high overall yield.

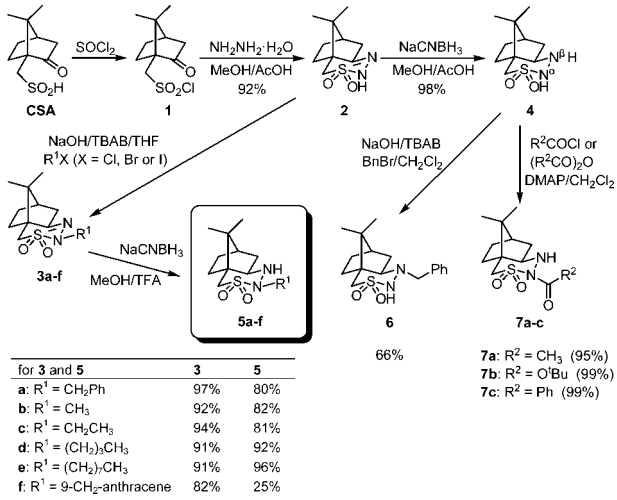
The concept behind the design of this sulfonyl hydrazine catalyst is the α-heteroatom effect.[7,8] It is well-established that the nucleophilicity of an amine will be greatly enhanced if a heteroatom is attached to it. For example, as compared to imine formation from aldehyde with amine, oxime and hydrazone are more readily formed from hydroxyamine (*O*-substituted amine) and hydrazine (*N*-substituted amine), respectively. It has been suggested that enhancing the nucleophilicity of the amine

[†] Exchange Student from the National Tsing Hua University, Taiwan,
[‡] Exchange Student from the Wuhan University, China.

(1) (a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (c) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.

10.1021/ol8005826 CCC: $40.75
Published on Web 05/16/2008

Scheme 1. Preparation of the Camphor Sulfonyl Hydrazines (CaSH)



for **3** and **5**	**3**	**5**
a: $R^1 = CH_2Ph$	97%	80%
b: $R^1 = CH_3$	92%	82%
c: $R^1 = CH_2CH_3$	94%	81%
d: $R^1 = (CH_2)_3CH_3$	91%	92%
e: $R^1 = (CH_2)_7CH_3$	91%	96%
f: R^1 = 9-CH_2-anthracene	82%	25%

nitrogen will accelerate the formation of the active imine ion intermediate in the catalytic cycle of an organocatalysis reaction.[9]Therefore, by attaching a heteroatom onto the amine nitrogen, one should be able to design a better organocatalyst. For example, Ogilvie has recently reported that conformationally rigid cyclic hydrazide is a new scaffold for organocatalysis.[9c,d]

We screened the efficiencies of simple hydrazines and other heteroatom-substituted amines and found that the effects were minimal. By modifying the hydrazine to sulfonyl-substituted hydrazine, we observed a satisfactory catalytic effect. Camphor is selected to provide the chiral scaffold of the sulfonyl hydrazine organocatalyst.

Unsubstituted CaSH **4** did show some catalytic effect in the Diels−Alder reaction. However, the yield and percent ee were poor (Table 1, entry 1). We then move to investigate the N^{α}- or N^{β}-substituted CaSH. Interestingly, cyclic sulfonyl hydrazine **4** exhibits good selectivity between *N*-acylation and *N*-alkylation. Acylation (acetyl, ^{t}BOC, and benzoyl, **4** to **7**, Scheme 1) took place exclusively at the α-nitrogen, while alkylation (**4** to **6**) went after the β-nitrogen only. These four N^{α}-acylated (**7a**−**c**) and N^{β}-benzylated (**6**) CaSHs gave better chemical yields than unsubstituted CaSH **4** in catalytic Diels−Alder reactions between cyclopentadiene and cinnamaldehyde (Table 1, entries 2−5). Moderate *endo* enantioselectivities were observed for **7b** and **6** (entries 3 and 5).

