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Chiral bis-trifluoromethanesulfonylamide as a chiral Brønsted acid catalyst for the asymmetric hetero Diels–Alder reaction with Danishefsky's diene

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Abstract—Bis-trifluoromethanesulfonylamide (bis-triflylamide) itself works as an efficient chiral Brønsted acid catalyst for the hetero Diels–Alder reactions between Danishefsky's diene and glyoxylate or phenylglyoxal presumably through double hydrogen bonding.

The development of highly efficient asymmetric catalysts is one of the most important subjects in modern organic synthesis.[1] In view of the growing interest in metal-free green catalysis, a number of organocatalysts or chiral Brønsted acid catalysts have been developed.[2,3] In 1995, we already reported the development of lanthanide bis-trifluoromethanesulfonylamide (bis-triflylamide) as a chiral catalyst for the hetero Diels–Alder (HDA) reaction[4] with Danishefsky's diene. Upon addition of water to the reaction mixture, significant increase was observed not only in the enantioselectivity but also in the chemical yield (Scheme 1).[5] It can be rationalized that the added water acts as a proton source and that the protonated bis-triflylamide effectively acts as a chiral Brønsted acid catalyst.

We report here the catalytic activity of bis-triflylamide as a chiral Brønsted acid catalyst for the HDA reaction between Danishefsky's diene and glyoxylate to substantiate our rationale. Bis-triflylamide has intrinsic Brønsted acidity[6] due to the electronegative effect of trifluoromethanesulfonyl substituent and is expected to be a chiral Brønsted acid catalyst for the HDA reaction.

First, we searched for effective bis-triflylamides as Brønsted acid catalysts for the HDA reaction under the reported conditions[4] except for the absence of water and a lanthanide complex (Scheme 1 and Table 1). Among these chiral bis-triflylamides, (*R*,*R*)-1,2-*N*,*N*′-bis-(trifluoromethanesulfonylamino)-1,2-diphenylethane (DPENTf) itself gave the highest enantioselectivity (75% ee) (entry 2). On the other hand, (*R*)-2,2′-bis-(trifluoromethanesulfonylamino)-1,1′-binaphthyl (DABNTf) of higher acidity,[7] only provided a moderate enantioselectivity at low (−78 °C) reaction temperature (entry 8). Other aromatic chiral Brønsted acids, such as (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol (6,6′-Br_2-BINOL) and (*R*)-3,3′-diphenyl-1,1′-bi-2-naphthol (3,3′-Ph_2-BINOL) afforded lower enantioselectivity. Aliphatic diol (−)-4,5-bis[hydroxyl(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolane (TADDOL), which was reported by Rawal and co-workers[8] as an excellent chiral acid in the reaction with amino-substituted dienes, gave, however, low enantioselectivity (entry 11). It was thus shown that bis-triflylamides, especially DPENTf gave the highest enantioselectivity in the asymmetric HDA reaction with Danishefsky's diene.

This DPENTf-catalyzed HDA reaction was carried out in a wide variety of organic solvents[9] to give a varying degree of enantioselectivity (Table 2). Especially in less polar media such as toluene, higher enantioselectivity (63–67% ee) was obtained (entries 1 and 2). In contrast, in more polar media such as acetonitrile, lower enantioselectivity (25% ee) was observed (entry 7). It can be assumed that hydrogen bonding between glyoxylate and DPENTf is more effective in less polar solvents.

