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Design of Phosphinic Acid Catalysts with the Closest Stereogenicity at the α-Position: Synthesis and Application of α-Stereogenic Perfluoroalkyl Phosphinic Acid Catalysts

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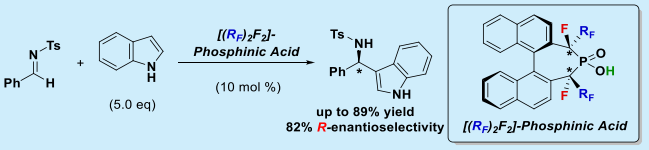
Supporting Information

ABSTRACT: Chiral C_2-symmetric phosphinic acids were designed based on sterically demanding and helical chiral perfluoroalkyl groups at the closest α-position advancing asymmetric reaction environment and catalytic activity. The perfluoroalkyl catalysts, $[(CF_3)_2F_2]$ and $[(C_2F_5)_2F_2]$ phosphinic acids, were synthesized via a stereoselective addition/cyclization sequence of methyl phosphinate and deoxofluorination. These new classes of Brønsted acid catalysts were applied to an asymmetric Friedel−Crafts reaction to give up to 89% yield and 82% *R*-enantioselectivity, which is higher than those obtained with the parent phosphoric acid (42% and 55.5% *S*).



Organocatalysts have attracted interest as the third pillar of the asymmetric catalysts since the 1990s, after bio- and metal catalysts, in the areas of easy synthetic operation, lower toxicity, inexpensiveness, no sensitivity toward moisture and air, and wide varieties of catalyst designs.[1−6] In the field of chiral Brønsted acid catalysis,[7−11] binaphthol-based chiral phosphoric acid catalysts, developed by Inanaga,[12,13] Akiyama,[14,15] and Terada,[16] have been actively studied and utilized for asymmetric organic synthesis (Figure 1, bottom).[17−21] Chiral phosphoric acid catalysts have been developed with chiral skeletons including TADDOL,[22] VAPOL,[23] SPINOL,[24] and others.[25−29] One of the approaches for improving the catalytic activity is to increase the acidity by *N*-triflyl phosphoramides,[30] bis-phosphoric acids,[31] and imidodiphosphorimidate.[32] Nevertheless, asymmetric organic transformations that should be brushed up by chiral phosphoric acids still remain. Therefore, novel methodologies to construct superior chiral environments and architecture loading to more efficient asymmetric induction should be developed.

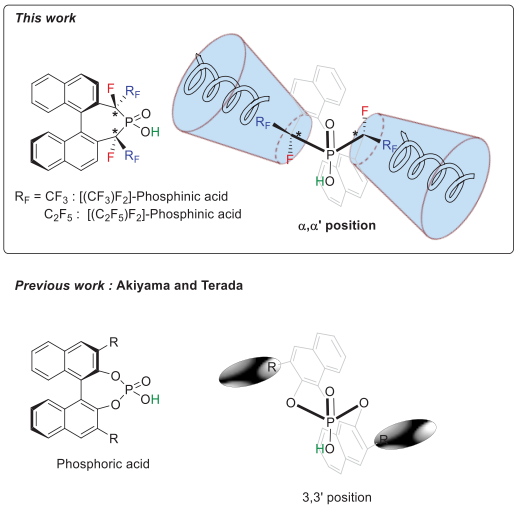


Figure 1. Fluorinated phosphinic acids as a novel structural motif of chiral Brønsted acid catalysts.

Fluorine shows the largest electronegativity and induces a strong electron-withdrawing substituent effect.[33−35] Therefore, use of fluorine-containing functional groups is promising to increase the acidity of the parent acids remarkably. Berkowitz has reported that the acidity of phosphonic acids bearing a difluoromethylene group at the α position of the phosphorus atom showed notable increase of acidity compared with the phosphoric acid.[36] Perfluoroalkyl group is known to not only show a strong electron-withdrawing substituent effect but also adopt helical chirality.[37−41]

Herein, we report the design of new chiral phosphinic acid catalysts bearing perfluoroalkyl groups (Figure 1, top). The fluorinated phosphinic acids are expected to show higher catalytic activity and enantioselectivity on the basis of steric and electronic effects. In addition, the fluoroalkyl groups construct helical environments, which would be effective to promote unique chiral induction. The chiral phosphinic acid catalysts have C_2-symmetry, and fluoroalkyl functional groups (R_F = CF_3, C_2F_5, etc.) come into close proximity to the reaction site hopefully through construction of an excellent asymmetric reaction field. The catalytic activity of the chiral phosphinic acids was evaluated through the Friedel−Crafts reaction as a proof of concept.

