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Chiral Pyridinium Phosphoramide as a Dual Brønsted Acid Catalyst for Enantioselective Diels–Alder Reaction

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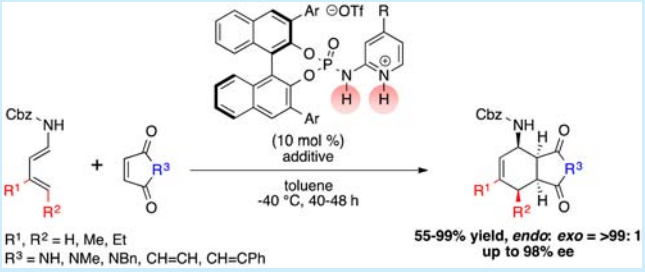
Supporting Information

ABSTRACT: Chiral pyridinium phosphoramide **1·HX** was designed to be a new class of chiral Brønsted acid catalyst in which both the pyridinium proton and the adjacent imide-like proton activated by the electron-withdrawing pyridinium moiety could work cooperatively as strong dual proton donors. The potential of **1·HX** was shown in the enantioselective Diels–Alder reactions of 1-amino dienes with various dienophiles including *N*-unsubstituted maleimide, which has yet to be successfully used in an asymmetric Diels–Alder reaction.



Dual hydrogen bonding (DHB) catalysts have received much attention in the area of enantioselective synthesis.[1] The tight complexes formed by DHB donors and Lewis basic substrates through secondary interactions can contribute to higher reactivities and stereoselectivities compared to single hydrogen bonding (HB) catalysts with similar acidity. Having identified thioureas as one of the most promising scaffolds in neutral DHB catalysis, much effort has been dedicated to exploring alternative motifs, which address some of its drawbacks such as reactivity, selectivity, and the scope of reactions.[2] As a result, several scaffolds such as guanidines,[3] squaramides,[4] and silanediols[5] were identified, yielding better results than thioureas in some cases (Figure 1). In parallel with the development of Brønsted acid catalysts,[6,7] other approaches to expand the potential of DHB catalysis have centered around ionic HB donors such as guanidinium,[8] aminopyridinium,[9] (amino)quinolinium,[10,11] and phosphonium.[12] The enhanced acidity of a DHB donor or dual Brønsted acid in ionic catalysts is expected to result in higher reactivity while maintaining the stereoselectivity of their bidentate nature.

In this context, we focused our attention on the possibility of pyridinium amide **1′·HX** as a highly acidic dual Brønsted acid catalyst that could be produced by protonation of 2-aminopyridine **1′** bearing an electron-withdrawing group (EWG) on the amino group (Figure 1). In the structure of **1′·HX**, we envisioned that the pyridinium moiety should function as an additional EWG for the adjacent amino group based on its cationic character, generating an acidic *N*-H proton between two EWG, like an imide. Subsequently, the imide-like proton cooperating with the pyridinium proton in **1′·HX** could result in a strong dual proton donor compared to *N*-alkylaminopyridinium derivatives.[13] With this concept in mind, chiral pyridinium phosphoramide **1·HX** was designed. Herein, we report newly designed ionic Brønsted acid catalysts and their application to an enantioselective Diels–Alder reaction.