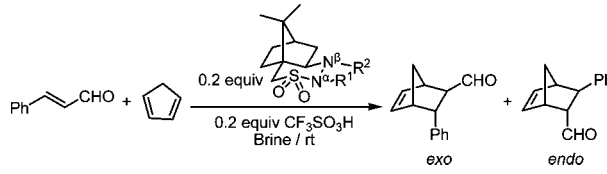
The last variation, the N^{α}-alkylated CaSH, could not be prepared directly by alkylation of **4**, to which alkylation proceeded after the β-nitrogen. The N^{α}-alkylated CaSHs were eventually synthesized by first alkylation of cyclic hydrazone **2** under phase transfer condition then followed by reduction with sodium cyanoborohydride in the presence of trifluoroacetic acid. The first N^{α}-alkylated CaSH, N^{α}-benzyl camphor sulfonyl hydrazine **5a**, prepared by us performed pretty well as an organocatalyst for the Diels−Alder reaction. In brine with trifluoromethanesulfonic acid as cocatalyst, a chemical yield of 90% with 80% *endo* ee was achieved (entry 6).

By comparing the results between N^{β}-benzyl CaSH **6** (entry 5) and N^{α}-benzyl CaSH **5a** (entry 6), it is obvious that N^{α}-alkylated CaSH is a better catalytic system than the N^{β}-alkylated variant. Before we further fine-tune the structure of our catalysts, the role of the acid cocatalyst was addressed. We found that the strongest acid may not necessarily be the best cocatalyst and the results were summarized in Table 2.

It was found that less acidic trichloroacetic acid is also an effective cocatalyst (entry 2). In particular, when the loading was reduced to 0.1 equiv, the yield was good and the percent ee of the *endo* isomer was up to 86% (entry 3). Further reducing the amount of acid used did not afford better results (entry 4). Meanwhile, the brine was switched to water to investigate whether the hydrophobic effect[5] did exist (entry 5). It took 2 days for the reaction in water to complete as compared to 8 h in brine. Also, both the chemical yield and enantioselectivity are higher in brine than in water. *p*-Toluenesulfonic acid and 3,5-dinitrobenzoic acid were also tested but the results were inferior (entries 6 and 7).

After acid cocatalyst was successfully fine-tuned, we moved on to investigate the effect of the alkyl group on the

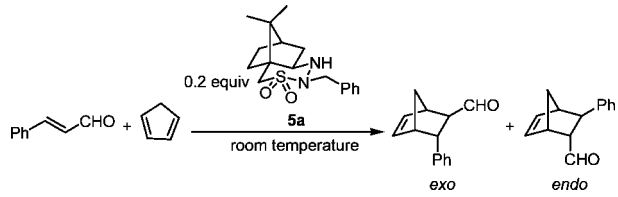
Table 1. Enantioselective Diels−Alder Reaction Catalyzed by *N*-Acylated and *N*-Benzylated Camphor Sulfonyl Hydrazines



entry	catalyst	R^1	R^2	yield (%)	*exo*:*endo*[a]	*endo* ee[b] (%)
1	**4**	H	H	18	1:1.4	32
2	**7a**	CH_3CO	H	35	1:1.4	18
3	**7b**	*t*-BOC	H	68	1:1	56
4	**7c**	C_6H_5CO	H	30	1:1.2	18
5	**6**	H	$C_6H_5CH_2$	30	1:1.4	53
6	**5a**	$C_6H_5CH_2$	H	90	1:1.3	80

[a] Determined by ^{1}H NMR. [b] *Endo* enantiomeric excess was determined by ^{1}H 400 MHz NMR of the corresponding (*R*,*R*)-(+)-hydrobenzoin acetal of the aldehyde.[9c]

Table 2. Effects of Acid Cocatalyst and Reaction Medium on Enantioselective Diels−Alder Reactions Catalyzed by **5a**



entry	acid (equiv)	solvent	time (h)	yield (%)	*exo*:*endo*	*endo* ee (%)
1	F_3CSO_3H (0.2)	brine	8	90	1:1.3	80
2	Cl_3CCOOH (0.2)	brine	8	85	1:1.2	82
3	Cl_3CCOOH (0.1)	brine	8	90	1:1.2	86
4	Cl_3CCOOH (0.05)	brine	96	73	1:1.1	65
5	Cl_3CCOOH (0.1)	H_2O	48	82	1:1.2	84
6	*p*-toluenesulfonic acid (0.1)	brine	48	48	1:0.9	59
7	3,5-dinitrobenzoic acid (0.1)	brine	48	32	1:1	31

α-nitrogen. A series of N^{α}-alkylated CaSHs were synthesized in high yields by the above-mentioned procedures (Scheme 1, **5a**−**f**). Their performance as enantioselective organocatalysts in Diels−Alder reactions was tested by using trichloroacetic acid as cocatalyst in brine (Table 3).