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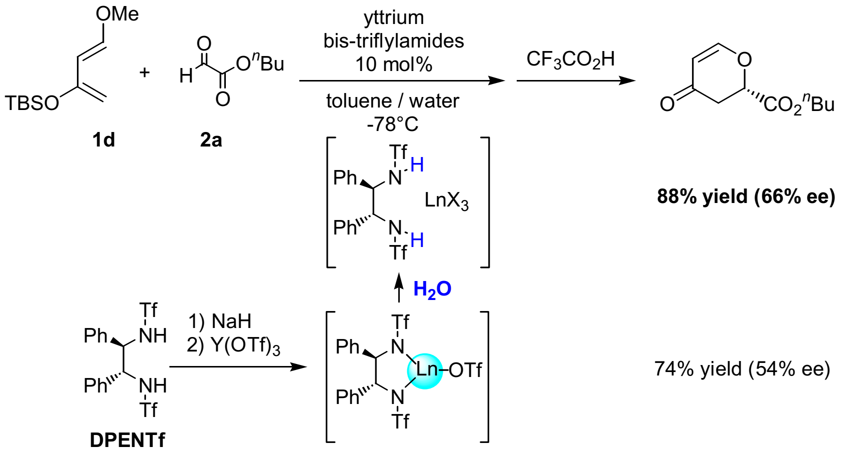
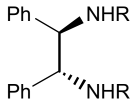
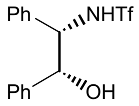
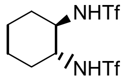
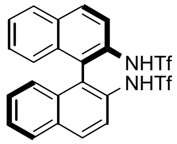


Scheme 1. Hetero Diels–Alder reaction catalyzed by chiral lanthanide complexes.

Table 1. Chiral Brønsted acid catalysts in the hetero Diels–Alder reaction[a]

Entry	Chiral catalyst			Temperature (°C)	Yield (%)[b] (% ee[c])	Config.[d]
1				−20	55 (58% ee)	*S*
2		DPENTf	R = Tf	−78	**39 (75% ee)**	*S*
3		DPENTs	R = Ts	−20	28 (21% ee)[f]	*S*
4		DPEN	R = H	−20	21 (2% ee)	*S*
5				−20	84 (24% ee)[g]	*R*
6				−20	54 (10% ee)	*S*
7		DABNTf		−20	57 (57% ee)	*R*
8				−78	17 (58% ee)[e]	*R*
9	(*S*)-6,6-Br_2-BINOL			−20	65 (2% ee)	*S*
10	(*R*)-3,3-Ph_2-BINOL			−20	67 (5% ee)	*S*
11	(−)-TADDOL			−20	55 (5% ee)	*S*

[a] All reactions were carried out using 0.12 mmol of Danishefsky's diene **1d**, 0.1 mmol of butyl glyoxylate **2a** and 10 mol % of a catalyst in toluene.

[b] Isolated yield.

[c] Determined by HPLC analysis using DAICEL CHIRALPAK AD.

[d] Determined by comparison of the HPLC retention time with the literature data.

[e] 30 mol % of a catalyst was used.

[f] CH_2Cl_2 was used as solvent.

[g] TIPS diene (**1e**) was used.

By exchanging the substituents of Danishefsky's diene and glyoxylate, not only the chemical yield but also the enantioselectivity significantly increased (Table 3). The change of the siloxy groups from TMS (**1c**) to bulky TBDPS (**1f**) led to significant increase in the chemical yield from 43% to 75% (entries 3 and 6). The enantioselectivity also increased up to 76% ee at −78 °C, by further increase in the steric demand of the siloxy group up to TIPS (entry 8). In contrast, relatively less sterically demanding ethyl glyoxylate (**2b**) provided higher chemical yield (87%) and enantioselectivity (86% ee).

The present DPENTf-catalyzed HDA reaction with TIPS-substituted Danishefsky's diene is also applicable to phenylglyoxal (Table 4). The change of glyoxylate to phenylglyoxal as a dienophile gave equally high enantio- selectivity (87% ee) (entry 1). Substituted phenylglyoxals[10] were also examined to afford high enantioselectivity (entries 2 and 3).

