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A Disulfonimide Catalyst for Highly Enantioselective Mukaiyama–Mannich Reaction

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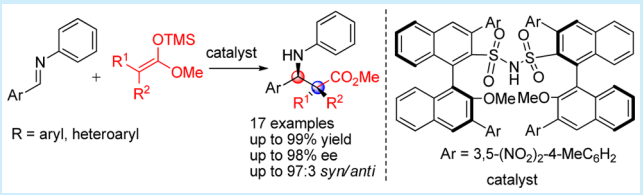
Supporting Information

ABSTRACT: A new BINOL-derived chiral disulfonimide has been developed by introducing 4-methyl-3,5-dinitrophenyl substituents at its 3- and 3′-positions. This chiral disulfonimide catalyst displays high catalytic efficacy toward the asymmetric Mukaiyama–Mannich reaction of imines with ketene silyl acetals leading to β-amino acid esters in good yields (up to 99%) with high diastereoselectivities (*syn*/*anti* up to 97:3) and enantioselectivities (up to 98% ee). The long-standing problem of the chiral phosphoric acid-catalyzed asymmetric Mukaiyama–Mannich reaction that requires a 2-hydroxyphenyl moiety was solved by this disulfonimide catalyst.



A great breakthrough reported by Akiyama's group[1] and Terada's group[2] in 2004 demonstrated that chiral binaphthol-derived phosphoric acids are efficient and highly enantioselective catalysts for addition reactions to imines. During the past decade, the field of asymmetric Brønsted acid catalysis has attracted great attention from the synthetic chemical community. One of the significant tasks in that field is the design and synthesis of new Brønsted acid catalyst scaffolds to overcome certain limitations in this area, such as low reactivity and the limitation of the scope of substrates.[3] For example, in 2006 our group[4] developed a more acidic *N*-triflyl phosphoramide catalyst for asymmetric Diels–Alder reactions. In 2008, a chiral BINOL-disulfonic acid was reported as a strong chiral Brønsted acid for direct asymmetric Mannich-type reaction by Ishihara's group.[5] In the same year, List's group[6] reported a sulfonic acid as strong Brønsted acid for Hosomi–Sakurai reactions. In 2009, List's group[7] and Giernoth's group[8] reported a new type of chiral disulfonimide derived from a binaphthyl skeleton. Chiral disulfonimide catalysts have recently been recognized as powerful silicon-based Lewis acid catalysts as well as chiral Brønsted acid catalysts for asymmetric Mukaiyama aldol reactions,[7] vinylogous and bisvinylogous variants,[9] hetero-Diels–Alder reactions,[10] methallylations,[11] Mukaiyama–Mannich reactions,[12] vinylogous Mukaiyama–Mannich reactions,[13] asymmetric Torgov cyclization,[14] Abramov reactions,[15] reduction reactions[16] and so on.[17,18] However, some simple substrates that do not have sterically demanding groups or bulky substituents are still not suitable for enantioselective transformations. This might be because current catalysts cannot provide a very compact chiral microenvironment to achieve a high level of enantioinduction.[19] Recently, List's group developed a new class of imidodiphosphoric acid catalysts with a confined active site that have proven to be highly efficient catalysts for asymmetric acetalization,[19a,b] enantioselective sulfoxidation,[19c] asymmetric carbonyl–ene cyclization,[19d] asymmetric oxa-Pictet–Spengler reaction,[19e] asymmetric Prins cyclization,[19f,g] and so on.[19h] The design of new disulfonimide catalysts that have a sterically highly demanding chiral microenvironment similar to List's imidodiphosphoric acid catalysts was highly desirable to allow some challenging substrates to proceed in an enantioselective fashion (Scheme 1).

