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Design of Chiral Bis-phosphoric Acid Catalyst Derived from (*R*)-3,3′-Di(2-hydroxy-3-arylphenyl)binaphthol: Catalytic Enantioselective Diels−Alder Reaction of α,β-Unsaturated Aldehydes with Amidodienes

Norie Momiyama,*[,†] Tohru Konno,[†] Yuichi Furiya,[†] Takeaki Iwamoto,[†] and Masahiro Terada*[,†,‡]

[†]Department of Chemistry and [‡]Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Aoba-ku, Sendai 980-8578, Japan

Supporting Information

ABSTRACT: Chiral bis-phosphoric acid **1** was designed to identify a new class of structural features in chiral Brønsted acid catalysts. X-ray diffraction analysis revealed the single atropisomer **1**, bearing *S* axial chirality at 3,3′-biaryl substituents on (*R*)-binaphthyl and intramolecular hydrogen bonding between the two phosphoric acid moieties. The newly designed bis-phosphoric acid **1** was evaluated in the Diels−Alder reaction of α,β-unsaturated aldehydes **4** with 1-*N*-acylamino-1,3-butadienes **3**. After systematic variation of the catalyst substituents, as well as the *N*-acyl substituents of 1,3-butadiene, the use of an *N*-Cbz amidodiene **3a** in the presence of bis-phosphoric acid **1e** with a 2,4,6-tri-isopropylphenyl group was found to be optimal to yield the 1*S*,6*R* enantiomeric product **5aa** in a Diels−Alder reaction of acrolein (**4a**). Application of this method to substituted substrates was found to be an efficient approach to the enantioselective synthesis of 3- and 3,6-substituted cyclic formylcarbamates **5**. The specific character as well as the utility of **1e** was further established by comparing its enantioselectivity, absolute stereochemistry, and catalytic efficiency with those of mono-phosphoric acid **2**.

Integration of hydrogen bonding into the design of asymmetric catalysis has become widespread. Excellent progress has been made in developing chiral hydrogen-bonding donor catalysts and chiral Brønsted acid catalysts.[1] Of the various chiral Brønsted acids reported to date, an axially chiral scaffold with C_2 and pseudo-C_2 symmetry is representative; in particular, binaphthol-derived chiral Brønsted acids dominate the field. Common tactics for the catalyst design have been to introduce acidic motifs at the 2,2′-position and substituents at the 3,3′-position on the binaphthyl skeleton. Although this design has proven to afford a very useful chiral environment in surveys of a variety of reaction processes,[2] the judicious introduction of these design elements at distinctive positions would provide a new and fruitful opportunity for the design and utilization of chiral Brønsted acid catalysts (Figures 1 and 2). We describe herein the design of chiral bis-phosphoric acids **1**[3] and demonstrate their potential as chiral Brønsted acid catalysts in the catalytic enantioselective

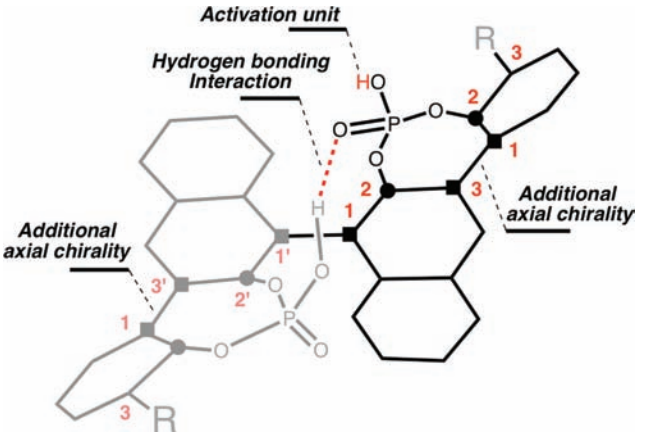


Figure 1. Design concept for bis-phosphoric acids **1**.

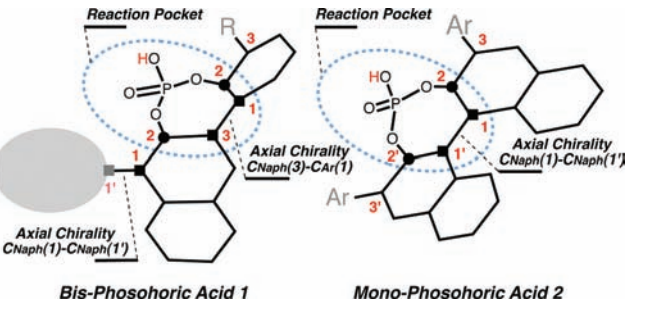
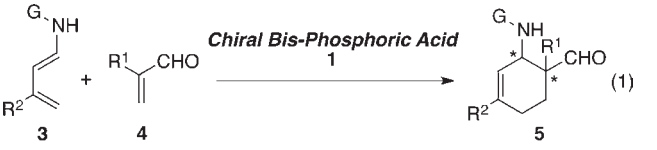


Figure 2. Difference of chiral scaffold.

