

A Powerful Chiral Counteranion Motif for Asymmetric Catalysis**

Pilar García-García, Frank Lay, Patricia García-García, Constantinos Rabalakos, and Benjamin List*

Complementing metal salts and enzymes, organic molecules have recently emerged as a third class of general enantioselective catalysts.^[1–3] As particularly successful strategies, Lewis base organocatalysis and Brønsted acid organocatalysis have inspired several dozens of highly useful reactions. However, important challenges remain. Among them are 1) the evaluation of previously unexplored organic functional groups, 2) the development of high turnover number catalysts, and 3) the activation of simple aldehydes. Herein we report progress towards meeting these challenges. We have identified the chiral disulfonimide functional group as a powerful motif for asymmetric catalysis. In a first example, we show that a highly active and selective disulfonimide catalyst accelerates the asymmetric Mukaiyama aldol reaction.

This reaction is an archetypical transformation of simple aldehydes used as electrophiles in combination with enol silanes as nucleophiles. The reaction is typically catalyzed by Lewis acids and asymmetric versions have traditionally defined the state of the art in chiral Lewis acid catalysis.^[4] Important contributions have come from various research groups^[5–13] but high catalyst loadings are typically required. A chiral titanium catalyst developed by Carreira et al. has proven particularly general and is used at relatively low catalyst loadings (0.5–5 mol %).^[4] An elegant and complementary approach using chiral Lewis bases has been designed by Denmark et al.^[14] Very recently, even hydrogen-bonding Brønsted acid catalysis has found utility for Mukaiyama aldol reactions.^[15–16] While Rawal and co-workers found chiral diols to catalyze this reaction with good enantioselectivity, Jørgensen and co-workers described moderately enantioselective bis(sulfonamide) catalysts. However, high catalyst loadings and highly activated substrates are generally required with these systems.

In a parallel development, relatively strong chiral Brønsted acid catalysts have recently emerged. As a partic-

ularly successful motif, Terada and Akiyama introduced binol-derived phosphoric acids of type **1** (see Table 1) for the activation of imines.^[17,18] Nakashima and Yamamoto^[19] designed the corresponding *N*-triflyl phosphoramides of type **2**, which are more acidic and have significantly expanded the substrate scope by allowing the use of ketones as electrophilic substrates.^[20] However, neither phosphoric acids nor *N*-triflyl phosphoramides have proven sufficiently active for the utilization of unfunctionalized aldehydes,^[21] a particularly important substrate class for asymmetric catalysis.

Our research group is currently exploring alternative chiral Brønsted acid motifs. Especially, very strong chiral “super Brønsted acids”^[22] have great potential for high-performance asymmetric catalysis in general and are particularly promising for the activation of important but less basic substrate classes such as aldehydes and olefins.^[23,24] In addition, their corresponding bases should be useful in applications of asymmetric counteranion-directed catalysis (ACDC).^[25–27]

Recently, a highly acidic binaphthyl-derived chiral disulfonic acid catalyst has been designed and synthesized.^[28–30] The corresponding chiral cyclic disulfonimides have been unknown but appeared to us as a particularly promising chiral catalyst motif.^[31] We were fascinated with the possibility that chiral binaphthyl-derived sulfonic acids and disulfonimides may resemble the relative reactivity of triflic acid (TfOH) and of triflylimide (Tf₂NH), which are both powerful Brønsted acid catalysts. In addition, their corresponding silylated species could be promising chiral Lewis acid catalysts: Although TfOH ($pK_a = -5.9$ in water) is much more Brønsted acidic than Tf₂NH ($pK_a = 1.7$ in water), the relationship is reversed if one regards the Lewis acidity of the corresponding silylated species—TMSNTf₂ is a much stronger Lewis acid than TMSOTf.^[32,33] Furthermore, of particular interest to us is the C₂-symmetric binaphthyl disulfonimide topology, which differs significantly from that of the corresponding pseudo-C₂-symmetric phosphoric acids. Analysis of the atom connectivity and three dimensional structures of models revealed that the proton-carrying functional group is buried deeper in the chiral pocket of the disulfonimide than in that of the corresponding phosphate. Such a situation could possibly lead to an enhanced stereochemical communication between catalyst and substrate (Scheme 1).

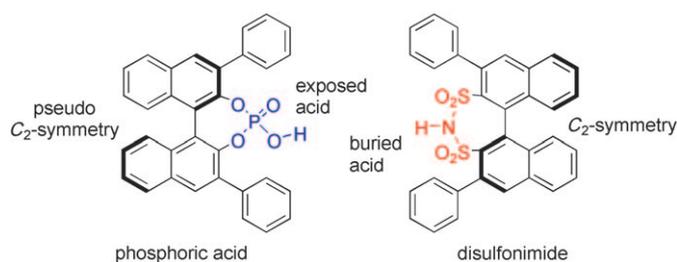
Indeed, a comparison of phosphoric acid **1** and phosphoramidate **2**, with the previously unknown disulfonic acid **3** and disulfonimide **4**, in the catalysis of the Mukaiyama aldol reaction of naphthaldehyde **5a** with ketene acetal **6a** revealed catalyst **4** to not only be far more active than the alternative catalysts **1–3** but to also provide aldol product **7a** with high enantioselectivity of 90:10 e.r. (Table 1).^[34]

[*] Dr. P. García-García,^[†] F. Lay,^[‡] Dr. P. García-García, Dr. C. Rabalakos, Prof. Dr. B. List
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2999
E-mail: list@mpi-muelheim.mpg.de

[†] These authors contributed equally.

