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Molecular Design of a Chiral Brønsted Acid with Two Different Acidic Sites: Regio-, Diastereo-, and Enantioselective Hetero-Diels–Alder Reaction of Azopyridinecarboxylate with Amidodienes Catalyzed by Chiral Carboxylic Acid–Monophosphoric Acid

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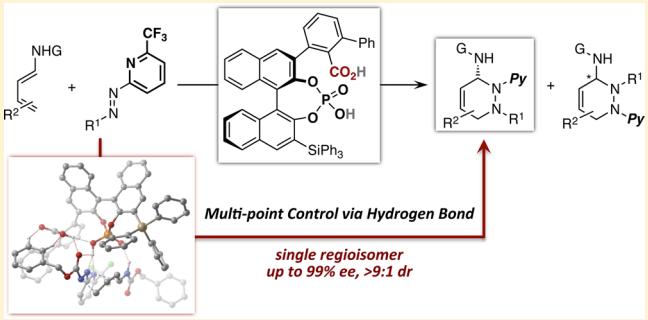
Supporting Information

ABSTRACT: A chiral Brønsted acid containing two different acidic sites, chiral carboxylic acid–monophosphoric acid **1a**, was designed to be a new and effective concept in catalytic asymmetric hetero-Diels–Alder reactions of azopyridinecarboxylate with amidodienes. The multipoint hydrogen-bonding interactions among the carboxylic acid, monophosphoric acid, azopyridinecarboxylate, and amidodiene achieved high catalytic and chiral efficiency, producing substituted 1,2,3,6-tetrahydropyridazines with excellent stereocontrol in a single step. This constitutes the first example of regio-, diastereo-, and enantioselective azo-hetero-Diels–Alder reactions by chiral Brønsted acid catalysis.



INTRODUCTION

Chiral Brønsted acid catalysis has recently been recognized as one of the fundamental tools in asymmetric synthesis.[1] A number of useful chiral Brønsted acids have been developed with appropriate acidic functional groups. Many such catalysts incorporate two of the same type of acidic functional groups, while others have one acidic site in a seven-membered ring structure, such as those in binaphthyl systems. Furthermore, combinations of these have effectively produced powerful chiral Brønsted acid catalysts.[2] In this context, we have been fascinated for some time with the development of hetero-combined Brønsted acid catalyst systems,[3] with a particular focus on combinations of monophosphoric acids[4] with other Brønsted acids.[5] Despite having the potential for unprecedented catalytic activity because of a distinctive hydrogen-bond interaction using each acidic functional group, such a design concept remains poorly studied in the development of chiral Brønsted acid catalysts.

Encouraged by recent reports from our group,[6] we became interested in hydrogen bond-mediated multipoint control[7] with two different acidic functional groups in catalytic asymmetric reactions. We report herein a chiral Brønsted acid catalyst with two different acidic sites, carboxylic acid–monophosphoric acid (Figure 1), designed specifically to elaborate the chiral environment using properly oriented multiple hydrogen bonds during catalysis. Describing primary interactions, an

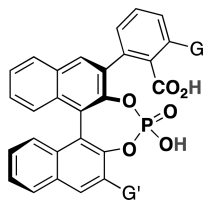


Figure 1. (*R*)-1,1′-Binaphthol-derived chiral carboxylic acid–monophosphoric acid.

Received: July 11, 2016
Published: August 16, 2016

DOI: 10.1021/jacs.6b07150
J. Am. Chem. Soc. 2016, 138, 11353–11359

*intra*molecular hydrogen bond between carboxylic acid and monophosphoric acid would allow the catalyst to establish a favorable diastereomeric structure for high stereoselectivities[3c,d,6] (Figure 2). This intramolecular hydrogen bond design