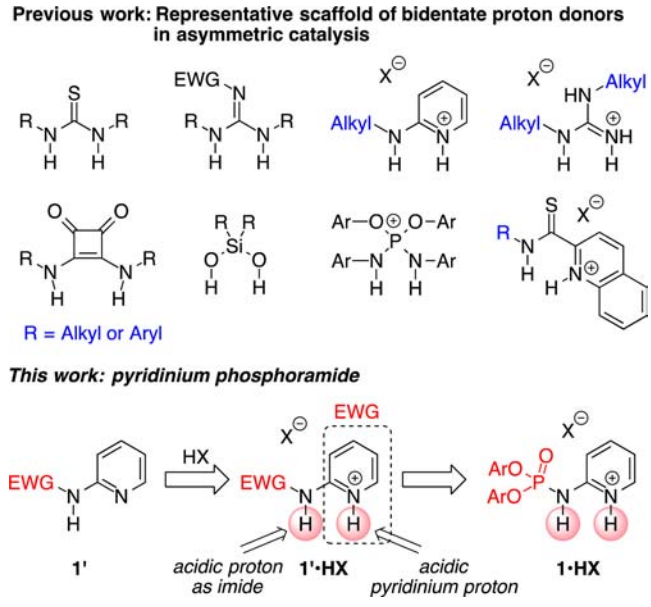


Figure 1. Neutral and ionic dual hydrogen bonding catalysts in asymmetric synthesis.

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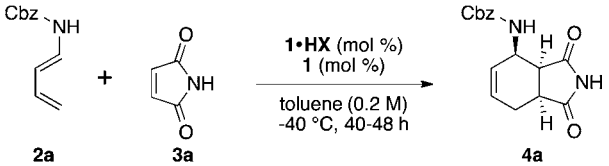
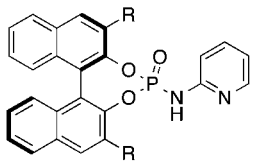
In preliminary screening of catalysis by pyridinium phosphoramide **1·HX** consisting of pyridyl phosphoramide **1**[14] and strong Brønsted acid (**HX**), we found **1a·TfOH** catalyzed a Diels–Alder reaction of *N*-Cbz-1-amidodiene **2a** and *N*-H maleimide **3a** to afford endoadduct **4a** in good yield and excellent diastereoselectivity as well as moderate enantioselectivity (Table1, entry 1).[15] Interestingly, addition

Table 1. Optimization of the Reaction Conditions[a]





1a R = Ph
1b R = Mesityl
1c R = 3,5-$(CF_3)_2$-C_6H_3
1d R = 4-*t*Bu-C_6H_4
1e R = 4-Ph-C_6H_4
1f R = 4-Mesityl-C_6H_4
1g R = 4-(*m*-xylyl)-C_6H_4
1h R = 4-(2-naphthyl)-C_6H_4

			4a	
entry	**1·HX** (mol %)	**1** (mol %)	% yield[b]	% ee[c]
1	**1a·TfOH** (10)	0	70	50
2	**1a·TfOH** (10)	5	66	67
3	**1b·TfOH** (10)	5	31	0
4	**1c·TfOH** (10)	5	44	29
5	**1d·TfOH** (10)	5	67	80
6	**1e·TfOH** (10)	5	67	84
7	**1f·TfOH** (10)	5	99	70
8	**1g·TfOH** (10)	5	77	72
9	**1h·TfOH** (10)	5	92	79
10	**1e·TfOH** (10)	10	100	90
11	**1e·TfOH** (7.5)	7.5	94	72
12	**1e·Tf_2NH** (10)	5	47	80
13[c]	**1e·MsOH** (10)	5	40	23

[a]Reactions were performed with 0.4 mmol of **2a**, 0.2 mmol of **3a** and toluene (1 mL) in the presence of catalyst as shown. See the Supporting Information for details. [b]Isolated yield as single diastereomer. [c]Determined by chiral HPLC.

