DOI: 10.1002/adsc.201000438

Second Generation CaSH (Camphor Sulfonyl Hydrazine) Organocatalysis. Asymmetric Diels–Alder Reactions and Isolation of the Catalytic Intermediate

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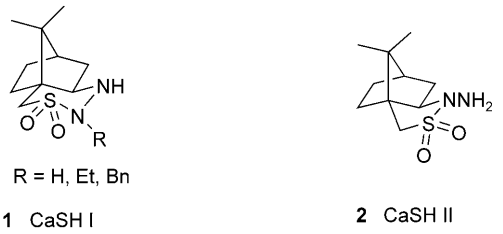
Received: June 6, 2010; Published online: September 2, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000438.

Abstract: In one step, the well known chiral auxiliary, Oppolzer's camphor sultam, is turned into the new generation camphor sulfonyl hydrazine (CaSH II) organocatalyst. With the primary hydrazine functionality external to the tricyclic structure, CaSH II is active towards ketone substrates in asymmetric Diels–Alder reactions. The iminium intermediate of the catalytic cycle was isolated. When it was put back into the solution reaction system, the same level of yield and stereoselectivity was observed. Based on these observations, we argue that organocatlyst is actually an *in situ* chiral auxiliary.

Keywords: asymmetric Diels–Alder reaction; camphor sulfonyl hydrazine; CaSH; hydrazines; organocatalysis



Scheme 1. Camphor sulfonyl hydrazines.

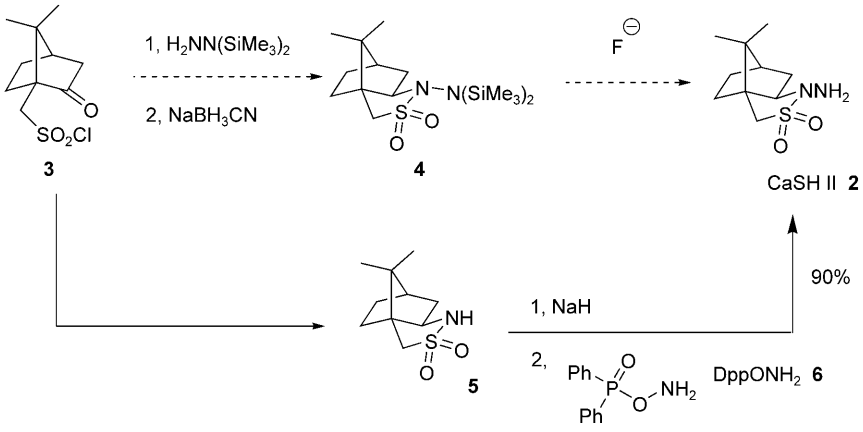
Enantioselective organocatalysis, the use of small organic molecules to catalyze asymmetric transformations, is unarguably one of the most exciting research areas in synthetic organic chemistry in recent years.[1] Various catalytic systems have been developed and put into practice for the synthesis of chiral molecules. Among different types of organocatalysts,[2] Lewis base catalysts were first developed and have been widely applied to various types of asymmetric transformations.

Among the Lewis base organocatalysts reported in the literature, almost all of them are either secondary or primary amines,[3] and many of them are derived from naturally occurring amino acids. Recently, based on the concept of α-heteroatom effect,[4] we reported the first example of using hydrazine as a new functionality for Lewis base organocatalysis. CaSH I, camphor sulfonyl hydrazine (**1**, Scheme 1), was prepared and demonstrated as an effective organocatalyst for asymmetric Diels–Alder,[5] indole alkylation,[6] and aza-Michael additon reactions.[7]

CaSH I is quite active towards aldehyde substrates. However, its reactivity towards ketones is rather limited. Actually, it is rather common in secondary amine organocatalysis that they are less reactive towards ketones than aldehydes. Steric hindrance may be one of reasons for this difference in reactivity.