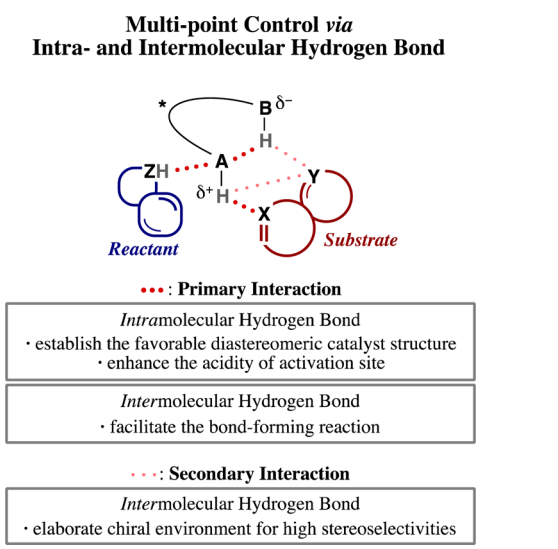


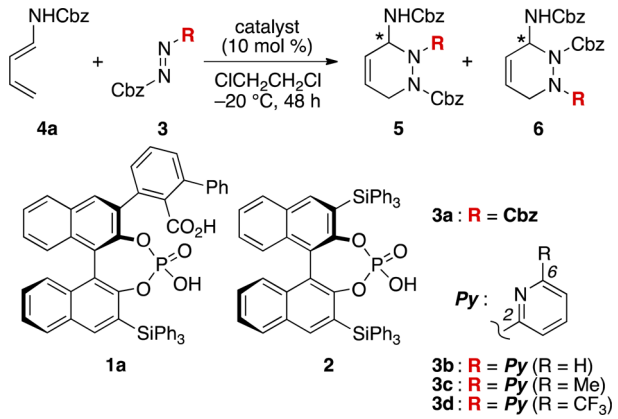
Figure 2. Design concept of a chiral Brønsted acid with two different acidic sites: Multipoint control by *intra*- and *inter*molecular hydrogen bond. AH/BH indicates either CO_2H/PO_3H or PO_3H/CO_2H. X/Y/Z indicates Lewis basic sites such as O, N, etc.

would not only regulate the diastereomeric catalyst structure but also result in the increased acidity of the catalyst, enabling catalytic activity that would be entirely unique when compared to chiral Brønsted acids with one acidic functional group. *Inter*molecular hydrogen bonds among the catalyst, the substrate, and the reactant are responsible for facilitating the bond-forming reaction. In addition, we envisioned that a secondary, weaker interaction would exist as an *inter*molecular hydrogen bond between the acidic functional groups and Lewis basic sites of the substrates, and this would contribute to the stereo- and regioselectivity of the reaction.

RESULTS AND DISCUSSION

1. Enantioselective Hetero-Diels–Alder Reaction of Azocarboxylates with *N*-H-Amidodienes. Enantioselective hetero-Diels–Alder reactions[8] of azocarboxylates with *N*-H-amidodienes were selected as an initial probe to test the hypothesis that multiple hydrogen bonds will provide enhanced reactivity and selectivity in catalysis.[9,10] Initial experiments used two types of azocarboxylates, **3a** and **3b**, as the hydrogen bond acceptors with the carboxylic acid–monophosphoric acid **1a** (Table 1, entries 1 and 2). The reaction of dibenzyl azodicarboxylate (**3a**) gave no Diels–Alder product at −20 °C in 1,2-dichloroethane (entry 1).[11] On the other hand, the reaction of 2-azopyridinecarboxylate (**3b**),[12] which contained a relatively basic pyridine nitrogen when compared with the carbonyl oxygen of the Cbz group, gave rise to products **5** and **6** (entry 2).[13,14] Although the reaction of **3b** was not fruitful with regard to yield and regioselectivity, the observed ee of both regioisomers were quite high.[15] To confirm the role of the pyridine nitrogen,[12b,16] the reaction of 2-azo*phenyl*carboxylate was attempted, and no product was observed under the same conditions. These experiments reveal that the hydrogen bond