Finally, the double or single hydrogen bonding between DPENTf and carbonyl compounds was examined by ^1H NMR analysis[11] of DPENTf and symmetrical ketone **3**

Table 2. Effect of solvent on the HDA reaction[a]

Entry	Solvent	Dielectric constant[b]	Yield (%)[c]	ee (%)[d]
1	Toluene	2.4	59	63
2	Et_2O	4.3	33	67
3	CH_2Cl_2	8.9	57	45
4	BTF	9.2	39	45
5	AcOEt	6.0	20	31
6	THF	7.6	49	17
7	MeCN	37.5	26	25

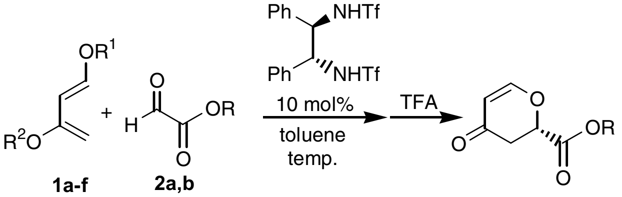
[a] Unless otherwise indicated, reactions were carried out using 0.12 mmol of Danishefsky's diene **1d**, 0.1 mmol of butyl glyoxylate **2a** and 5 mol % of a catalyst at −20 °C.

[b] At 25±5 °C.

[c] Isolated yield.

[d] Determined by HPLC analysis using DAICEL CHIRALPAK AD.

Table 3. HDA reaction catalyzed by (*R*,*R*)-DPENTf[a]



1a-f **2a,b**

1a R^1 = ^{t}Bu, R^2 = TMS **1b** R^1 = ^{i}Pr, R^2 = TMS **2a** R = ^{n}Bu
1c R^1 = Me, R^2 = TMS **1d** R^1 = Me, R^2 = TBS **2b** R = Et
1e R^1 = Me, R^2 = TIPS **1f** R^1 = Me, R^2 = TBDPS

Entry	**1** (R^1, R^2)	**2** (R)	Temperature (°C)	Yield (%)[b] (% ee[c])
1	**1a**	**2a**	−20	23 (23% ee)[d]
2	**1b**	**2a**	−20	34 (41% ee)[d]
3	**1c**	**2a**	−20	43 (55% ee)
4	**1d**	**2a**	−20	55 (58% ee)
5	**1e**	**2a**	−20	74 (65% ee)
6	**1f**	**2a**	−20	75 (64% ee)
7	**1d**	**2a**	−78	39 (75% ee)[e]
8	**1e**	**2a**	−78	54 (76% ee)[e]
9	**1e**	**2a**	−78	87 (86% ee)[e]

[a] All reactions were carried out using 0.12 mmol of Danishefsky's diene **1**, 0.1 mmol of glyoxylate **2** and 10 mol % of a chiral catalyst for 4 h unless otherwise mentioned.

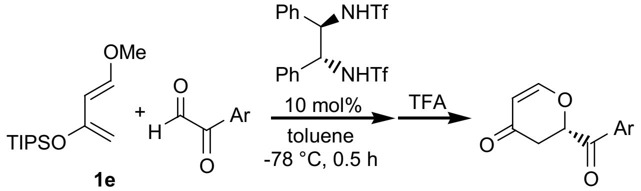
[b] Isolated yield.

[c] Determined by HPLC analysis using DAICEL CHIRALPAK AD.

[d] 5 mol % of a catalyst was used.

[e] Reaction time 0.5 h.

Table 4. Hetero Diels–Alder reaction with glyoxal[a]



1e

Entry	Ar	Yield (%)[b] (% ee[c])
1	Ph	67 (87% ee)[d]
2	*p*-CF_3Ph	74 (78% ee)[d]
3	*p*-MeOPh	46 (77% ee)[d]

[a] Unless otherwise mentioned, all reactions were treated with 10 mol % of a chiral catalyst in toluene at −78 °C for 0.5 h.

[b] Isolated yield.

[c] Determined by HPLC analysis using DAICEL CHIRALPAK AD.

[d] The absolute configuration was not determined.