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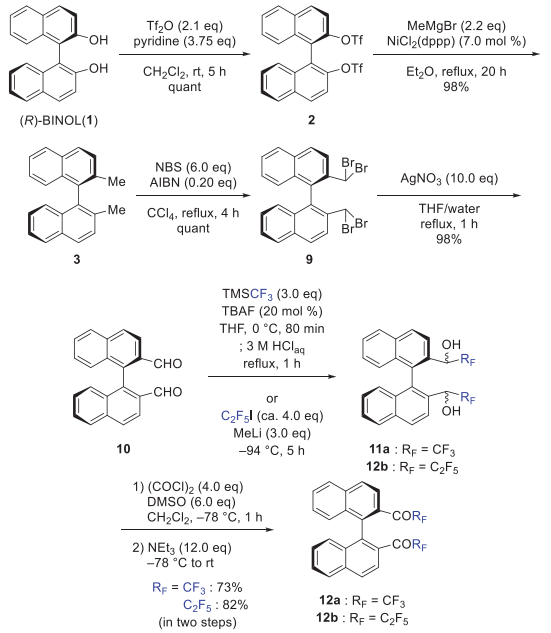
We planned to synthesize chiral fluoroalkylated phosphinic acids, $[(CF_3)_2F_2]$, and $[(C_2F_5)_2F_2]$ phosphinic acids, on the basis of the stereoselective addition/cyclization sequence of methyl phosphinate as the key step. Commercially available chiral (*R*)-BINOL (**1**) was converted into the triflate, and Kumada−Tamao−Corriu cross-coupling reaction of **2** gave 2,2′-dimethyl-1,1′-binaphtalene **3** almost quantitatively. Bromination of **3** gave tetrabromide **9** followed by treatment of silver nitrate gave dialdehyde **10** in excellent yield.[42] Subsequently, the fluoroalkylated diol was synthesized from dialdehyde by nucleophilic fluoroalkylation: For trifluoromethylation, Ruppert−Prakash reagent was used.[43] For pentafluoroethylation, Gassman's method was employed.[44] Swern oxidation of diol (**11a**, **11b**) gave diketone (**12a**, **12b**) in excellent yields in two steps (Scheme 1).

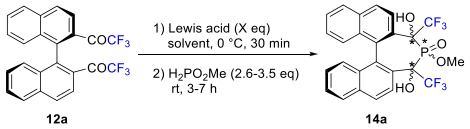
Scheme 1. Synthesis of perfluoroalkyl diketone



We initiated our diastereofacial selective addition/cyclization sequence of methyl phosphinate, while Feng reported the enantioselective hydrophosphonylation of trifluoroacetophenones using chiral amino alcohol-derived Al(III) catalysts.[45] Screening of achiral Lewis acids (Table 1), $Ti(OiPr)_4$, $AlEt_3$, and $AlEt_2Cl$, gave complex reaction mixtures (entries 1−6). Using $BF_3{\cdot}OEt_2$ gave phosphinic ester **14a** in 81% conversion and moderate diastereoselectivity (entry 7). Bulky $B(C_6F_5)_3$ improved diastereoselectivity, but yield was decreased (entry 8). The use of TBME instead of THF as a solvent improved both yield and diastereoselectivity (entry 9).

In order to determine the relative stereochemistry of diastereomers, we examined the dealkylation of the phosphinic ester **14a**. Since the phosphinic ester **14a** has an axial chirality of binaphthyl skeleton, asymmetric carbons, and a center on phosphorus, four diastereomers are conceivable (Figure 2, top). Deprotection of **14a** by sodium iodide proceeded smoothly, and as the asymmetric center on the phosphorus atom disappears due to the rapid exchange of the acidic proton of phosphinic acid **15a**, the same phosphinic acid was obtained from **d3** and **d4**, so that the number of diastereomers was decreased from 4 to 3 (Figure 2, bottom). Phosphinic acids

Table 1. Screening of the Lewis Acid for the Stereoselective Addition/Cyclization Sequence



12a 14a

entry	Lewis acid (equiv)	solvent	product (**d1**/**d2**/**d3**/**d4**)[a] (%)	recov (%)
1	$Ti(OiPr)_4$ (1.0)	THF	complex mixture	nd
2	$Ti(OiPr)_4$ (2.0)	THF	complex mixture	nd
3	$AlEt_3$ (1.0)	THF	complex mixture	nd
4	$AlEt_3$ (2.0)	THF	complex mixture	nd
5	$AlEt_2Cl$ (1.0)	THF	complex mixture	nd
6	$AlEt_2Cl$ (2.0)	THF	complex mixture	nd
7	$BF_3{\cdot}OEt_2$ (2.0)	THF	43:12:21:5	<1
8	$B(C_6F_5)_3$ (2.0)	THF	29:8:20:8	<1
9	$BF_3{\cdot}OEt_2$ (2.0)	TBME	58/6/18/11	<1

[a]Yields were determined by ^{19}F NMR.