of 0.5 equiv of pyridylphosphoramide **1a** relative to **1a·TfOH** increased the enantioselectivity (entry 2). To further improve enantioselectivity, a variety of derivatives of chiral phosphoramide **1** having different Ar groups on the 3,3′-position of the binaphthyl backbone were tested. *Ortho*- or *meta*-substituted phenyl rings on the 3,3′-position dramatically reduced reactivity and enantioselectivity (entries 3 and 4). On the other hand, *para* substitution by a *tert*-butyl group resulted in increased enantioselectivity (entry 5). After various catalysts bearing *para*-substituted phenyl groups were tested (entry 5–9), we identified **1e·TfOH** as having the highest enantioselectivity (entry 6). Increasing the amount of pyridylphosphoramide **1e** improved both reactivity and selectivity, though 20 mol % of chiral catalyst in total must be used (entry 10). Unfortunately, decreasing the amount of **1e·TfOH** and **1e** to 7.5 mol % gave inferior selectivity relative to both entry 6 and 10 (entry 11). Furthermore, we confirmed that the catalyst counteranion, derived from achiral Brønsted acid, affected the reaction efficiency (entries 6, 12, and 13). The more basic mesylate anion had a deleterious effect on enantioselectivity, which indicated that the stability of the resulting ionic complex due to acid–base interaction is related to stereoselectivity in this reaction (entry 13). At this stage, we speculated that a proton of the ionic Brønsted acid catalyst could dissociate to the basic component in the reaction such as a counteranion or imide carbonyl group, which would produce an achiral strong Brønsted acid causing undesired racemization (Figure 2).[16]

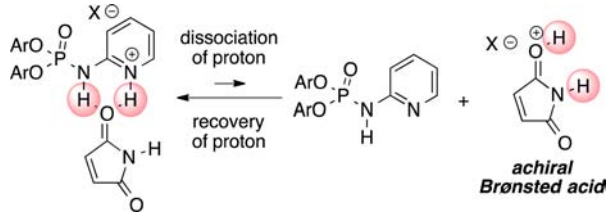
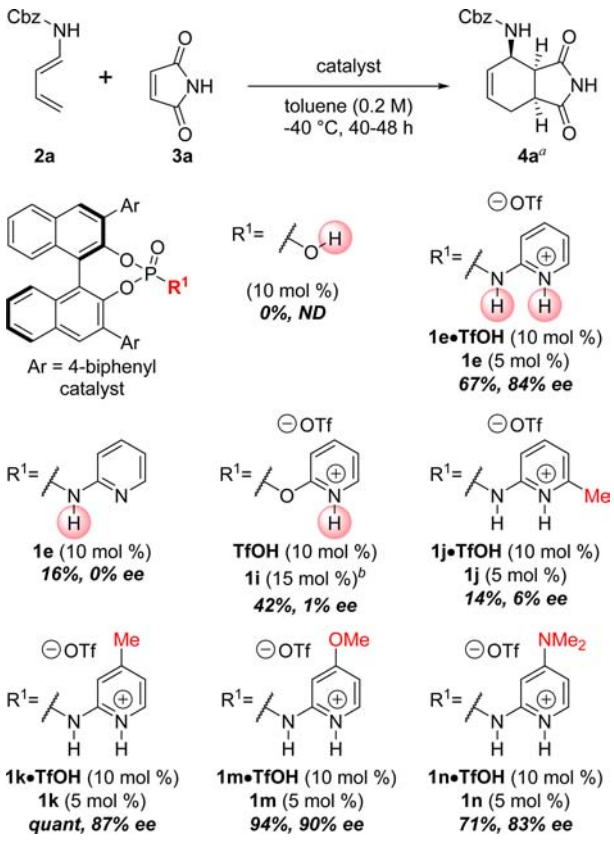


Figure 2. Plausible equilibrium of ionic Brønsted acids.

The increased enantioselectivity by addition of pyridine derivatives **1a** or **1e** can be explained as due to the pyridine moiety inhibiting racemization by recovery of a proton from the achiral Brønsted acid (entries 1 and 2, 6 and 10).

Encouraged by the preliminary results, we next investigated the function of the pyridinium phosphoramido moiety bearing two acidic protons as follows (Scheme 1, R^1). Using the same reaction conditions as **1e·TfOH**, a corresponding chiral phosphoric acid (R^1 = OH) afforded no cyclized product. Removal of TfOH from **1e·TfOH** resulted in unreactive and

Scheme 1. Optimization of Aminopyridine Moiety in Catalyst 1



[a]Isolated yield as single diastereomer. [b]**1i·TfOH** was prepared in situ. See the Supporting Information for details.