Table 1. Catalytic Enantioselective Hetero-Diels–Alder Reaction of 2-Azocarboxylate with Amidodienes[a]



entry	catalyst	3	yield (%)[b]	5:6[c]	ee (%)[d] 5	ee (%)[d] 6
1	**1a**	**3a**	<1	–	–	
2	**1a**	**3b**	41	2.4:1	79	74
3	**1a**	**3c**	61	>9:1	88	–
4	**1a**	**3d**	52	>99:1	97	–
5[e]	**1a**	**3d**	89	>99:1	99	–
6[f]	none	**3d**	49	1:2	–	–
7[g]	**2**	**3d**	25	1.9:1	32	29

[a]Reactions were conducted with 1.0 equiv of **3** and 1.0 equiv of **4a** in the presence of 10 mol % catalyst in 1,2-dichloroethane at −20 °C for 48 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC. [e]Reaction was conducted with 1.0 equiv of **3** and 2.0 equiv of **4a** in the presence of MS 4 Å and 5 mol % **1a** in dichloromethane at −60 °C for 24 h. [f]Reaction was conducted at room temperature for 12 h. [g]Reaction was conducted with 1.0 equiv of **3** and 2.0 equiv of **4a** in CH_2Cl_2 at −40 °C.

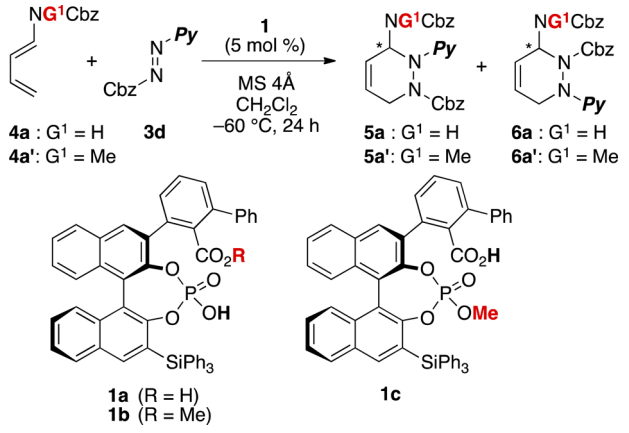
acceptor such as pyridine nitrogen is the requirement in the **1a**-catalyzed azo-hetero-Diels–Alder reaction.

To improve the stereoselectivity in the system of 2-azopyridinecarboxylate, substitution at the 6-position of the 2-azopyridine was explored; a substituent at the vicinal position of pyridine nitrogen was expected to favorably influence the chiral environment of the transition state (entries 3 and 4). Fascinatingly, improvements in both the regio- and enantioselectivities were indeed realized with the reaction of **3c** and **3d**. The best result was obtained with the reaction of 6-trifluoromethyl-2-azopyridinecarboxylate (**3d**), providing product **5a** with 97% ee as a single regioisomer (entry 4). Finally, high yields and complete regio- and enantioselectivities were achieved under the optimized reaction conditions; i.e., 2 equiv of **4a** and 1 equiv of **3d** were stirred in the presence of molecular sieves 4 Å and 5 mol % **1a** at −60 °C (entry 5). For comparison, the reaction in the absence of catalyst yielded not only **5a** but also a considerable amount of **6a** (entry 6). Finally, when the reaction was conducted in the presence of chiral monophosphoric acid **2**, the yield and stereoselectivity decreased significantly (entry 7).[17] These observations clearly indicate the significant effects of carboxylic acid–cyclic monophosphoric acid **1a** in this transformation.

To gain further insight into the importance of the phosphoric acid and carboxylic acid groups of the catalyst, as well as the N–H proton of the amidodiene, we conducted experiments varying these functional groups (Table 2). Methylcarboxylate–phosphoric acid **1b** and carboxylic acid–phosphoric acid