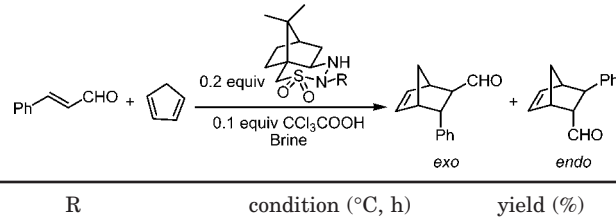
The results indicated that the N^{α}-alkylated hydrazines are good organocatalysts. Almost all of the N^{α}-alkylated CaSHs gave outstanding performance except **5f** (entry 8). Among all the N^{α}-alkylated catalysts, **5a** (N^{α}-benzyl) and **5c** (N^{α}-ethyl) gave the best results. They can catalyze the reaction efficiently even at 0 °C with good chemical yields and up to 90% and 93% *endo* ee respectively (entries 3 and 7). However, as for similar organocatalytic Diels−Alder reactions reported in the literature,[9,10] the *endo*/*exo* diastereoselectivity is also not very good in our case.

To extend the scope of our catalytic system, we chose the best performing catalyst N^{α}-ethyl CaSH **5c** to carry out further studies with various alkyl- and aryl-substituted α,β-unsaturated aldehydes. The results are summarized in Table 4.

N^{α}-Ethyl CaSH is a good Diels−Alder organocatalyst for both the aliphatic and aromatic α,β-unsaturated aldehydes with good to excellent yields and enantioselectivities. In general, the enantioselectivity of the *endo* products is slightly better than that of the *exo* products. Aromatic dienophiles performed slightly better than aliphatic dienophiles on enantioselectivity, while aliphatic dienophiles had faster reaction rates than aromatic ones. For the *p*-chloro- and *p*-bromocinnamaldehyde, the *endo* enantiomeric excess was up to 96% in both cases (entries 7 and 8). Most of the reactions were carried out at 0 °C and these reactions could be completed within 6 to 12 h. Some cases were carried out at room temperature because these reactions were relatively slow at 0 °C (entries 4 and 6). The aromatic dienophiles with an electron withdrawing group had a faster reaction rate than those with an electron-donating group. Especially, for the case of *p*-nitrocinnamaldehyde, the reaction was completed in 8 h at 0 °C (entry 5). But for the case of *o*-nitrocinnamaldehyde, the poor solubility of the dienophile in the reaction medium slowed down the reaction rate (entry 6).

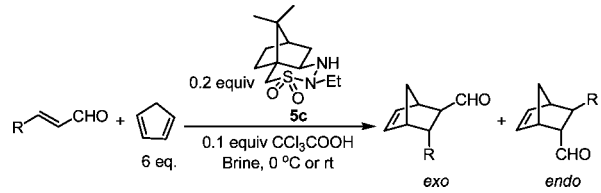
To address the stereochemistry of our reactions, we examined a molecular model of the proposed transition state of the iminium ion formed between N^{α}-ethyl CaSH (**5c**) and cinnamaldehyde as depicted in Figure 1.

Table 3. N^{α}-Alkylated CaSHs-Catalyzed Enantioselective Diels−Alder Reactions



entry	catalyst	R	condition (°C, h)	yield (%)	*exo*:*endo*	*endo* ee (%)
1	**5b**	CH_3	rt, 18	88	1:1	85
2	**5c**	CH_3CH_2	rt, 6	95	1:1.1	90
3	**5c**	CH_3CH_2	0, 12	92	1:1.1	93
4	**5d**	n-C_4H_9	rt, 40	85	1:1	82
5	**5e**	n-C_8H_{17}	rt, 24	88	1:1.1	88
6	**5a**	$C_6H_5CH_2$	rt, 8	90	1:1.2	86
7	**5a**	$C_6H_5CH_2$	0, 12	85	1:1.5	90
8	**5f**	9-CH_2-anthracene	rt, 48	48	1:1.5	29