In CaSH I, the active β-nitrogen is a secondary hydrazine. In this communication we would like to introduce a new generation CaSH organocatalyst. CaSH II (**2**), which is an isomer of CaSH I and shows excellent reactivity towards both aldehyde and ketone substrates. The active nitrogen of CaSH II is a primary hydrazine and is external to the tricyclic structure.

The synthetic approach to CaSH II is outlined in Scheme 2. Originally, we planned to prepare CaSH II *via* a similar route as for the synthesis of CaSH I by reacting camphor sulfonyl chloride **3** with bis-TMS-protected hydrazine followed by hydride reduction. CaSH II could then be prepared by de-protection of **4** with fluoride. However, this approach did not work as planned. Although bis-TMS-protected hydrazine is a known compound,[8] its preparation was found to be troublesome. We then moved to a more direct approach by amination of camphor sultam (Oppolzer's sultam).[9] Sultam **5** is a well known chiral auxiliary



Scheme 2. Synthesis of CaSH II.

that is commercially available or can be easily prepared from camphor sulfonyl chloride. After trying several electrophilic amination agents such as hydroxylamine-*O*-sulfonic acid.[10] (HOSA) and 1-oxa-2-azaspiro[2.5]octane,[11] we found that *O*-(diphenylphosphinyl)-hydroxylamine[12] ($DppONH_2$, **6**) gave the most satisfactory result. Treatment of camphor sultam **5** with NaH in THF followed by $DppONH_2$ afforded CaSH II in over 90% yield. The structure of CaSH II is confirmed by X-ray analysis (Figure 1).[13]

CaSH I is very reactive towards α,β-unsaturated aldehydes in Diels–Alder reactions, but its reactivity towards α,β-unsaturated ketones is very slow. Therefore, we picked Diels–Alder reactions with α,β-unsaturated ketones to probe the reactivity and selectivity of CaSH II. Being one of the most useful reactions for carbon-carbon bond formation and construction of carbocyclic systems, the Diels–Alder reaction is still one of the most studied and most utilized reactions in organic synthesis. In particular, the development of efficient catalytic systems to effect enantioselective variants has been the focus in asymmetric catalysis.[14]

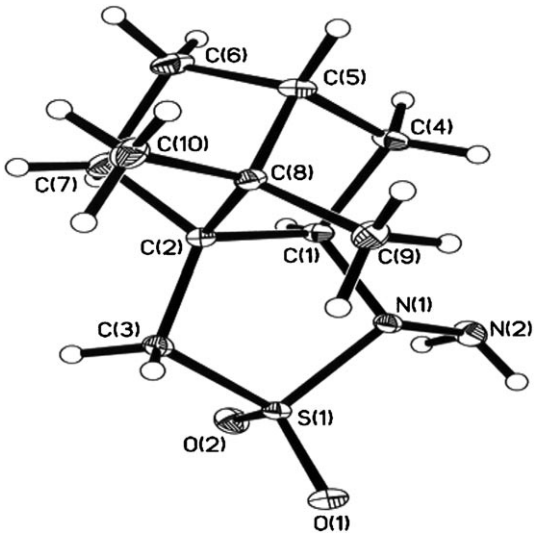
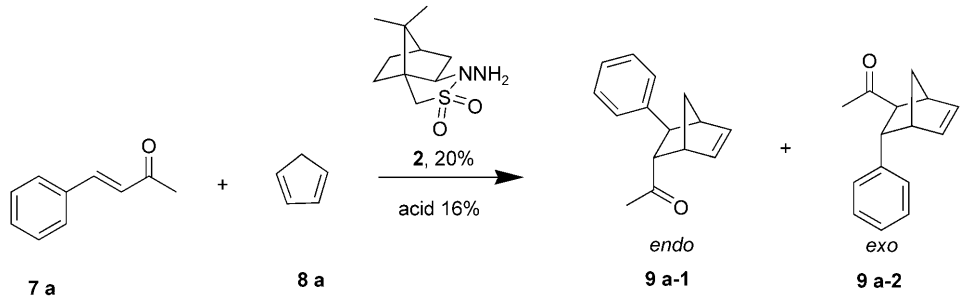


Figure 1. X-ray structure of CaSH II.