Diels−Alder reaction of α,β-unsaturated aldehydes **4** with amidodienes **3** (eq 1).[4−6]



Our new catalyst design was to introduce two cyclic phosphoric acid motifs[7,8] between the $C_{Naph}(2)$ and $C_{Ar}(2)$ positions

Received: August 29, 2011
Published: November 08, 2011

dx.doi.org/10.1021/ja2081444 | *J. Am. Chem. Soc.* 2011, 133, 19294–19297

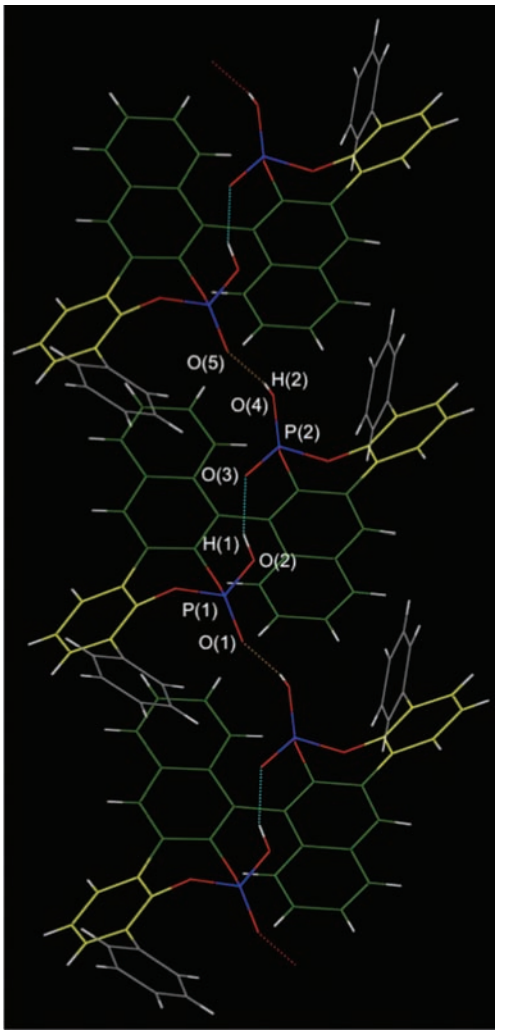


Figure 3. Hydrogen-bonding network in **1a**. Intramolecular hydrogen bonding (light blue line, O(3)···O(2) = 2.490 Å) and intermolecular hydrogen bonding (orange line, O(5)···O(4) = 2.503 Å).

and between the $C_{Naph}(2')$ and $C_{Ar}(2)$ positions, which would have the following characteristics (Figures 1 and 2): (i) The acidity of one phosphoric acid H could be enhanced as an activation unit through the interaction by the intramolecular hydrogen bonding[9] between two acidic moieties,[10] facilitating the reaction compared with that involving mono-phosphoric acid **2**.[11,12] (ii) The axial chiralities at $C_{Naph}(3)-C_{Ar}(1)$ and $C_{Naph}(3')-C_{Ar}(1)$ would be created as a novel chiral scaffold, leading to triple axial chirality in a single binaphthyl unit.[13] (iii) The substituent at $C_{Ar}(3)$ would provide an effective chiral pocket around the reaction sphere.

To assess the validity of this catalyst design, we synthesized chiral bis-phosphoric acid **1** from a chiral binaphthol-derived tetraphenol, (*R*)-3,3′-di(2-hydroxy-3-arylphenyl)-2,2′-dihydroxy-1,1′-binaphthyl.[14,15] Single-crystal X-ray diffraction analysis of **1a** successfully verified its three-dimensional molecular structure,[16,17] thereby revealing the hydrogen bonding between the phosphoryl groups (intramolecular hydrogen bonding O(3)···O(2) = 2.490 Å and intermolecular hydrogen bonding O(5)···O(4) = 2.503 Å in Figure 3) and establishing its (*S*)-configuration in both the axial chirality of $C_{Naph}(3)-C_{Ar}(1)$ and $C_{Naph}(3')-C_{Ar}(1)$ (Figure 4). Importantly, among at least three