DOI: 10.1021/jacs.6b07150
J. Am. Chem. Soc. 2016, 138, 11353–11359

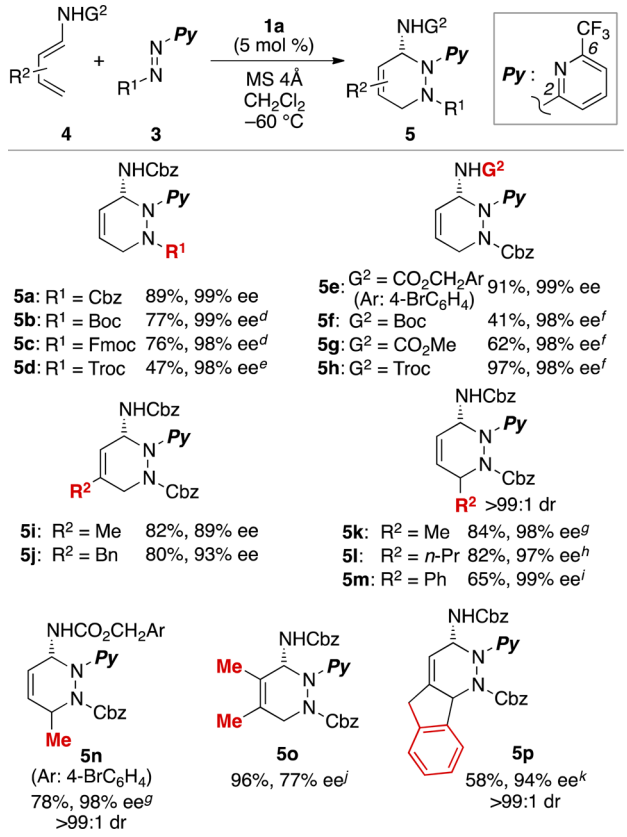
Table 2. Control Experiments[a]



entry	1	G[1]	yield (%)[b]	5:6[c]	ee (%)[d] 5	ee (%)[d] 6
1	**1a**	H	89	>99:1	99	–
2	**1b**	H	29	2.2:1	6	11
3	**1c**	H	<1	–	–	–
4	**1a**	Me	10	>99:1	36	–

[a]Reactions were conducted with 1.0 equiv of **3d** and 2.0 equiv of **4a** in the presence of 5 mol % catalyst and MS 4 Å in CH_2Cl_2 at −60 °C for 24 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC.

Chart 1. Reaction Scope[a,b,c]



[a]Reactions were conducted with 1.0 equiv of **3** and 2.0 equiv of **4** in the presence of 5 mol % catalyst and MS 4 Å in CH_2Cl_2 at −60 °C for 24 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]45 h. [e]55 h. [f]40 h. [g]−40 °C, 48 h. [h]−40 °C, 72 h. [i]10 mol %, −20 °C, 72 h. [j]−60 °C, 72 h. [k]10 mol %, −40 °C, 48 h.

methylester **1c** were synthesized, and the reactions of **3d** with **4a** were examined in the presence of these catalysts (entries 1 and 2). We confirmed that the carboxylic acid moiety significantly affected the reactivity and selectivity of the present azo-hetero-Diels–Alder reaction; replacement of the carboxylic acid with a methylcarboxylate considerably decreased not only the yield but also the regio- and enantioselectivities (entry 1 vs 2, compare also with entry 7 of Table 1). Moreover, methyl phosphate **1c** was unable to catalyze the reaction under the same conditions (entry 3). We also found that the reaction with *N*-Me-amidodiene **4a′** gave excellent regioselectivities, albeit with extremely poor catalytic and chiral efficiency (entry 4).[18] These results strongly imply that the phosphoric acid–carboxylic acid moieties, the 6-trifluoromethylpyridine substituent, and the N–H of the amidodienes are required to facilitate both the selectivity and reactivity of the reaction. We presume the intra- and intermolecular hydrogen-bonding interactions among these contribute to creating the chiral environment to produce the excellent regio-, diastereo-, and enantioselectivity of this reaction.

The scope of the azo-hetero-Diels–Alder reaction was investigated (Chart 1). High enantiomeric excess was observed with **5a**—**5h** regardless of the acyloxy group on both 2-azopyridines **3** and amidodienes **4**. Moreover, a variety of 3- and 4-substituted amidodienes were applicable to give **5i**—**5n** in good yields, with high enantioselectivities. In the cases of 4-substituted compounds, the products **5k**—**5n** were obtained as single diastereomers. When 2,3-disubstituted amidodiene was used, the enantiomeric excess of **5o** dropped significantly. In contrast, 3,4-disubstituted amidodiene gave **5p** in high enantiomeric excess, but the yield was moderate.