We are indeed pleased to find that CaSH II, as a primary hydrazine, is much more reactive than CaSH I towards ketone substrates. In the presence of HCl (added as 1 M ether solution) as the acid additive, the Diels–Alder reaction between α,β-unsaturated ketone **7a** and cyclopentadiene took place smoothly in $CHCl_3$, THF, and toluene at room temperature with good isolated yields, *endo*/*exo* selectivities and enantioselectivities (entries 1 to 3, Table 1). However, in MeOH/H_2O or *tert*-butyl methyl ether (TBME), only trace amounts of the product could be detected (entries 4 and 5). Nonetheless, to our surprise and delight, a white precipitate was formed when the HCl salt of CaSH II was mixed with ketone **7a** in TBME.

The HR-MS data of the white precipitate confirmed that it is the iminium ion **11** (Figure 2) formed between the ketone and CaSH II (HR-MS: $m/z =$ 359.1789; calcd. for $C_{20}H_{27}N_2O_2S$: 359.1793). When the iminium salt suspended in $CHCl_3$ was briefly treated with solid $NaHCO_3$, two isomeric imine compounds could be isolated by column chromatography. ^1H and ^{13}C NMR ($\delta = 176.5$ and 174.6 for the imine carbons) also confirmed the structure of **11** with a *Z*/*E* ratio of 1:1. When the white precipitate **11** was re-dissolved in $CHCl_3$ at room temperature in the presence of cyclopentadiene and some more added HCl, the Diels–Alder reaction took place readily and resulted in the same level of yield (94%) and enantioselectivity (88% *ee*) as compared to the normal catalytic reaction in the same solvent (compare entry 1 of Table 1). This provides concrete evidence that iminium salt **11** is the reactive intermediate of this CaSH II-catalyzed Diels–Alder reaction.[15] The reactive intermediate in a Lewis base-catalyzed reaction could be isolated and then put back into solution to complete the reaction. With the isolation of intermediate **11**, we propose that the Lewis base organocatalyst is

Table 1. Optimization of reaction conditions.



Entry	Solvent	Acid additive	*T/t* [°C/h]	Yield [%]	*endo/exo*[a,b]	*ee*[b] of *endo* [%]
1	$CHCl_3$	HCl/ether	0/48	94	98:2	80
2	THF	HCl/ether	r.t./24	90	96:4	82
3	toluene	HCl/ether	r.t./12	82	97:3	84
4	MeOH/H_2O [4/1]	HCl/ether	r.t./24	trace	–	–
5	TBME	HCl/ether	r.t./24	trace	–	–
6	toluene	benzoic acid	r.t./24	trace	–	–
7	toluene	TCA	r.t./24	91	96:4	78
8	toluene	TFA	r.t./12	90	96:4	74
9	toluene/THF [4/1]	TfOH	−20/48	70	98:2	88

[a] The *exo/endo* ratios were determined by ^{1}H NMR.
[b] Determined by chiral HPLC using a Chiralcel OD-H or AD-H column.