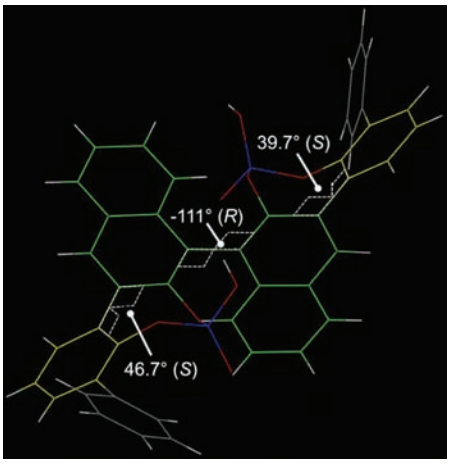
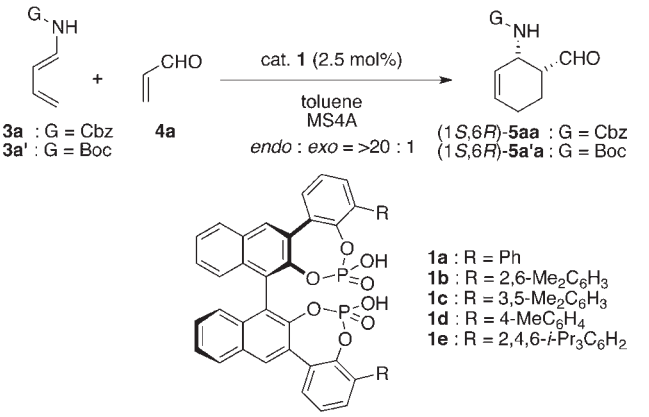


Figure 4. X-ray diffraction analysis of **1a** (R = Ph).

Table 1. Reaction of Acrolein (4a) with 1-*N*-Acylamino-1,3-butadiene 3a or 3a′ [a]



entry	cat. **1**	G	yield (%)[b]	ee (%)[c]
1[d]	**1a**	Cbz	37	88
2[d]	**1a**	Boc	29	76
3[e]	**1a**	Cbz	73	90
4[e]	**1b**	Cbz	63	95
5[e]	**1c**	Cbz	72	84
6[e]	**1d**	Cbz	59	90
7[e]	**1e**	Cbz	79	99
8[e,f]	**1e**	Cbz	86	99

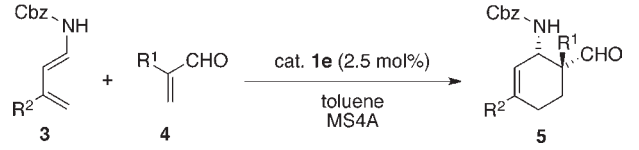
[a] Reactions were conducted with 1 equiv of **3a** or **3a′** and 1.5 equiv of **4a** in the presence of 2.5 mol % **1** in toluene at −80 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 0.1 M solution. [e] 0.2 M solution. [f] 3 equiv of **4a**.

possible atropisomers whose axial chiralities of $C_{Naph}(3)-C_{Ar}(1)$, $C_{Naph}(3')-C_{Ar}(1)$ are either (*R*,*R*), (*S*,*S*), or (*R*,*S*), the single atropo diastereomer was successfully provided, presumably due to the assistance of intramolecular hydrogen bonding between two phosphoric acid moieties.

With the newly developed chiral bis-phosphoric acid **1** in hand, we next focused on the evaluation of its ability for the catalytic enantioselective Diels−Alder reaction of acrolein (**4a**) with 1-*N*-acylamino-1,3-dienes (Table 1). The initial experiments revealed

dx.doi.org/10.1021/ja2081444 |*J. Am. Chem. Soc.* 2011, 133, 19294–19297

Table 2. Reaction Scope[a]



entry	R^1	R^2	5	yield (%)[b]	ee (%)[c]
1	H (**4a**)	H (**3a**)	**5aa**	79	99
2[d]	H (**4a**)	H (**3a**)	**5aa**	86	99
3	Me (**4b**)	H (**3a**)	**5ab**	90	98
4	Et (**4c**)	H (**3a**)	**5ac**	89	98
5	Bn (**4d**)	H (**3a**)	**5ad**	91	97
6[d]	H (**4a**)	Me (**3b**)	**5ba**	86	99
7[d]	H (**4a**)	*i*-Pr (**3c**)	**5ca**	92	99
8[d]	H (**4a**)	Bn (**3d**)	**5da**	74	98
9[d]	Me (**4b**)	Me (**3b**)	**5bb**	74	95
10	Me (**4b**)	*i*-Pr (**3c**)	**5cb**	68	98
11	Me (**4b**)	Bn (**3d**)	**5db**	48	98
12	Me (**4b**)	Et (**3e**)	**5eb**	52	99