2. Computational Study by Density Functional Theory (DFT) Calculations. To explore the hydrogen-bonding network in the present catalysis, theoretical investigations of the detailed transition state (TS) models were conducted on the **1a**-catalyzed reaction of **3d** with **4a** using density functional theory (DFT) calculations.[19] Regarding the axial chirality of the phenyl–naphthyl axis in **1a**, both DFT calculations and X-ray diffraction analysis showed the (*S*)-configuration is more stable than the (*R*)-configuration due to the intervention of hydrogen bond between carboxylic acid and monophosphoric acid.[20] The control experiments shown in Table 2 suggest that the phosphoric acid moiety is needed to promote the present azo-hetero-Diels–Alder reaction and the carboxylic acid moiety plays an important role in achieving the high chemical yields and selectivities. Under this hypothesis, we focused on TS models in which **3d** and **4a** are activated by the phosphoric acid moiety of **1a**. Based on the previously reported theoretical study of the bis-phosphoric acid catalysis,[6b] various coordination models were explored (Figure 3a). There are two possibilities of the carboxylic acid-bridged **1a** structures: **1a**-model A and **1a**-model B. In spite of the thermodynamic stability of **1a**-model B, the most energetically favored TS structures include **1a**-model A (see Supporting Information). This is due to the enhancement of the acidity[6,21] while keeping the basicity in the phosphoric acid and phosphoryl oxygen residues, both which induce the strong interaction with **3d** and **4a**. Regarding diastereomeric TSs derived from **1a**-model A corresponding to the enantiofacial selection of **4a** (leading to (*R*) and (*S*) enantiomers of **5a**, **TSr**, and **TSs**), the relative orientation of **3d** (**TS_endo**, **TS_exo**), and three coordination modes (**TS1**: N^1, H^0; **TS2**: O^2, H^0; **TS3**: N^3, H^0) were