On the other hand, the key to the successful application of chiral phosphoric acids in asymmetric catalysis is their bifunctional nature. Because of the presence of both a Brønsted acidic site and a Lewis basic site on phosphoric acid catalysts, render themselves to have a possibility of the formation of dual activation via hydrogen-bonding interactions with substrates such as imines.[3] For example, chiral phosphoric acid-catalyzed Mukaiyama–Mannich reactions require a 2-hydroxyphenyl moiety of the aldimine for the formation of the tight cyclic transition state between the phosphoric acid and aldimine. However, very simple imines containing no 2-hydroxyphenyl moiety are very challenging substrates, and only moderate enantioselectivity has been achieved (39% ee), as reported by Akiyama[1] (Scheme 2). Our group[20] developed a Brønsted acid-assisted chiral Brønsted (chiral BBA) acid catalyst for asymmetric Mukaiyama–Mannich reactions with imines containing no 2-hydroxyphenyl moiety, and moderate enantioselectivity was achieved (69% ee). Recently, our group developed[21] a powerful BINOL-derived chiral phosphoric acid catalyst for highly enantioselective (up to >99% ee) and diastereoselective (*syn*/*anti* up to >99:1) asymmetric Mukaiyama–Mannich reactions. However, simple imines containing no 2-hydroxyphenyl moiety are still not suitable substrates for this

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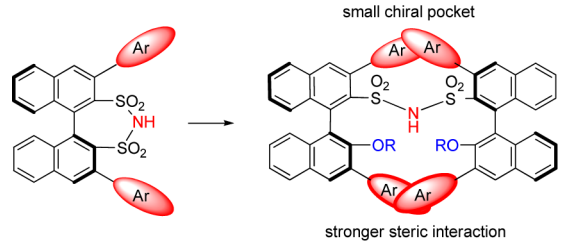
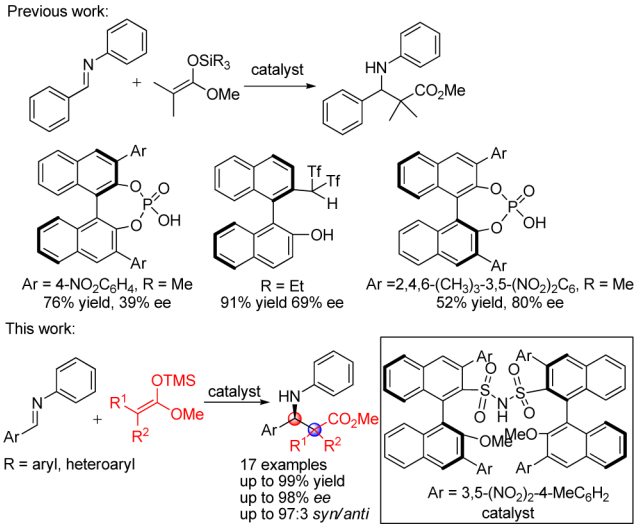
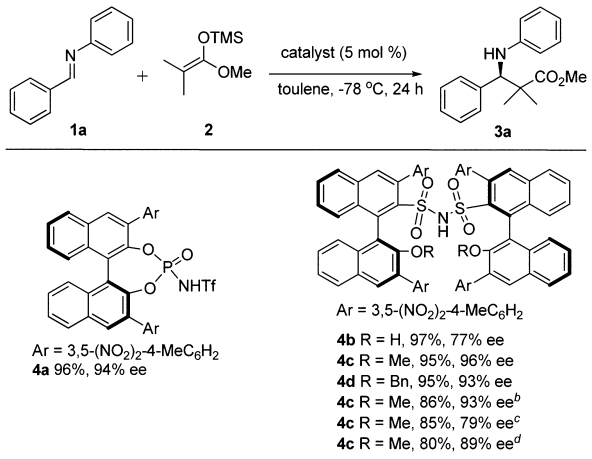
Scheme 1. New Catalyst Design



Scheme 2. Chiral Acid Catalysts for Mukaiyama–Mannich Reactions



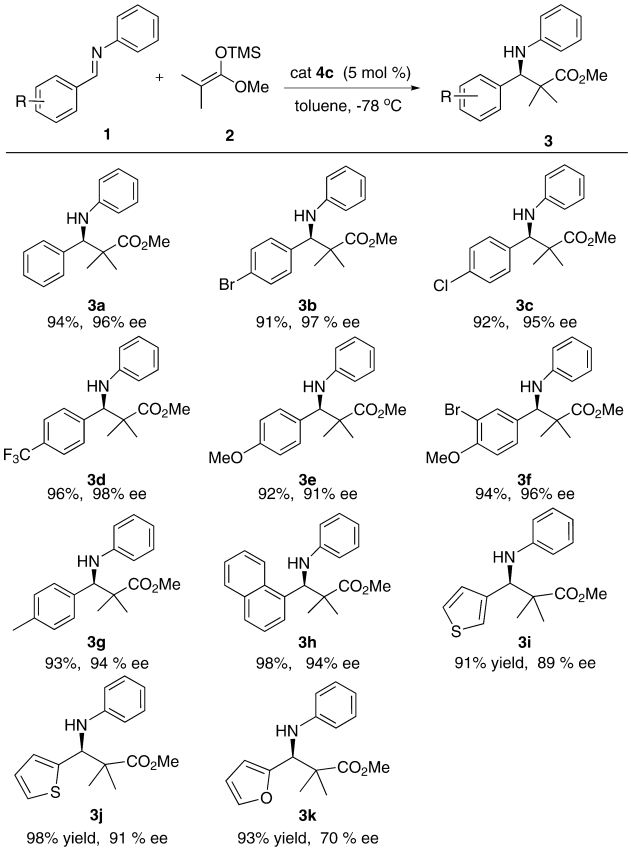
Scheme 3. Optimization of the Mannich Reaction with Various Chiral Catalysts[a]