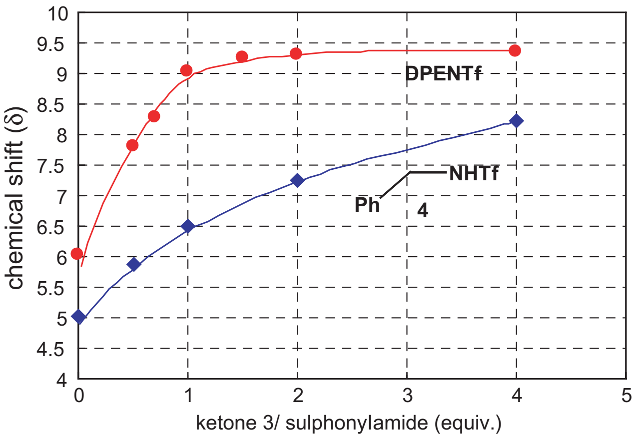
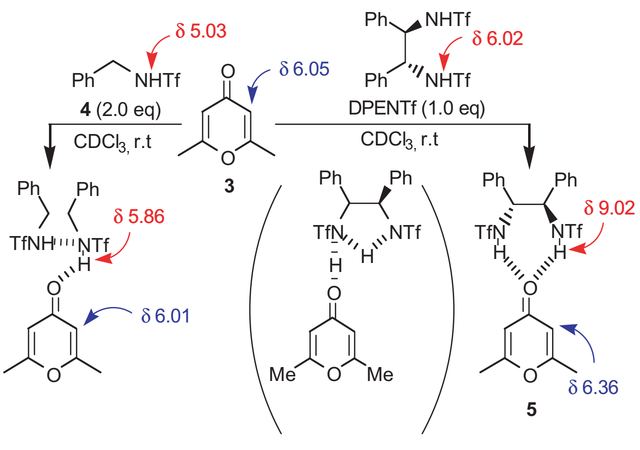


Figure 1. ^1H NMR chemical shift of DPENTf amide protons versus equivalents of ketone **3**.

(Scheme 2).[12] The symmetrical complex **5** of DPENTf and ketone **3** was only observed in ^1H NMR. As ketone **3** was added, a downfield shift for the amide proton of DPENTf significantly increased, but no change was observed in the range of an equal to excess amount (catalytic conditions) of ketone **3** (Fig. 1). The original signals of the DPENTf amide proton and the olefin proton of ketone **3** appeared at δ 6.02 and 6.05 ppm, respectively. For a 1:1 mixture of ketone **3** and DPENTf, the downfield shifts for the olefin proton of ketone **3** from 6.05 to 6.36 ppm and for the amide proton of DPENTf from 6.02 to 9.02 ppm were observed. We further compared DPENTf with monosulfonylamide **4**. The chemical shift of DPENTf clearly indicated a saturated curve over 1 equiv. of ketone **3**. On the other hand, the chemical shift of sulfonylamide **4** gradually increased with increase of the molar amount of ketone **3**. Therefore, the significant downfield shifts and saturated curve in the case of DPENTf suggest the double hydrogen bonding system[14] of DPENTf and ketone **3** to form the highly symmetrical and rigid complex **5** rather than unsymmetrical **6**.

In summary, we have demonstrated that a chiral bis-triflylamide, especially DPENTf, works effectively as a



Scheme 2. Proposed hydrogen bonding.

chiral Brønsted acid catalyst for the HDA reactions with Danishefsky's diene through double hydrogen bonding.

Typical experimental procedure is described for the reaction of Danishefsky's diene and butyl glyoxylate: To a solution of (*R*,*R*)-1,2-*N*,*N*′-bis-(trifluoromethanesulfonylamino)-1,2-diphenylethane (0.01 mmol) in toluene (0.5 ml) was added *n*-butyl glyoxylate (0.10 mmol) and (*E*)-1-methoxy-3-[(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene (0.12 mmol) at −78 °C. After stirring for 30 min, the resultant mixture was added trifluoroacetic acid. After usual workup, the crude product was purified by silica gel column chromatography (hexane/AcOEt = 10:1) gave the desired hetero Diels–Alder adduct. The enantiomeric excess of the hetero Diels–Alder adduct was determined by chiral HPLC analysis (DAICEL CHIRALPAK AD column, hexane/*i*-PrOH = 90/10, flow rate 1.0 ml/min, t_R = 8.5 min (*R*), 11.3 min (*S*)).

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