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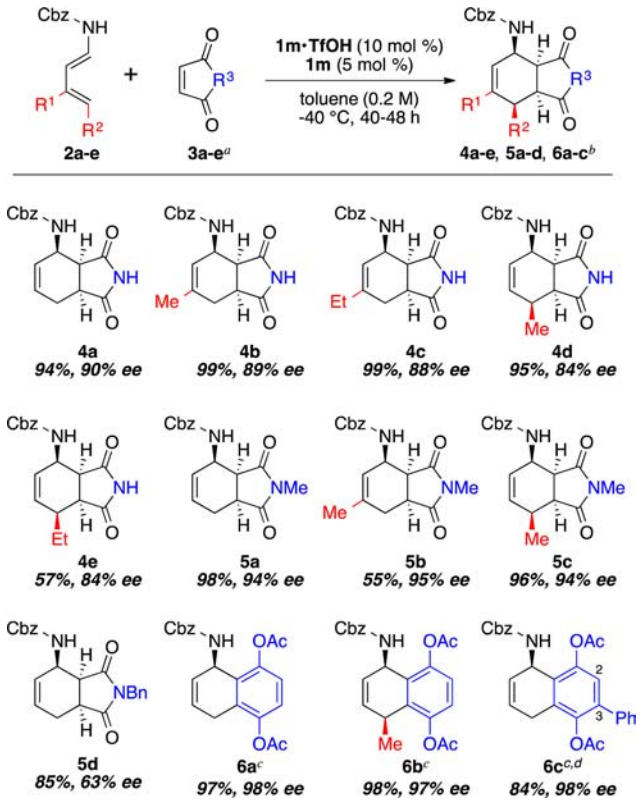
unselective catalyst **1e**. Notably, pyridinium phosphoric ester **1i** bearing one pyridinium proton and no phosphoramido *N*-H showed almost no enantioselectivity. These results clearly suggest that the simultaneous presence of both protons in pyridinium phosphoramide **1·HX** is necessary for high yield and enantioselectivity in this reaction. Toward further optimization of the catalyst structure, the basicity of the pyridine moiety in the catalyst was modified by introducing electron-donating groups on the pyridine ring to prevent dissociation of the proton from the ionic complex (Figure 2). To our delight, improvements in both reaction yield and enantioselectivity were observed when catalyst **1k·TfOH** or **1m·TfOH**[17] was used in place of **1e·TfOH**, whereas the use of **1j·TfOH** having a methyl group at the 6-position on the pyridine ring led to a poor result. Introduction of a strong electron-donating group such as a dimethylamino group was ineffective, implying a balance of the stability and acidity of the resulting pyridinium phosphoramide is crucial.

While *N*-Ar or *N*-bulky alkylmaleimides have been utilized in asymmetric Diels–Alder reactions to exploit enhanced reactivity as well as to easily discriminate their prochiral faces due to *N*-substituents, to the best of our knowledge, a catalytic method for the highly enantioselective Diels–Alder reaction of *N*-H maleimide was still lacking.[18] Having expected flexible utility of Diels–Alder adducts from *N*-H maleimide without cleavage of unnecessary *N*-substituent bonds in some cases, we examined the scope of the Diels–Alder reaction of various *N*-Cbz-1-amidodienes and *N*-H maleimides with **1m·TfOH** (Scheme 2). 3-Alkyl-substituted 1-amidodienes reacted with **3a** in a similar fashion, furnishing highly enantioenriched products **4b** and **4c**. 4-Alkyl-substituted 1-amidodienes were successfully employed to afford **4d** and **4e** with four contiguous stereocenters in diastereo- and enantioselective manners. In turn, the reaction with *N*-methylmaleimide **3b** bearing no acidic imide proton proceeded efficiently to give **5a–c** in higher enantioselectivity than the corresponding products **4a**, **4b**, and **4d** from **3a**. However, the presence of a bulkier benzyl group on maleimide led to lower enantioselectivity for **5d**. Not only maleimides but also benzoquinones could be employed in this Diels–Alder reaction with **1e·TfOH**, as chiral tetrahydronaphthalene **6a** and **6b** were obtained in excellent yields and enantioselectivities after acetylation of the unstable Diels–Alder adducts. When phenyl benzoquinone was used as a substrate, the catalyst could control enantioselectivity as well as regioselectivity of the double bond to afford one regioisomer **6c** preferably.

