Organocatalysis

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Towards High-Performance Lewis Acid Organocatalysis**

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Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *The combination of Lewis acid organocatalysis and internal hydrogen-bond assistance was used to develop a new type of highly active disulfonimide catalyst. The increased Lewis acidity was documented by activity comparisons as well as theoretical investigations. Finally, the potential of the hydrogen-bond-assisted disulfonimide catalyst was demonstrated by its application in an enantioselective transformation.*

Organocatalysis has grown significantly in recent years but the development of high-performance organocatalysts with turnover numbers exceeding 100 000 remains challenging.[1] A promising solution could involve acid catalysis and, since following the groundbreaking reports by Akiyama and Terada in 2004, Brønsted acid activation have become a major research area in organocatalysis.[2,3] Our laboratory currently explores Lewis acid organocatalysis, speculating that it ultimately may become an equally powerful tool. However, this field has proven challenging to explore.[4] Various contributions around the theme of Lewis acid organocatalysis[5–9] have recently inspired us to design and develop chiral disulfonimides (DSIs) as powerful and highly enantioselective Lewis acid catalyst precursors.[10] Disulfonimides are Brønsted acids per se,[11] but upon treatment with a silicon nucleophile, they are converted into Lewis acids by protodesilylation.[12] In contrast to previous chiral silicon-based Lewis acid catalysts, the silylated DSIs therefore do not need to be preformed.[13] Despite the attractive features of this type of Lewis acid organocatalysis, common bottlenecks include catalyst activity and versatility. In recent years, we have been investigating strategies towards the development of high-performance Lewis acid catalysis. We now report the design and exploration of particularly active DSI catalysts that are based upon the internal activation by alcohols as secondary interacting groups.[14]

We envisioned the bis-3,5-bis(trifluoromethyl)phenylmethanol group as a suitable candidate for the further activation of Brønsted or Lewis acids by means of internal hydrogen-bond activation.[14a] This particular substructure has already found utility in organocatalysts developed by the groups of Jørgensen, Hayashi,[15] and Maruoka,[16] in which its role has been steric encumbrance and substrate preorientation rather than to the internal activation of the catalyst itself. Hence we were interested to introduce this electron-poor biarylmethanol group to the 3,3′-positions of the C_2-symmetric disulfonimides (Figure 1).

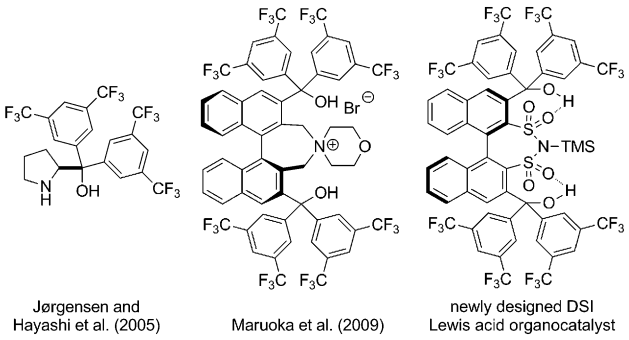

Figure 1. The 3,5-bis(trifluoromethyl)biarylmethanol group as an activating element in organocatalysis.

Common synthetic routes towards 3,3′-substituted BINOL-derived chiral catalysts are based on transition-metal-catalyzed cross-coupling reactions.[17,18] These procedures are efficient and reliable, but the overall atom economy is often diminished by protecting group manipulations.[19] From this point of view it would be desirable to open up synthetic pathways using unsubstituted catalyst molecules[20] introducing all further molecular complexity in *one* final step. Along these lines, the in situ lithiation/halogenation of the unsubstituted disulfonimide was reported by Lee et al., enabling convenient and efficient late-stage Suzuki couplings.[21] Apart from this particular study, the concept of lithiation by means of directed ortho-metalation (D*o*M) followed by alkylation for the synthesis of new chiral organocatalysts was not further examined, although the *ortho*-directing properties of, for example, SO_2NR_2 and $P(O)(tBu)_2$ groups are well known.[22] We found that (biaryl)hydroxyl acids (HYDRAs) can be synthesized directly from the corresponding unsubstituted disulfonimides.[23] The previously unknown compounds, for example diol **1a**, were accessed in a one-pot lithiation/alkylation sequence with

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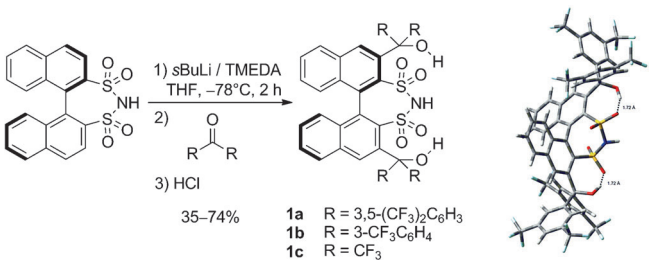