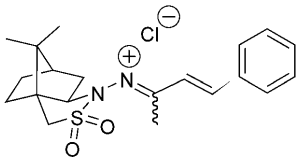


Figure 2. Isolated iminium ion **11**

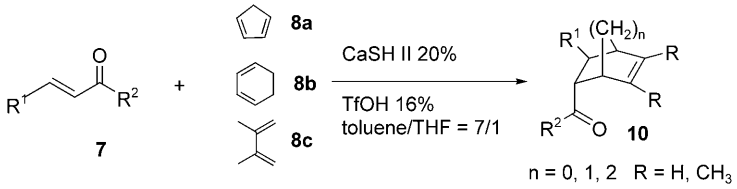
actually equivalent to an *in situ* chiral auxiliary. The organocatalyst forms a covalent iminium intermediate *in situ* with the ketone substrate, which is more reactive than the ketone itself[1d,16,17] and provides the stereochemical control of the enantioselective process. Of course, as different from the chiral auxiliary approach, the covalent intermediate in organocatalysis is not isolated but forms *in situ* in the catalytic cycle. After the reaction, the organocatalyst departs from the product and re-enters back to the catalytic cycle.

We also studied the effect of an acid additive on these CaSH II-catalyzed Diels–Alder processes. A weaker acid such as benzoic acid was not suitable while trichloroacetic acid (TCA, the best acid co-catalyst for the CaSH I system) and trifluoroacetic acid afforded comparable results as HCl (entries 6, 7, 8, Table 1.). Eventually, we found that triflic acid gave the best result in a toluene/THF (7:1) solvent system with 90% yield and 88% enantioselectivity (entry 9).

With these optimized conditions, we further explored the scope of the reaction. The results are summarized in Table 2. For β-aryl-substituted α,β-unsaturated ketones (**7a–l**, entries 1 to 12, Table 2), the product yields, *endo*/*exo* ratios and enantioselectivities are consistently high with the exception of an *ortho*-substituted aryl ketone (entry 6). Electron-withdrawing substituents on the aryl rings did not affect the enantioselectivities that much. However, an electron-donating group at the *para*-position such as 4-methoxy (entry 2) afforded 96% *ee*. As compared with methyl ketones, bigger ketones such as ethyl, *n*-propyl and phenyl in general afforded slightly poorer *ee* values (entries 8, 9, 10). Reactions with other dienes such as cyclohexa-1,3-diene and 2,3-dimethylbuta-1,3-diene also afforded reasonable enantioselectivities, but the reactions were much slower (entries 11 and 12). For the aliphatic α,β-unsaturated ketone (**7m**), the reaction could be carried at lower temperatures with moderate *ee* (entry 13). Assignments of the absolute configurations of the cycloadducts were based on optical rotations and literature precedents.

Once again, we have demonstrated that hydrazine is an effective functionality for organocatalysis. This supplements the uses of primary and secondary amines in this important research area. CaSH II has been synthesized by simply amination of camphor sultam. In one step, we have turned a well known chiral auxiliary, Oppolzer's sultam, into an organocatalyst. In contrasted to CaSH I, CaSH II exhibits excellent reactivity and selectivity towards ketone substrates in asymmetric Diels–Alder reactions with up to 96% *ee*. In principle, other secondary amine orga-

Table 2. Scope of CaSH II catalyzed Diels–Alder reactions.



Entry [**10**]	R^1/R^2/Diene **8**	*T*/*t* [°C/h]	Yield[c] [%]	*endo*/*exo*[a,b]	*ee*[b] of *endo* [%]
1 [**10a**]	4-MeC_6H_4/Me/**8a**	r.t./24	87	96:4	86
2 [**10b**]	4-$MeOC_6H_4$/Me/**8a**	r.t./24	89	96:4	96
3 [**10c**]	3-$MeOC_6H_4$/Me/**8a**	r.t./24	88	96:4	72
4 [**10d**]	4-$BrMeC_6H_4$/Me/**8a**	0/12	96	96:4	92
5 [**10e**]	3-$BrMeC_6H_4$/Me/**8a**	0/12	82	96:4	84
6 [**10f**]	2-$BrMeC_6H_4$/Me/**8a**	0/12	85	85:15	11
7 [**10g**]	4-$NO_2MeC_6H_4$/Me/**8a**	−20/48	93	96:4	84
8 [**10h**]	4-$MeOC_6H_4$/Et/**8a**	r.t./24	92	96:4	90
9 [**10i**]	4-$MeOC_6H_4$/*n*-Pr/**8a**	r.t./16	96	96:4	86
10 [**10j**]	4-$MeOC_6H_4$/Ph/**8a**	r.t./72	70	96:4	84
11 [**10k**]	4-$NO_2MeC_6H_4$/Me/**8b**	r.t./96	40	96:4	82
12 [**10l**]	4-$NO_2MeC_6H_4$/Me/**8c**	r.t/48	82	96:4	70
13 [**10m**]	Me/Et/**8a**	−20/48	91	96:4	82