The utility of chiral Diels–Alder adducts was demonstrated as shown in Scheme 3. The two imide carbonyl groups in **4a** were successfully differentiated by reduction with DIBAL-H to furnish hemiaminal **4ab** as a mixture of stereoisomers. Further reduction of **4ab** by triethylsilane in the presence of $BF_3{\cdot}OEt_2$ afforded the pyrrolidinone derivative **4ac** with all other functional moieties in **4a** remaining intact. The Cbz group could be removed by hydrogenolysis to give **4ad**, which was directly converted to Mosher amide **4ae** to determine the absolute configuration of **4a**.[19] Moreover, stereoselective epoxidation of the double bond in **5c** produced the unusual compound **5ca** having six contiguous *all-syn* asymmetric centers on the cyclohexane ring constructed by the Diels–Alder reaction.

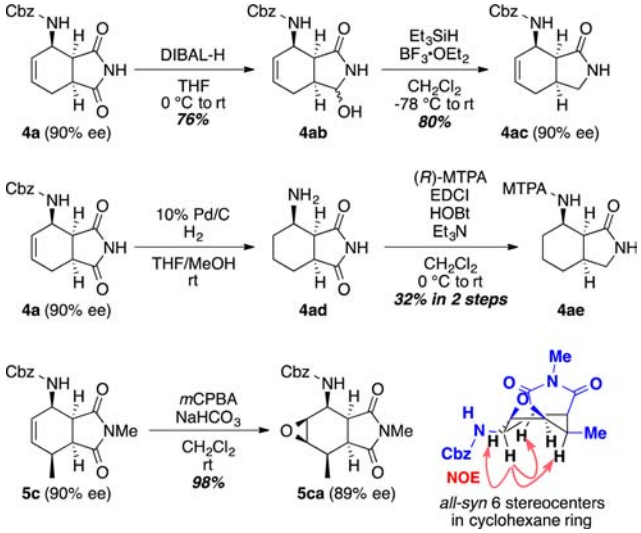
In conclusion, we have developed chiral pyridinium phosphoramides as dual Brønsted acid catalysts based on the concept that a cationic heterocycle functions as an electron-withdrawing group. Careful optimization of the structure of the catalysts enabled the first successful use of *N*-unsubstituted maleimide in highly enantioselective Diels–Alder reactions using various Cbz-protected 1-aminodienes. Through catalyst screening, it was shown that the characteristic two acidic

Scheme 2. Substrate Range of the Diels–Alder Reaction



[a]**3a**: *N*-H maleimide, **3b**: *N*-Me maleimide, **3c**: 1,4-benzoquinone, **3d**: 2-phenyl-1,4-benzoquinone, **3e**: *N*-Bn maleimide. [b]Isolated yields as single diastereomers. [c]**1e·TfOH** (10 mol %) and **1e** (5 mol %) were used as catalyst at −78 °C. The product was obtained after acetylation. [d]Regioisomer substituted with phenyl group at 2-position was also obtained (3-Ph:2-Ph = 4:1).

Scheme 3. Transformation of Optically Active Diels–Alder Adducts



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protons in pyridinium phosphoramide are essential for its catalytic reactivity and stereoselectivity. Future work in our laboratory will involve investigation of possible alternative acids for **1·HX** and extending the range of applications of the catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00608.

Experimental procedures and spectroscopic data of all new compounds (PDF)

X-ray crystal structural data for *rac*-**1m·TfOH** (CIF)

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Notes

The authors declare no competing financial interest.

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