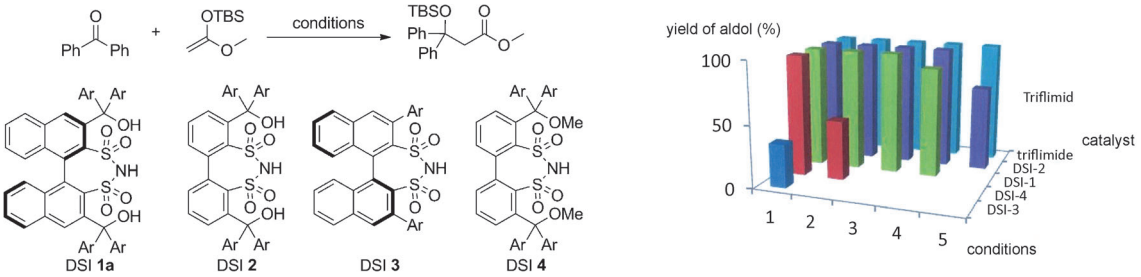
Scheme 1. Synthesis of (biaryl)hydroxy acids **1** and optimized structure (vacuum) of the HYDRA catalyst (BP86/SVP) **1a**.

bis[3,5-bis(trifluoromethyl)phenyl]methanone as an electrophile (Scheme 1).[24] In this way, the structurally complex disulfonimides **1** are available in five steps from BINOL. Remarkably the introduction of substituents in 3,3′-position is achieved without cross-couplings, which is usually a cumbersome step in the syntheses of BINOL-derived organocatalysts.[25]

With the new catalysts **1** in hand, we were interested in their structural features and catalytic properties and chose **1a** for in-depth investigations. As already mentioned, the presence of different Lewis basic sites offers the possibility of intramolecular hydrogen bonding. Unfortunately, the lipophilic character of the catalyst led to difficulties in its crystallization. Thus we tried to further elucidate its structure by molecular modeling (structures optimized at the BP86/SVP level) and NOESY ^{1}H NMR spectroscopy.[26] The optimized structure (Scheme 1) shows that the (biaryl)hydroxy groups indeed engage in an intramolecular hydrogen-bonding network (see the Supporting Information). The hydrogen bonds between the alcohol functions and the Lewis basic sites were calculated to be 1.72 Å long. This leads to a rather rigid diastereotopic orientation of the aryl groups, as confirmed by NOE effects studied by NMR spectroscopy.[27] We expected these hydrogen bonds to have an influence on the catalytic activity of the catalysts by enabling Brønsted acid assisted Lewis acid activation.[14a]

In order to test this hypothesis we chose the Mukaiyama aldol reaction of benzophenone, a challenging substrate in Lewis acid catalyzed aldol reactions, as a model reaction.[28] We started out by comparing the newly synthesized catalysts DSI-**1a** and its achiral analogue DSI-**2** to our benchmark disulfonimide **3**, under conditions where the latter gave partial conversion (conditions 1, Table 1). As additional references we also studied triflimide ($HNTf_2$) and DSI-**4**, the O-methylated analogue of catalyst **2**. Gratifyingly the newly synthesized HYDRA catalysts gave full conversion under these conditions as did our reference catalysts triflimide and **4**. We now proceeded to more challenging reaction conditions, in order to elucidate when incomplete conversion is obtained with the evaluated catalysts. The hypothesis that the free OH groups are responsible for activation was supported by the lower activity of DSI-**4**, which gave 48% yield (determined by NMR analysis) compared to the complete conversions obtained with triflimide, **1a**, and catalyst **2**, when only 1 mol% of catalyst was employed (conditions 2). After a further reduction of the catalyst loading, reaction time, and temperature (conditions 3 and 4), we obtained an 88% yield with DSI-**1a** while triflimide and catalyst **2** still converted all the starting material. Finally the activity limit of DSI-**2** was located, when we obtained 68% conversion in the presence of 0.5 mol% of the catalyst at 0°C in after a reaction time of 5 min (conditions 5).[29,30] From these results we could calculate approximate relative catalyst activities. The results show that our newly designed disulfonimides **1** and **2** are several orders of magnitude more active than either their 3,3′-arylated counterparts **3** or the variant lacking internal activation **4**.[31] In order to further rationalize the striking activity of our new catalyst motif, we decided to attempt to quantify the Lewis acidity of our catalysts. Towards

