Thesis Summary

Intramolecular Hydrofunctionalization Reactions of Alkenyl Amines Catalyzed by Disulfonimides

(ジスルホンイミドを用いたアルケニルアミンのヒドロアミノ化反応)

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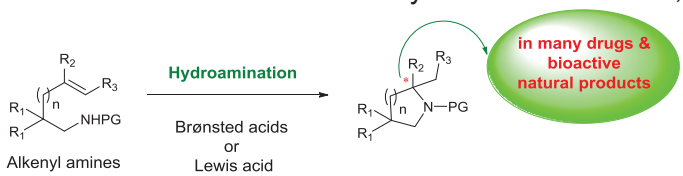
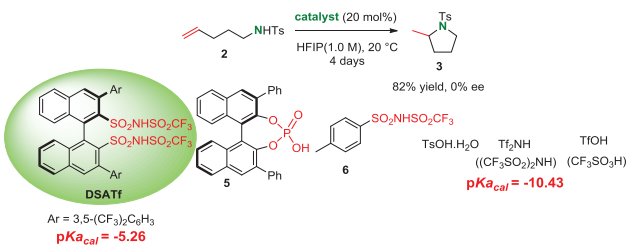
Nitrogen-atom containing heterocycles are the structural cores of enormous drugs and biologically active natural products[1]. Among the various approaches to the synthesis of chiral nitrogen-containing heterocycles, the hydroamination reaction of alkenyl amines catalyzed by Brønsted acids or Lewis acids has recently emerged as a particularly efficient method. There have been many reports on asymmetric hydroamination reactions using metal Lewis acids as catalysts. The use of Brønsted acids has been less studied because Brønsted acids are not sufficiently acidic to activate the olefin moiety. On the other hand, Lewis acidic metals can directly activate the olefin or amine moiety of the substrate. Thus, a few asymmetric hydroaminations of alkenyl amine with specific protecting groups, which are activated by Brønsted acid, have been developed.



In this study, in order to overcome acidity limitations of Brønsted acids for direct olefine activation on hydroamination, a new chiral BINOL-derived disulfonamide trifluoromethanesulfonate (**DSATf**) was designed, based on the strong acidity of Tf_2NH. The acidity of **DSATf** was estimated by the computational calculation of pK_a value in DMSO. The computationally predicted the pK_a value (–5.26) categorized **DSATf** as a strong Brønsted acid. **DSATf** was applied to the hydroamination of alkenyl amine **2** as a catalyst (Scheme 1). The hydroamination using **DSATf** proceeded smoothly and effectively even at 20°C in HFIP solvent, but no enantioselectivity was observed. The comparison of catalytic efficiencies of **DSATf** with several Brønsted acids on the hydroamination showed the catalytic ability order of Brønsted acids was: $TsOH{\cdot}H_2O$, Tf_2NH > TfOH ≈ **DSATf** >> TsNHTf (**6**) by considering the time profile of the chemical yield of **3** (Figure 1).



Scheme 1. DSATF-catalyzed hydroamination of **2**

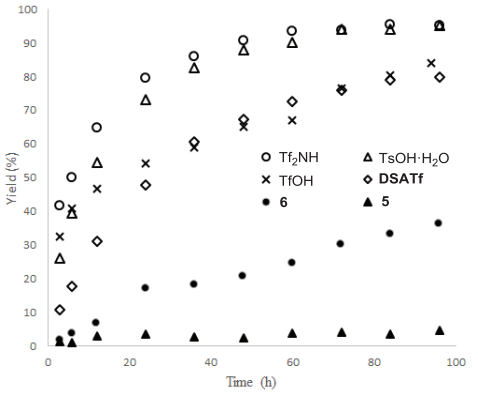
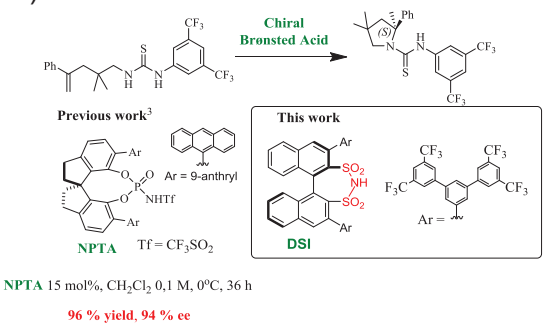


Figure 1. Time Profile of Chemical Yield of Pyrrolidine **3** in Hydroamination of **2**

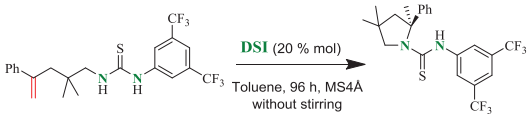
Liu and co-workers have reported an enantioselective hydroamination of alkenyl thioureas. The authors believe that the reaction proceeded by the activation of thiourea moiety by **NPTA**[3]. Next, a cyclic disulfonimide **DSI**[2] was selected as a Brønsted catalyst in order to achieve asymmetric induction on hydroamination (Scheme 2). The optimization of reaction conditions, including concentration, temperature and stirring of the