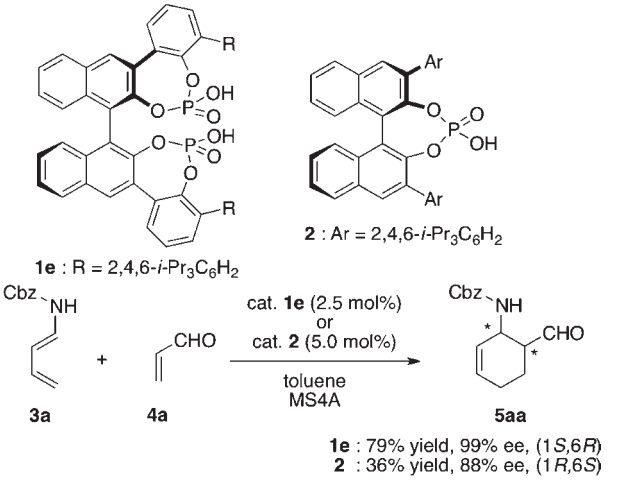
[a] Reactions were conducted with 1 equiv of **3** and 1.5 equiv of **4** in the presence of 2.5 mol % **1e** in toluene (0.2 M) at −80 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 3 equiv of **4** was used.

that the reactions proceeded with excellent endo selectivity to give a cycloadduct with good enantioselectivity. The reaction of *N*-Cbz amidodiene **3a** provided higher enantioselectivity than *N*-Boc amidodiene **3a′** (entries 1 and 2). Due to the very slow reaction under 0.1 M solution conditions, the chemical yield for this reaction was initially low (entry 1). In contrast, when the reaction was conducted in a 0.2 M solution, an increase in the reaction rate was observed, which improved the yield (entry 3). The enantiomeric excess showed a strong dependence on the aryl substituents R in the catalyst. Catalysts with a 2,6-substituted phenyl group exhibited higher enantioselectivity than their 3,5- or 4-substituted counterparts (entries 4−7). 2,4,6-Tri-isopropylphenyl substitution (**1e**) produced the best results, providing (1*S*,6*R*)-**5aa** in 99% ee (entry 7). Finally, reaction of 3 equiv of **3a** proceeded efficiently to yield endo adduct **5aa** at the highest yield with complete enantioselectivity (entry 8).

The scope of Diels−Alder reactions catalyzed by **1e** was examined (Table 2). High yields and excellent enantioselectivities in the α-position to the carbonyl group were obtained from the reaction of unsubstituted amidodiene **3a** (entries 3−5). The corresponding reaction of acrolein (**4a**) with 3-alkyl-substituted amidodienes **3** revealed that these substrates reacted equally selectively (entries 6−8). Although the reaction of methacrolein (**4b**) with 3-alkyl-substituted amidodienes **3** provided the desired cycloadducts in slightly lower yields than the corresponding reaction of **4a**, excellent enantioselectivities were obtained in all cases (entries 9−12).

The specific character and the utility of bis-phosphoric acid **1e** were further established by comparing the corresponding reaction using mono-phosphoric acid **2** (Scheme 1). We found that, even at a 5 mol % catalyst loading, **2** gave less than half the chemical yield of **5aa** than that obtained at a 2.5 mol % catalyst loading of **1e**. Furthermore, the reaction catalyzed by **2** was found to afford (1*R*,6*S*)-**5aa**, which is the opposite absolute

Scheme 1. Enantioselective Diels−Alder Reaction Catalyzed by Bis-phosphoric Acid 1e vs Mono-phosphoric Acid 2



configuration, when the product was formed via the reaction with **1e**. The quite different absolute stereochemistry observed for **5aa** suggests that the reaction catalyzed by **1e** occurred around the reaction sphere for the *S* axial chirality of C_{Naph}-(3)−C_{Ar}(1), not around that for the *R* axial chirality of binaphthyl. Importantly, higher enantioselectivity was obtained with **1e** than with **2**, probably due to the unique structure of **1e**. These results suggest that intramolecular hydrogen bonding between the two phosphoryl groups plays an essential role not only in producing higher catalytic activity but also in creating a precise chiral environment.

In summary, we developed chiral bis-phosphoric acid **1** bearing a new chiral scaffold with triple axial chirality assisted by intramolecular hydrogen bonding between two phosphoric acid moieties, and its potential as a chiral Brønsted acid catalyst has been demonstrated in the catalytic enantioselective Diels−Alder reaction of α,β-unsaturated aldehydes **4** with amidodienes **3**. Chiral bis-phosphoric acid **1e** is useful in realizing high enantioselectivities in a broad range of substrates. We believe that this design can be tailored for application in a variety of transformations. Further efforts to elucidate higher enantioselectivity by bis-phosphoric acid **1e** in the present reaction and to discover catalytic enantioselective variants of other processes are currently underway; the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization data, HPLC enantiomer analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
momiyama@m.tohoku.ac.jp; mterada@m.tohoku.ac.jp

■ ACKNOWLEDGMENT

Support was partially provided by JSPS via Grant-in-Aid for Scientific Research A (No. 20245021).

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