DOI: 10.1021/jacs.6b07150
J. Am. Chem. Soc. 2016, 138, 11353–11359

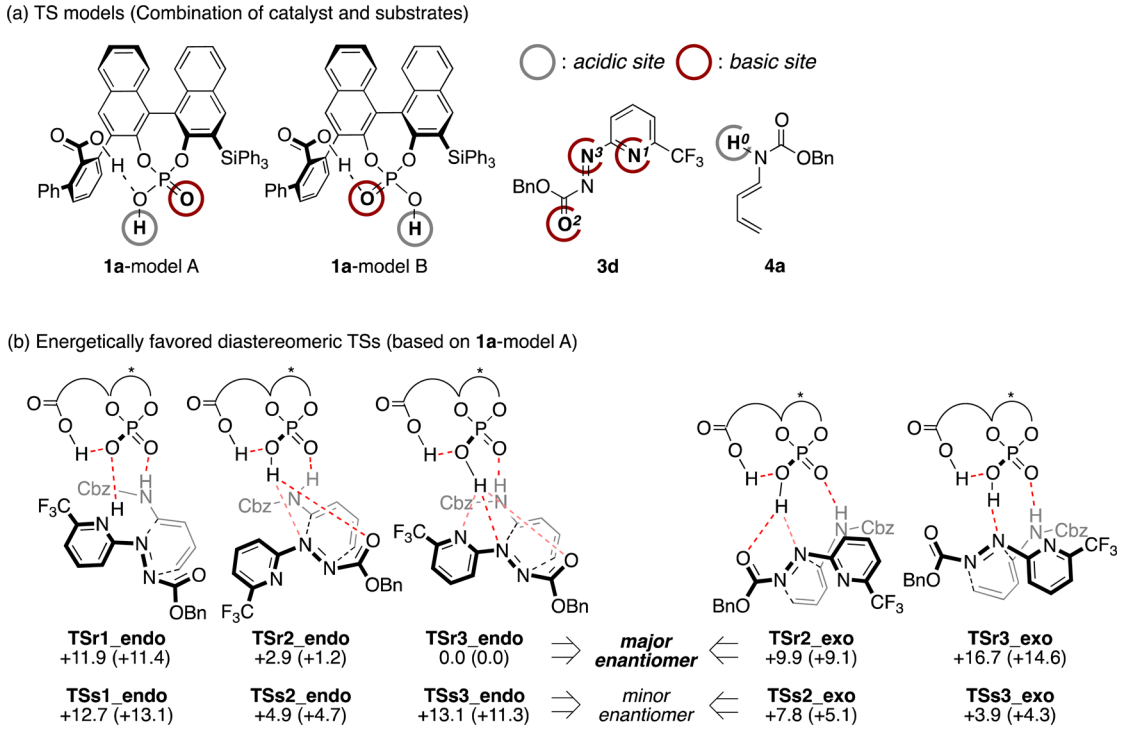


Figure 3. (a) Coordination models of diastereomeric TSs and (b) the relative energy differences of energetically favored diastereomeric TSs. Coordination modes: **TS1** (N^1, H^0), **TS2** (O^2, H^0), **TS3** (N^3, H^0).

compared (Figure 3b; see Supporting Information).[22] **TSr3_endo** leads to the major (*R*)-enantiomer and is energetically most favored of all of the diastereomeric TSs. For **TSs** leading to the minor (*S*)-enantiomer, **TSs2_endo** and **TSs3_exo** are located at a similar energy level, albeit 4.9 and 3.9 kcal/mol less stable, respectively, than the most stable **TSr3_endo**. These computational results are qualitatively consistent with the experimental results. In the energetically disfavored **TS1_endo**, pyridinium phosphate is formed through the proton transfer from the phosphoric acid moiety.[23]

To reveal the origin of the high enantioselectivity, the notable structural features of the relatively stable **TSr3_endo**, **TSs2_endo**, and **TSs3_exo** were investigated in detail (Figure 4). Both **3d** and **4a** fit well in the chiral space of **1a** constructed by the *intra*molecular hydrogen bond between two acidic functional groups in **TSr3_endo**. As predicted in our catalyst design discussed with Figure 2, there exist multiple secondary interactions—weak *inter*molecular hydrogen bonds—between **3d** and **1a** in **TSr3_endo**. Furthermore, the nonclassical CH/O hydrogen bonds are formed between the benzene ring (Cbz) of **3d** and the carboxylic moiety of **1a**. The lack of significant steric stress and the formation of the effective hydrogen-bonding network stabilize **TSr3_endo** (Figure 4a). In contrast, **TSs2_endo**, leading to the minor enantiomer, has unfavorable steric interactions between two aryl groups (Cbz and 6-trifluoromethylpyridine) of **3d** and the sterically demanding $SiPh_3$ group of **1a**. Such steric repulsions result in the lack of the hydrogen-bonding network between **3d** and **1a**, destabilizing **TSs2_endo** (Figure 4b). In a manner similar to **TSr3_endo**, both **3d** and **4a** are well oriented in the chiral space of **1a** in **TSs3_exo** without any unfavorable steric interactions with **1a**. As for **4a**, however, the C−N bond rotation leading to the facial selectivity inversion of **4a** (i.e., leading to minor enantiomer) induces the strong steric repulsion between the *N*-Cbz group and the diene moiety. This is responsible for destabilization of **TSs3_exo** (Figure 4c).

To identify the main factor in determining the relative energy difference among **TSr3_endo**, **TSs2_endo**, and **TSs3_exo**, a distortion/interaction analysis[24] was carried out (Table 3). The interaction energy difference between **1a** and **3d**/**4a** (ΔINT = +11.2 kcal/mol) has a larger impact on destabilization of **TSs2_endo** than other factors. On the other hand, the distortion energy difference of **3d**/**4a** (ΔDEF_{sub} = +4.8 kcal/mol), mainly derived from the steric interaction between the *N*-Cbz group and the diene moiety, exerts a significant influence in the stability of **TSs3_exo**. This is attributed to destabilization of **TSs3_exo**. These structural and distortion/interaction analyses indicate the elaborated chiral space and the effective hydrogen-bonding network derived from the two acidic functionalities in **1a** that synergistically control the stereoselectivity of **5**.