Scheme 2. Hydroamination of alkenyl amine with a thiourea protecting group.

reaction mixture, was examined (Table 1). When the reaction is carried out without stirring, the enantioselectivities remained almost the same (70 % ee) even when the reaction concentration decreased from 50 mM to 2.5 mM (entries 1, 3-6). When the amount of **DSI** increased from 20 % mol to 30 % mol, the chemical yield increased and the product with the best chemical yield (86 %) was obtained. At low temperature (0°C), the enantioselectivity could not be improved and the chemical yield also decreased (entries 2, 8). When the reaction was stirred, interestingly the chemical yield was dropped, but there was no change in enantioselectivity (entries 1,7). These results indicated that the dilute (2.5 mM) concentration and non-stirring of the reaction mixture were important factors in controlling the enantioselectivity.

Table 1. Optimization of reaction conditions[a]



entry	Conc. (mM)	temp. (°C)	yield (%)[b]	e.e.(%)[c]	entry	Conc. (mM)	temp. (°C)	yield (%)[b]	e.e.(%)[c]
1	50	20	78(63)[d]	68(69)[d]	5[e]	5	20	77	70
2	50	0	56	66	6[e]	2.5	20	64	70
3[e]	20	20	64	68	7[e,f]	2.5	20	86 (27)[d]	70(70)[d]
4[e]	10	20	80	69	8[e,f]	2.5	0	24	75

[a] Unless otherwise noted, reactions were performed with alkenyl thiourea (44 mmol), **DSI** (20 mol%), MS4Å (50 mg) in toluene at 20°C for 96 h. The reactions were performed in a 5-mm NMR tube under non-stirring. b. Isolated yield.
c. Determined by chiral stationary phase HPLC.
d. The reaction was performed in a test tube under stirring with a stirring bar.
e. The reaction was performed in a test tube under non-stirring.
f. 30 mol% of **DSI** was used.

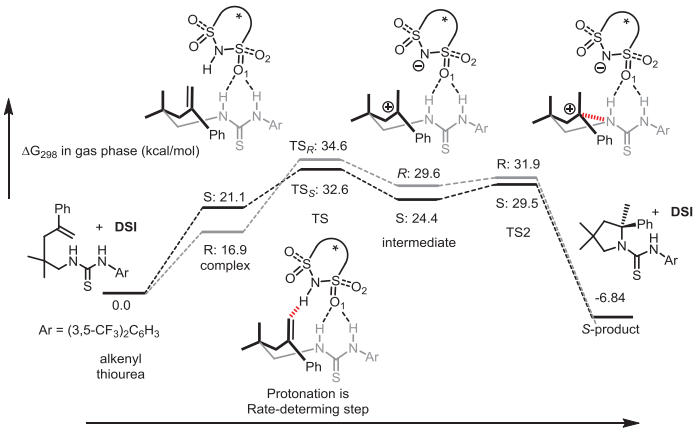


Figure 2. Calculated Gibbs energy profile for the **DSI**-catalysed hydroamination of alkenyl thiourea (at 298.15 K in toluene at the M06-2X/6 311+G(d,p)/SMD(toluene)//ONIOM(M06-2X/6-31G(d):HF/3-21G*) level of theory)

The computational study on **DSI**-catalyzed asymmetric hydroamination was also performed to understand the mechanism of the hydroamination and the origin of stereoselectivity (Figure 2). The Gibbs energy profile in toluene showed that **DSI** was activated by dual hydrogen bonding from thiourea moiety, and the reaction proceeded through a stepwise mechanism, in which the protonation of olefin was a rate-determining step. The structure TS_s, which generated the hydroamination product with the (*S*)-configuration, was energetically favored.

In conclusion, a new strong Brønsted acid **DSATf** has been developed. The computational prediction of pK_a value of **DSATf** categorized it as a strong Brønsted acid. **DSATf** catalyzed hydrofunctionalizations of alkenyl amines proceeded with high efficiency, but no enantioselectivity was observed. A cyclic **DSI** catalyzed asymmetric intramolecular hydroamination of alkenyl thioureas was also examined, and a cyclic amine was obtained in good chemical yield and moderate enantioselectivity under dilute conditions without stirring. The DFT calculation on hydroamination supported a mechanism, in which thiourea moiety of alkenyl amines acted as a hydrogen bond donor.

[Reference]
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2. Q.Wang, M. Leutzsch, M. Van Gemmeren, B. List, *J. Am. Chem. Soc*. **2013**,135, 15334-15337.
3. J.S. Lin, P. Yu, L. Huang, P. Zhang, B. Tan, X. Y. Liu, *Angew. Chem. Int. Ed.* **2015**, 54, 7847-7851.
[List of Publication]
1. Ryukichi Takagi, Yuichiro Sakai, Duyen Thi Duong, *Tetrahedron*. **2021**,132037.
2. Ryukichi Takagi, Duyen Thi Duong, Toshiya Ichiki, *Tetrahedron*. **2021**,132332.