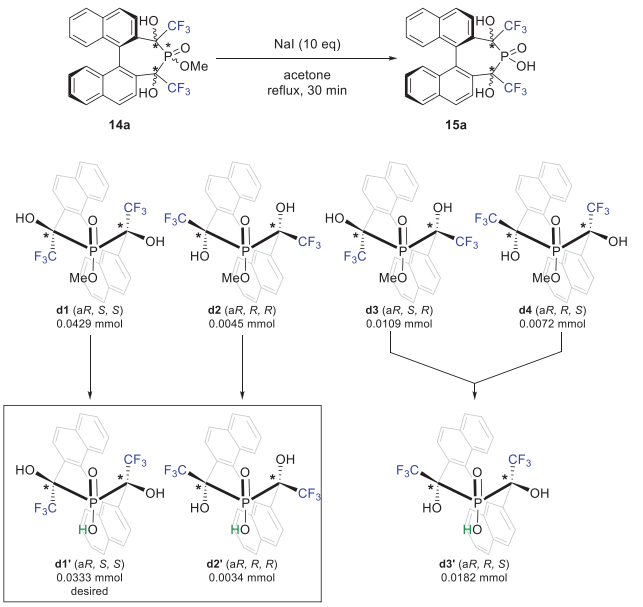


Figure 2. Demethylation and configurations of phosphinic ester **14a**.

derived from **d1** and **d2** have C_2-symmetry, and CF_3 groups are equivalent, while CF_3 groups of phophinic acids derived from **d3** and **d4** are not equivalent. Since the deoxofluorination reaction in the following step generally proceeds in the S_N2 reaction, **d1** is the desired diastereomer because the CF_3 groups positioned pseudoaxial in **d1** are transferred to pseudoequatorial via stereoinversion in the S_N2 deoxofluorination reaction.[46]

Based on the integration in ^{19}F NMR and ^{31}P NMR spectra before and after demethylation, the peaks of the diastereomer were assigned. Diastereomers **d1'** and **d2'** have C_2-symmetry. Based on these results of deoxofluorination, the major diastereomer **d1** was characterized as the desired one (Figure 3 and Figure 4). Similarly, the phosphinic ester **14b** bearing C_2F_5 groups was obtained in high yield and excellent diastereoselectivity in THF (Scheme 2).

Plausible reaction mechanism of stereoselective addition/cyclization reaction is as shown in Scheme 3. After methyl phosphinate becomes an active trivalent chemical species due to tautomerism, nucleophilic addition proceeds to a carbonyl

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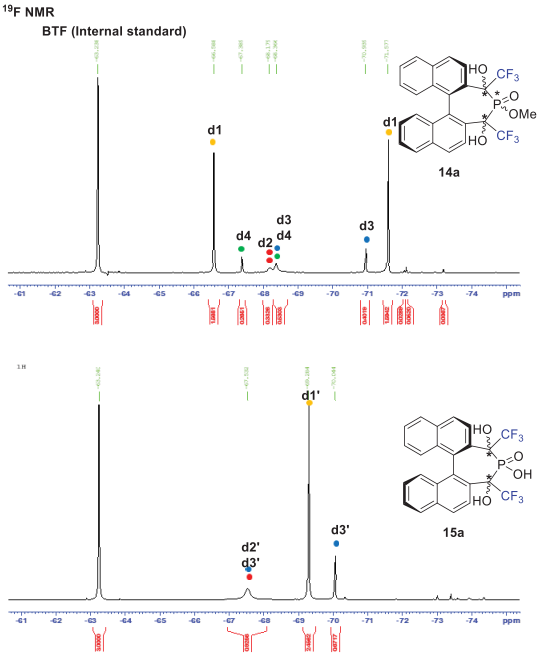


Figure 3. ^{19}F NMR of CF_3 phosphinic ester **14a** (top) and phosphinic acid **15a** (bottom).