Table 4. Enantioselective Diels−Alder Reactions between Cyclopentadiene and Various Dienophiles Catalyzed by N^{α}-Ethyl CaSH **5c**



entry	R	condition (°C, h)	yield (%)	*exo*:*endo*	*exo* ee[a] (%)	*endo* ee[a] (%)
1	methyl	0, 6	92	1:1.5		83
2	*n*-propyl	0, 6	71	1:1.3	66	90
3	phenyl	0, 12	92	1:1.1	78	93
4	*p*-methoxyphenyl	rt, 24	82	1:0.9	81	91
5	*p*-nitrophenyl	0, 8	99	1:1.1	81	91
6	*o*-nitrophenyl	rt, 24	94	1:2.5	72	90
7	*p*-chlorophenyl	0, 12	81	1:1.1	84	96
8	*p*-bromophenyl	0, 12	81	1:1.1	86	96

[a] The ee was determined by chiral HPLC analysis on the benzoylate derivation of the reduced alcohol and/or by ^{1}H NMR of the corresponding *(R,R)*-(+)-hydrobenzoin acetal derivatives of the aldehydes. The absolute configurations were assigned by correlation to literature[9c] reported NMR spectra of the *(R,R)*-(+)-hydrobenzoin acetal of the major cycloadducts.

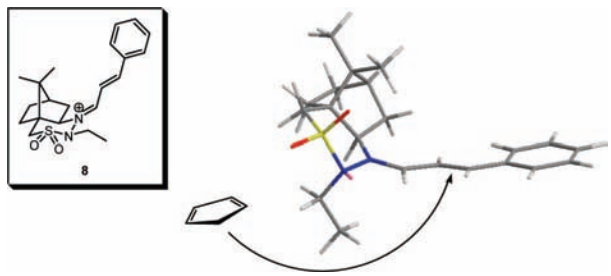


Figure 1. Iminium ion intermediate **8**.

The top face of **8** is blocked by the dimethyl groups of the camphor scaffold. Cyclopentadiene approached from the bottom face leading to the observed products. In the case of N^{α}-CH_2-anthracene-substituted CaSH (**5f**), the substituent is so bulky that the bottom face is also blocked. This led to poor chemical yield and enantioselectivity as observed (Table 3, entry 8).

In summary, a new type of organocatalyst, N^{α}-alkylated camphor sulfonyl hydrazine (CaSH), was developed. The CaSH-catalyzed asymmetric Diels−Alder reaction afforded good to excellent chemical yields and enantioselectivity. The reactions were carried out at 0 °C or room temperature in brine without any added organic solvent. The application of our CaSH catalyst in other asymmetric transformations is in progress.

Acknowledgment. Financial support from the Faculty Research Grant (FRG/07-08/II04) and the CERG Grant from the University Grant Committee are acknowledged.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8005826

(2) (a) Crow, J. M. *Chem. World* **2007**, *August*, 50. (b) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584. (c) Pizzarello, S.; Weber, A. L. *Science* **2004**, *303*, 1151. (d) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

(3) (a) List, B. *Chem. Commun.* **2006**, 819. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (f) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (g) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (h) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3. (i) Nájera, C. *Synlett* **2002**, 1388. (j) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (k) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (l) Shirakawa, S.; Yamamoto, K.; Kitamura, M.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 625. (m) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (n) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.

(4) Some recent examples of "in water" reactions: (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966. (b) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734. (c) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (d) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801. (e) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. (f) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. (g) Gryko, D.; Saletra, W. J. *Org. Biomol. Chem.* **2007**, *5*, 2148. (h) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew Chem., Int. Ed.* **2007**, *46*, 3798. (i) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593.

(5) (a) Sarma, D.; Kumar, A. *Org. Lett.* **2006**, *8*, 2199. (b) Kumar, A. *Chem. Rev.* **2001**, *101*, 1. (c) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (d) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

(6) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

(7) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154.

(8) (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Cavill, J. L.; Elliott, R. L.; Evans, G.; Jones, I. L.; Platts, J. A.; Ruda, A. M.; Tomkinson, N. C. O. *Tetrahedron* **2006**, *62*, 410.

(9) (a) Cavill, J. L.; Peters, J.-U.; Tomkinson, N. C. O. *Chem. Commun.* **2003**, 728. (b) Dirksen, A.; Hackeng, T. M.; Dawson, P. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 7581. (c) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141. (d) Lemay, M.; Aumand, L.; Ogilvie, W. W. *Adv. Synth. Catal.* **2007**, *349*, 441.

(10) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Gotoh, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 2859. (c) Selkälä, S. A.; Tois, J.; Pihko, P. M.; Koskinen, A. M. P. *Adv. Synth. Catal.* **2002**, *344*, 941.