■ CONCLUSIONS

We have developed a chiral Brønsted acid with two different acidic sites, carboxylic acid−monophosphoric acid **1a**, and this novel catalyst structure has proven to be a highly effective catalyst for asymmetric hetero-Diels−Alder reactions between 6-trifluoromethyl-2-azopyridinecarboxylates and *N*-H-amidodienes. The reactions proceed in good yields and excellent regio-, diastereo-, and enantioselectivities with a wide range of substituent patterns. A mechanistic study by DFT calculations revealed that the multipoint hydrogen-bonding interactions among the carboxylic acid, monophosphoric acid, 2-azopyridinecarboxylate, and *N*-H-amidodiene moieties are key in this catalysis. The two Brønsted acidic sites, the carboxylic acid and monophosphoric acid groups, cooperatively function to result in high catalytic and chiral efficiencies. The present work represents the first successful design of a combined carboxylic

DOI: 10.1021/jacs.6b07150
J. Am. Chem. Soc. 2016, 138, 11353−11359

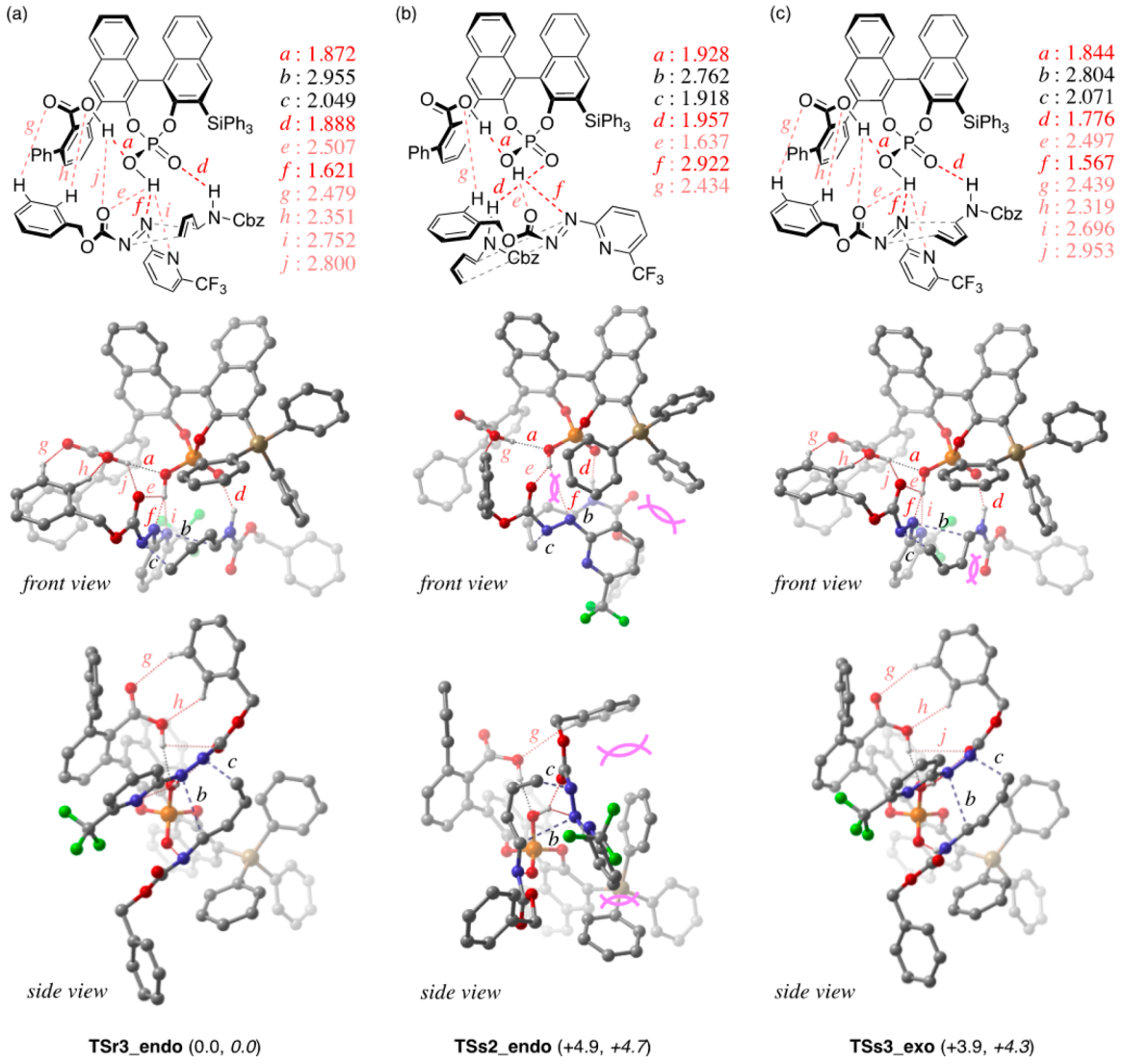
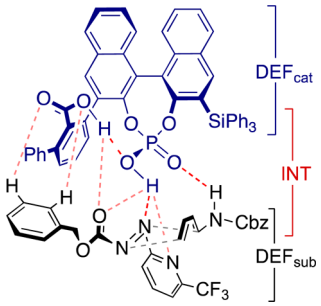