[a]Reaction conditions: All reactions were performed at −78 °C for 24 h under nitrogen with **1** (0.1 mmol, 1.0 equiv), **2** (0.3 mmol, 3.0 equiv), and catalyst **4** (0.005 mmol, 5 mol %) in toluene (1 mL), unless otherwise noted. Product ee values were determined by HPLC on a chiral stationary phase. [b]Catalyst loading 2.5 mol %. [c]Catalyst loading 1.0 mol %. [d]At −90 °C for 48 h.

catalyst; only moderate enantioselectivity was obtained (80% ee). Inspired by the successful applications of chiral disulfonimide catalysts[17] and imidodiphosphoric acid catalysts[19] in asymmetric organocatalysis, we now have designed a new type of chiral disulfonimide catalyst that has a similar active site

Scheme 4. Scope of the Disulfonimide-Catalyzed Enantioselective Mannich-Type Reaction[a]



[a]Reaction conditions: All reactions were performed at −78 °C for 24 h under nitrogen with **1** (0.1 mmol, 1.0 equiv), **2** (0.3 mmol, 3.0 equiv), and catalyst **4c** (0.005 mmol, 5 mol %) in toluene (1 mL). Product ee values were determined by HPLC on a chiral stationary phase.

as List's imidodiphosphoric acid catalysts in order to address the limitation of chiral phosphoric acids that requires double activations to achieve high enantioselectivity. We envisage that such a chiral disulfonimide will enable imines containing no 2-hydroxyphenyl moiety to proceed smoothly via single-site interactions. Meanwhile, this chiral disulfonimide provides a constrained chiral microenvironment and allows the simple substrate to have a strong steric interaction with the catalyst to achieve a high level of enantiocontrol. In this context, we disclose an efficient chiral disulfonimide catalyst based on a binaphthyl skeleton for symmetric Mukaiyama–Mannich reactions, and the corresponding products were obtained in good yields with excellent enantioselectivities (up to 98% ee) and good diastereoselectivities (up to 97:3 *syn*/*anti*).

We initially investigated the acid-catalyzed Mukaiyama–Mannich reaction of imine **1a** with ketene silyl acetals **2** and tested catalysts **4a–d**. The results are shown in Scheme 3. In our previous work,[20] the *N*-triflyl phosphoramide catalyst **4a** was an efficient catalyst for this model reaction and gave good enantioselectivity (96% yield, 94% ee). We turned to designing a new class of disulfonimide catalysts to improve enantioselectivity further. We envisaged that the introduction of a nitro group serving as electron-withdrawing substituent on the catalysts would enhance their acidity. To our delight, catalyst **4b** bearing the 3,5-dinitro-4-methylphenyl group led to a smooth Mukaiyama–Mannich reaction, giving **3a** in excellent

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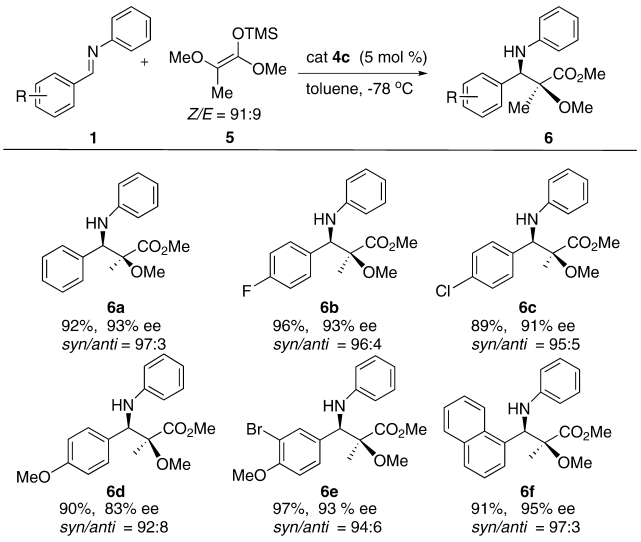
Scheme 5. Scope of the Disulfonimide-Catalyzed Diasteroselective and Enantioselective Mannich-Type Reaction[a]