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC using a Chiralcel OD-H or AD-H column.
[c] Yield refers to isolated materials after purification by flash chromatography on silica gel.

nocatalysts could also be transformed to the corresponding hydrazine organocatalysts *via* a similar electrophilic amination approach.

In addition, the key iminium intermediate of the Lewis base catalytic process was also isolated. When it was put back to the solution reaction system, the same level of yield and selectivity was observed. This unambiguously proves the intermediacy of the Lewis base organocatalysis. Based on this observation, we argue that the organocatalyst is actually an *in situ* chiral auxiliary.

Experimental Section

Preparation (−)-2,10-*N*-Aminocamphorsultam (CaSH II, 2)

Sodium hydride (60% dispersion in mineral oil, 100 mg, 2.5 mmol) was added to a stirred solution of (−)-2,10-camphorsultam (430 mg, 2 mmol) in THF (20 mL) at 0 °C. After 10 min, $DppONH_2$[12b] (700 mg, 3 mmol) was added in one portion and the slurry was stirred for 4 h at room temperature. The solid was removed by filtration and the filtrate was concentrated to get a white solid. The white solid was purified by recrystallization using CH_2Cl_2 and hexane (1 mL: 10 mL) to afford **2**; yield: 415 mg (90%); mp 119–121 °C; $[\alpha]_D^{23}$: −72 $cm^3 g^{-1} dm^{-1}$ (*c* 1.03 $g cm^{-3}$ in, CH_2Cl_2); IR (neat): ν = 3351, 3000, 2957, 2869, 1616, 1479, 1454, 1427, 1278, 1261, 1061, 811, 567, 555 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.50 (br, 2H) 3.18 (dd, 2H, *J* = 14 Hz), 2.88 (q, 1H, *J* = 4 Hz), 2.12 (m, 1H), 1.93–1.70 (m, 4H), 1.41 (m, 1H), 1.28 (m, 1H), 1.15 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.1, 47.7, 47.5, 47.1, 44.4, 35.3, 32.6, 27.1, 20.5, 19.8. HR-MS: *m*/*z* = 231.1179, calcd. for $[M+H]^+$ ($C_{10}H_{19}N_2O_2S$): 231.1162.

General Procedure for CaSH II-Catalyzed Diels–Alder Reactions

To a mixture of Cash II (**2**, 0.04 mmol, 9.12 mg) and the α,β-unsaturated ketone (0.2 mmol) in 1 mL of dried toluene/THF (7/1) were added dropwise 1.5 mL of trifloromethanesulfonic acid solution (4.8 mg, 320 mg mL^{-1}, toluene/THF = 4/1). After stirring at −20 or 0 °C for 15 min, freshly distilled cyclopentadiene (4 mmol) was added. The reaction mixture was kept at −20, 0 °C or room temperature until consumption of the starting ketone (tracked by TLC). The reaction mixture was directly purified by column chromatography, first with pure PE then PE/EtOAc from 15/1 to 10/1 to give the pure Diels–Alder adducts.

Acknowledgements

Finical support from the Faculty Research Grants (FRG1/08-09/058 and FRG2/09-10/039) and the Hong Kong Research Grant Council is gratefully acknowledged. A. W. M. Lee thanks the Nagoya University for the award of the RCMS Visiting Professorship.

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