Figure 4. Length of hydrogen bonds, front and side views of 3D structures, the relative energies (in plain, kcal/mol), and the relative Gibbs free energies (in *italics*, kcal/mol) of (a) **TSr3_endo**, (b) **TSs2_endo**, and (c) **TSs3_exo**.

Table 3. Distortion/Interaction Analysis of TSr3_endo, TSs2_endo, and TSs3_exo (kcal/mol)



entry	TS	ΔDEF_{cat} [a]	ΔDEF_{sub} [a]	ΔINT [b]
1	**TSr3_endo**	0	0	0
2	**TSs2_endo**	−6.4	+0.1	**+11.2**
3	**TSs3_exo**	+1.5	**+4.8**	−2.4

[a] ΔDEF = DEF(**TS**) − DEF(**TSr3_endo**). [b] ΔINT = INT(**TS**) − INT(**TSr3_endo**).

acid−phosphoric acid in chiral Brønsted acid catalysis, and further studies on chiral Brønsted acids with different acidic sites are underway in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07150.

Experimental details, characterization data, HPLC enantiomer analysis, NMR spectra for new compounds, X-ray diffraction analysis, and Cartesian coordinates (PDF)

Crystallographic data for **1a** and regioisomers **5e/6** (CIF, CIF, CIF)

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DOI: 10.1021/jacs.6b07150
J. Am. Chem. Soc. 2016, 138, 11353−11359

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support was partially provided by IMS, JSPS via Grant-in-Aid for Scientific Research C (No. 23550114) for N.M., and Grant-in-Aid for Scientific Research on Innovative Area "Advanced Molecular Transformations by Organocatalysts" from MEXT, Japan (No. 23105002 for M.T., No. 23105005 for M.Y.)". We sincerely thank Dr. Koji Yamamoto, Research Center of Integrative Molecular System, Institute for Molecular Science for the X-ray crystallographic analysis of **5e**, and Fuji Silysia Chemical Ltd. for the gift of CHROMATOREX-DIOL. N.M., T.F., and K.Y. gratefully acknowledge JST-ACCEL for financial support. H.T. acknowledges JSPS for a Research Fellowship for Young Scientists. K.F. thanks the Yoshida Scholarship Foundation.

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(18) The reaction of **3d** with 1-methoxybuta-1,3-diene was also attempted in the presence of 10 mol % **1a**. The reaction gave the product at 0 °C for 20 h; however, the yield and selectivities were insufficient (yield of two isomers: 22%, regioisomer ratio: 49/1, ∼40% ee for major regioisomer).

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DOI: 10.1021/jacs.6b07150
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DOI: 10.1021/jacs.6b07150
J. Am. Chem. Soc. 2016, 138, 11353−11359