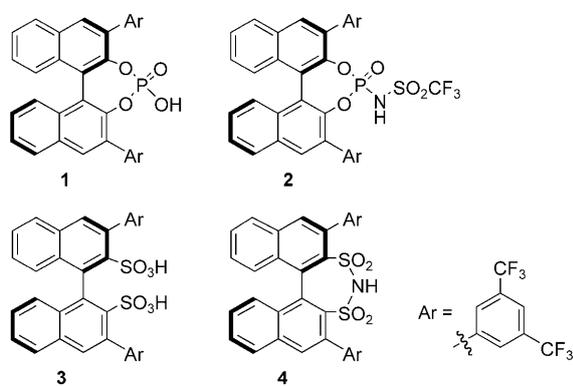
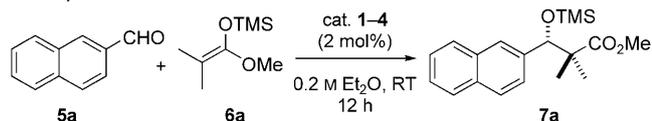
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Scheme 1. Analysis of the structural topology differences of the phosphoric acid and disulfonimide catalyst motifs.

Table 1: Evaluation of different chiral acid catalyst motifs in the Mukaiyama aldol reaction.



Entry	Catalyst	Yield [%] ^[a]	e.r. ^[b,c]
1	1	< 2	–
2	2	< 2	–
3	3	< 2	–
4	4	> 99	90:10

[a] Yield determined by ¹H NMR spectroscopy using triphenylmethane as the internal standard. [b] Determined by HPLC on a chiral stationary phase. [c] See the Supporting Information for the determination of the absolute configuration.

Disulfonimide **4** proved to be a highly active catalyst of the Mukaiyama aldol reaction and gave full conversion to the desired product **7a** even at -78°C . Moreover, at this temperature, the enantioselectivity increased to 97:3 e.r. (Table 2, entry 1). These reaction conditions could be applied to several different substrate combinations with good results (Table 2).

The reaction is well suited for isobutyrate-derived ketene acetals, which react with aromatic aldehydes to give the corresponding aldol products **7a–c** in high yields and enantioselectivities ($\geq 95:5$ e.r.; Table 2, entries 1–3). An α,β -unsaturated aldehyde could also be used with the same nucleophile to give the desired product **7d** in good yield and with an e.r. of 97:3 (Table 2, entry 4). Even the more challenging acetate-derived ketene acetal could be used and upon reaction with different aldehydes provided the corresponding products **7e–h** in excellent yields and high enantio-

Table 2: Preliminary substrate scope of the Mukaiyama aldol reaction catalyzed by disulfonimide **4**.

Entry	Product 7	Catalyst loading [mol%]	Yield [%] ^[a]	e.r. ^[b]
1		2	98	97:3
2		2	78	95:5
3		2	98	96:4
4		2	82	97:3
5		2	92	96:4
6 ^[c,d]		0.1	70	90:10
7		2	93	92:8
8 ^[c,e]		0.1	80	90:10
9 ^[c,e]		0.05	70	90:10
10 ^[f,g]		2	86	86:14
11		2	95	93:7
12		0.1	90	93:7
13 ^[h]		0.05	90	93:7
14 ^[f,i]		0.01	88	88:12
15 ^[e,k]		5	46	91:9
16 ^[g,l]		5	59	75:25

[a] Yield of isolated product. [b] Determined by GC or HPLC on a chiral stationary phase. [c] -45°C . [d] 96 h. [e] 112 h. [f] Reaction in pentane. [g] Room temperature. [h] 0.1 M concentration. [i] 0°C . [j] 72 h. [k] 2 M concentration. [l] 49 h.

selectivities (Table 2, entries 5, 7, 10, and 11). In these cases, we also investigated the effect of lowering the catalyst loading on the outcome of the reactions. An amount of only 0.1 mol % turned out to be sufficient to give the desired products **7e,f,h** in good to excellent yields while maintaining high enantioselectivity (Table 2, entries 6, 8, and 12). Even lower catalyst amounts can be used with good results (Table 2, entries 9, 13, and 14) and product **7h** was obtained in high yield and an e.r. of 88:12 with a remarkably low catalyst loading of 0.01 mol %.