[a]Reaction conditions: All reactions were performed at −78 °C for 24 h under nitrogen with **1** (0.1 mmol, 1.0 equiv), **5** (0.3 mmol, 3.0 equiv), and catalyst **4c** (0.005 mmol, 5 mol %) in toluene (1 mL). Product ee values were determined by HPLC on a chiral stationary phase. The diastereoselectivity ratios were determined by ^{1}H NMR analysis.

yield with moderate enantioselectivity (97% yield, 77% ee). Furthermore, catalyst **4c** bearing a methoxy group resulted in a higher enantioselectivity (95% yield, 96% ee) compared with catalyst **4a**. Catalyst **4d** bearing a benzyl group gave the corresponding product in good yields but with a slightly lower enantioselectivity (93% ee). Next, the catalyst loading and reaction temperature were investigated. It is noteworthy that the enantioselectivity dropped sharply when the catalyst loading was decreased to 1.0 mol %. A slightly lower enantioselectivity (89% ee) was observed at lower temperature (−90 °C).

With the optimized reaction conditions in hand, the scope of the disulfonimide **4c**-catalyzed Mukaiyama−Mannich reaction was explored, and the results are shown in Scheme 4. Aldimines derived from aromatic aldehydes bearing either an electron-withdrawing group (e.g., Br, Cl) or an electron-donating group (e.g., OMe, Me) work very well, furnishing the corresponding products **3a−g** in good yields with excellent enantioselectivities (up to 98% ee). Furthermore, reactions with aldimines derived from heterocyclic or bulky aromatic aldehydes proceed smoothly, delivering the corresponding products **3h−k** in good yields with excellent enantioselectivities.

Furthermore, the scope of these chiral disulfonimide **4c**-catalyzed symmetric Mukaiyama−Mannich reactions were expanded by employing more challenging ketene silyl acetals bearing two different substituents on the vinyl carbon, and the results are shown in Scheme 5. Ketene silyl acetal **5** (*E*/*Z* = 91:9) prepared from methyl 2-methoxypropanoate delivered the product **6a** in high yields with good diastereo- and enantioselectivity. Remarkably, this protocol could construct two vicinal tertiary and quaternary stereogenic centers in single step. Next, the scope of the imines was investigated, and a variety of aldimines with either an electron-donating group or an electron-withdrawing group were found to work very well, delivering products **6b−f** with good diastereoselectivities (*syn*/*anti* up to 97:3) and excellent enantioselectivities (up to 95% ee). The absolute configuration of the major isomer of **6e** was determined to be (2*S*,3*R*) by X-ray analysis.[22]

In summary, we have successfully developed a powerful BINOL-derived chiral disulfonimide catalyst bearing 4-methyl-3,5-dinitrophenyl substituents. The utility of this chiral disulfonimide catalyst was demonstrated by an asymmetric Mukaiyama−Mannich reaction of imines with ketene silyl acetals to afford *β*-amino acid esters in good yields with excellent diastereo- and enantioselectivities. In particular, this disulfonimide catalyst overcomes the long-standing limitation of the chiral phosphoric acid-catalyzed asymmetric Mukaiyama−Mannich reaction, namely, the requirement of the 2-hydroxyphenyl moiety. Further exploration of the application of this disulfonimide catalyst is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02262.

Experimental details, characterization data for all compounds, and copies of HPLC data and ^{1}H and ^{13}C NMR spectra (PDF)
Crystallographic data for **6e** (CIF)
Crystallographic data for **6e** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Professor Dieter Enders on the occasion of his 70th birthday.

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(22) The relative and absolute stereochemistry of the major isomer of **6e** was determined to be (2*S*,3*R*) by X-ray analysis (see the Supporting Information), and those of others were surmised by analogy.

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