Table 1: Comparison of HYDRA catalysts with triflimide in the Mukaiyama aldol reaction of benzophenone.[a]



Conditions [a]		DSI-**3**	DSI-**4**	DSI-**1a**	DSI-**2**	$HNTf_2$
1	catalyst (5 mol%), RT, 2 h	35%	>98%	>98%	>98%	>98%
2	catalyst (1 mol%), RT, 2 h	–	48%[c]	>98%	>98%	>98%
3	catalyst (0.5 mol%), RT, 0.5 h	–	–	>98%	>98%	>98%
4	catalyst (0.5 mol%), 0°C, 0.5 h	–	–	88%[c]	>98%	>98%
5	catalyst (0.5 mol%), 0°C, 5 min	–	–	–	68%[c]	>98%
	relative catalytic activity	1	7	400	1900	–

[a] The reactions were conducted on a 0.1 mmol scale at a concentration of 0.2 M. [b] Yield obtained with the corresponding catalyst, determined by ^{1}H NMR analysis using triphenylmethane as an internal standard added after the reaction had been halted by addition of saturated $NaHCO_3$ solution. [c] Average of three reactions.

this goal we wanted to apply the method described by the Hilt group, where ^{2}H NMR shifts are utilized to determine the strength of organic Lewis acids and, which was shown to correlate well with the observed catalytic activity of Lewis acids.[32] To our disappointment, this method turned out to be unsuitable for our catalyst systems. While we could observe the expected shift of the deuterium signals qualitatively, a quantitation was made impossible by strong line-broadening and the long-term instability of our silylated catalysts in the absence of an electrophile.[33]

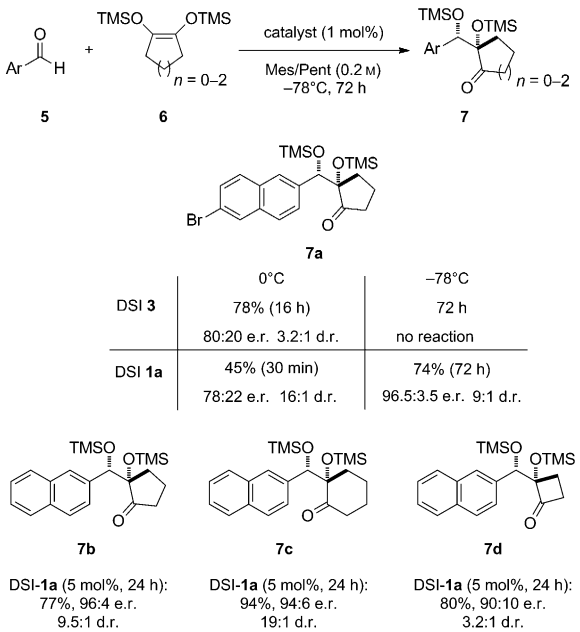
We therefore turned our attention to another well-established method for the quantification of Lewis acidities, namely the computational determination of fluoride ion affinities (FIA) using an isodesmic computational approach, which was first described by Christe and Dixon for inorganic Lewis acids and has been used successfully for the characterization of Lewis superacids.[34] As this method has not been widely used to characterize silicon-centered Lewis acids, we also computed FIA values for some common organic silyl species as references (Table 2).[35,36]

Table 2: Fluoride ion affinities (FIAs) of our disulfonimide catalysts and reference compounds at the BP86/SVP level with and without solvation.[35]

Entry	Silicon Lewis acid	FIA ΔH [kcal mol^{-1}]	FIA ΔU in CH_2Cl_2 [kcal mol^{-1}]	Catalytic activity (qualitative)
1	TMS-Cl	56.2	52.2	low
2	TMS-I	79.2	72.5	
3	TMS-*o*-benzene disulfonimide	81.7	65.3	medium
4	TMS-OTf	82.8	68.0	
5	TMS-**3**	93.7	69.3	
6	TMS-NTf_2	96.2	76.2	high
7	TMS-**1**	109.9	79.1	

The results obtained are in good agreement with the qualitative trends in activity displayed by the silicon Lewis acids studied. The relative ranking of trimethylsilyl chloride, iodide, triflate, and triflimide were as expected (Table 2, entries 1, 2, 4 and 6).[37] The ranking of TMS-*o*-benzene disulfonimide and the TMS adduct of DSI-**3** is also in good agreement with the activities observed in our earlier studies (entries 3 and 5).[10] Finally the computational determination of our new Lewis acid catalyst TMS-**1** as more Lewis acidic than TMS-triflimide represents a slight deviation from our experimental findings (entries 6 and 7). It should be noted, however, that the difference in the computed FIA values considering solvation in dichloromethane is merely 2.9 kcal mol^{-1}. Such a difference could potentially be overcompensated by steric effects for electrophiles larger than the fluoride ion. On the other hand, the large difference in activity relative to other silyl Lewis acids such as TMS-**3** and TMS triflate is clearly reflected by the differences in the FIA of roughly 10 kcal mol^{-1}, with and without solvation.