Finally, aliphatic aldehydes were also tested and provided pivaldehyde- and hydrocinnamaldehyde-derived products **7i** and **7j** with good yields and reasonably good enantioselectivities (Table 2, entries 15 and 16).

There are two plausible mechanistic pathways that explain the observed reactivity. Accordingly, the acid may directly protonate the aldehyde to form an ion pair in analogy to the mechanism proposed for the analogous phosphoric-acid-catalyzed Mukaiyama–Mannich reaction.^[35]

Alternatively, the catalyst may be first silylated by the ketene acetal, thus providing an *N*-silyl disulfonimide that could activate the aldehyde through *O*-silylation. As catalyst activity does not seem to correlate to Brønsted acidity, the latter Lewis acid mechanism seems to be more likely. In addition, preliminary NMR studies suggest this mechanism to be operative.^[34] Thus, we could show by NMR spectroscopy that the ketene acetal rapidly silylates catalyst **4**. The resulting species indeed promotes the aldol process and does so even in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine. This base inhibits any potential Brønsted acid catalysis and has previously been used to differentiate between Lewis acid and Brønsted acid catalyzed pathways.^[36] According to the mechanistic scheme, the actual catalyst is *N*-silyl imide **8**, which is generated upon initial reaction of catalyst **4** with the ketene acetal (Scheme 2). Aldehyde activation is then realized through silyl transfer from imide **8** to generate an oxonium ion. Asymmetric induction occurs by stereochemical communication within ion pair **9**, consisting of the disulfonimide anion and the *O*-silylated oxonium cation. Its reaction with the ketene acetal then provides product **7a** through ion pair intermediate **10**. This mechanistic proposal is in line with our recently introduced concept of asymmetric counteranion-directed catalysis.^[25–27]

The powerful Lewis acidity of catalyst **8** may result from the steric requirements of its constituents. The space demand

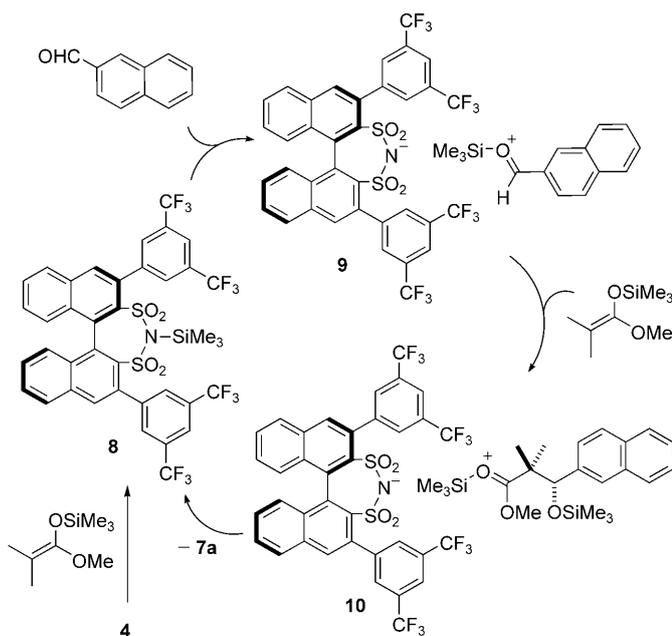
of the two large silyl and disulfonimide fragments of structure **8** should weaken the covalent bond between them, thus resulting in a more ionic-like situation that resembles the “frustrated Lewis pair” motif of Stephan and co-workers.^[37]

In summary, with the presented chiral disulfonimide structure, we have designed a powerful new motif for asymmetric catalysis. As a first illustration, a highly efficient and enantioselective Mukaiyama aldol reaction has been developed. Turnover numbers of up to 8800 could be achieved. Such numbers are rare in organocatalysis and to the best of our knowledge are unprecedented in enantioselective Mukaiyama aldol reactions, thus illustrating the potential of this catalyst type for high-performance asymmetric catalysis. The proposed mechanism immediately suggests a general solution to problems of asymmetric Lewis acid catalysis that are associated with non-enantioselective “background” reactions promoted by the achiral R₃Si-cation.^[38] Therefore, species **8** represents a powerful catalyst for asymmetric silicon catalysis and a number of reactions catalyzed by TMSNTf₂, and similar catalysts should be now accessible in an enantioselective fashion. The designed chiral disulfonimide motif is also expected to find applications in other areas. Thus, various reactions that can be catalyzed by Tf₂NH and related structures^[22] may now be conducted in an asymmetric manner. More significantly, its corresponding base, the disulfonimide anion, should be of use as a new powerful chiral anion for ACDC in combination within various catalyst motifs including transition metal ions and organic cations. Ultimately, the prospect arises that even more active catalysts will be developed leading to high-performance organocatalysis and Lewis acid catalysis with turnover numbers possibly rivaling those seen with the very best transition metal catalysts and biocatalysts.

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Scheme 2. Proposed catalytic cycle.

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