Having established the extraordinarily high catalytic activity of our catalysts, we wondered about their applicability in the enantioselective catalysis of reactions that are hard to achieve with other chiral catalysts. One such reaction is the Mukaiyama aldol reaction using 1,2-bis(trimethylsilyloxy)-cycloalkenes, which due to the absence of strong polarization in the C–C double bond are less nucleophilic than analogous silyl enol ethers.[38] We thus chose the addition of nucleophile **6** to aldehyde **5** as a test system to compare our disulfonimide catalysts **1** and **3** (Scheme 2).



Scheme 2. The first enantioselective Mukaiyama aldol reaction with 1,2-bis(trimethylsilyloxy)cycloalkenes.

Using 1,2-bis(trimethylsilyloxy)cyclopentene **6a** we compared the two catalysts at 0 °C, where disulfonimide **3** gave reasonable conversion (78 % yield after 16 h) but only modest enantio- and diastereoselectivity. Notably a yield of 45 % could be obtained in only 30 min with catalyst **1a** under these conditions. While a comparable enantioselectivity was observed, the diastereoselectivity of this reaction was clearly superior. However, owing to the high activity of disulfonimide **1a** we could lower the reaction temperature significantly and under optimized conditions we obtained product **7a** in good enantio- and diastereoselectivity, while the reference catalyst **3** gave no product under the same conditions.[39,40] When 2-naphthaldehyde served as the substrate, nucleophiles **6** of different ring sizes could be employed, giving adducts **7b–d** in good to excellent yields and enantioselectivities.

In summary, we have introduced a new motif for high-performance Lewis and potentially Brønsted acid organocatalysis, namely (biaryl)hydroxyl acids (HYDRAs). Our catalyst synthesis relies on a single lithiation(D*o*M)/alkylation step to introduce the 3,3′-substituents, allowing for the potential generation of catalyst libraries in a single step. The HYDRA-DSI catalysts were found to be exceptionally active Lewis acid precursors, allowing for the catalysis of Mukaiyama aldol reactions at rates unprecedented in Lewis

acid organocatalysis. The observed activities could be rationalized by the calculation of FIAs for the catalytically active species and comparison with previously known silyl Lewis acids. We could furthermore highlight the potential of these catalysts as new lead structures in asymmetric counteranion-directed catalysis (ACDC),[41] by applying catalyst **1a** in enantioselective Mukaiyama aldol reactions with normally only moderately reactive 1,2-bis(trimethylsilyloxy)cycloalkenes. We believe that our HYDRA catalysts hold great promise in both enantioselective and non-enantioselective catalysis and research towards further applications of these powerful catalysts is currently underway in our laboratories.

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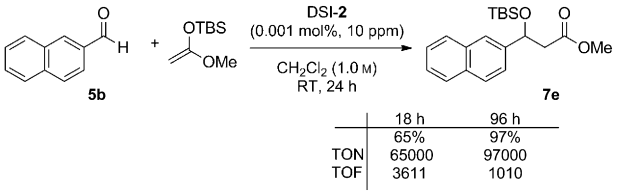
carried out with as little as 10 ppm of catalyst. After 18 h aldol product **7e** was obtained in 65% NMR yield. The reaction reached completion after 96 h (97% NMR yield).



	18 h	96 h
	65%	97%
TON	65000	97000
TOF	3611	1010

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[39] The absolute configuration of the product was determined by conversion to the acetonide and X-ray analysis of the crystals obtained from this derivative. See the Supporting Information for details.

[40] We also tested the other newly synthesized catalysts in this reaction. For the corresponding screening of catalysts, see the Supporting Information.

[41] For selected reviews on ACDC, see: see: a) M. Mahlau, B. List, *Angew. Chem.* **2013**, *125*, 540 – 556; *Angew. Chem. Int. Ed.* **2013**, *52*, 518 – 533; b) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603 – 614; c) M. Mahlau, B. List, *Isr. J. Chem.* **2012**, *52*, 630 – 638; d) L. Ratjen, S. Müller, B. List, *Nachr. Chem.* **2010**, *58*, 640 – 646.