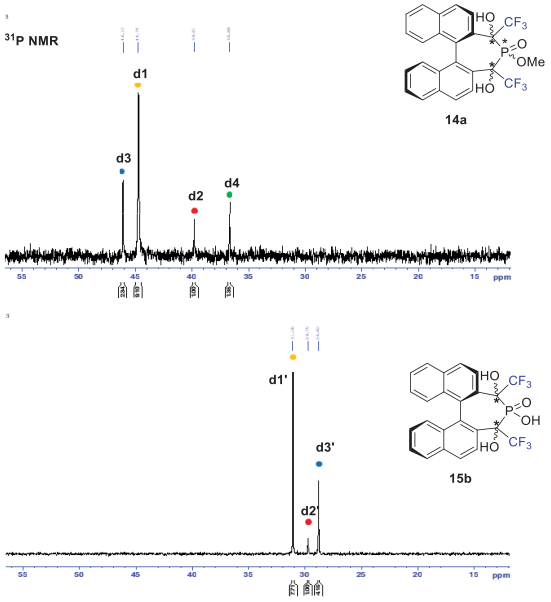
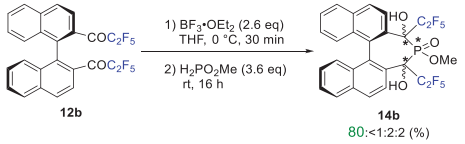


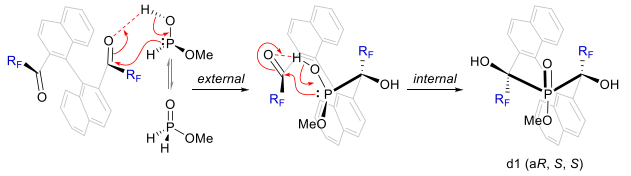
Figure 4. ^{31}P NMR of CF_3 phosphinic ester **14a** (top) and phosphinic acid **15a** (bottom)

Scheme 2. Stereoselective Addition/Cyclization Sequence of Methyl Phosphinate to C_2F_5 Diketone 12b



group[47] activated by the Lewis acid, and subsequently, intramolecular nucleophilic addition proceeds. The key to the high diastereoselectivity of the reaction sequence is the high level of recognition of the *Re* and *Si* faces of the carbonyl

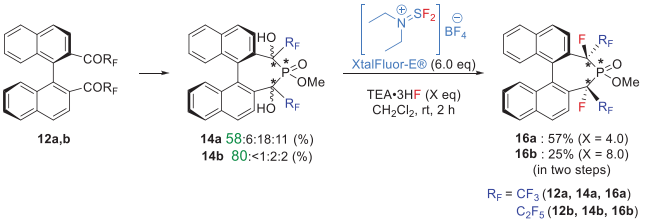
Scheme 3. Plausible Reaction Mechanism of Stereoselective Addition/Cyclization Reaction



group in the nucleophilic addition of methyl phosphinate in inter- and then intramolecular additions. The nucleophilic methyl phosphinate would approach from outside to the carbonyl group (*Re*-face) in the first step and from inside to the carbonyl group (*Si* face) in the second step. Therefore, **d1** is obtained as the main product. Compared with the case of the CF_3 group, the C_2F_5 group is bulky, so that the diastereoselectivity of **14b** is much improved (Scheme 2).

Subsequently, the deoxygenative fluorination reaction proceeded smoothly by treatment of **14a** with Xtalfluor-E and TEA·3HF as an additive, and a fluorinated product **16a** was obtained as a single isomer in 57% yield over the two steps. In the case of **14b** having C_2F_5 groups, the use of an excess amount of TEA·3HF gave the fluorinated product **16b** (Scheme 4).

Scheme 4. Deoxygenative Fluorination of 14a and 14b



The structure of racemic **16b** was confirmed by X-ray crystallography, indicating that the stereochemistry of **16a** and **16b** was (a*RS*,*RS*,*RS*). Perfluoroalkyl groups are positioned in a pseudoequatorial orientation in the binaphthyl backbone accompanying the helical chirality and come forward into close proximity to the reaction site (Figure 5).

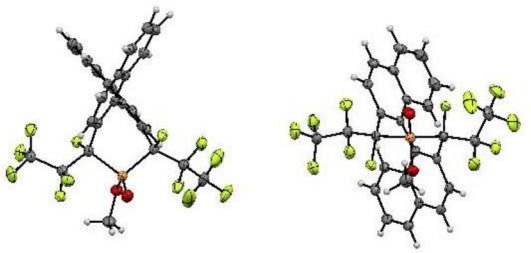


Figure 5. X-ray structure of **16b**.

Finally, deprotection of **16a** and **16b** by sodium iodide smoothly proceeded and gave phosphinic acids **17a** and **17b** (Scheme 5).

The catalytic activity and enantiocontrolling ability of the new chiral Brønsted acids **17a,b** were evaluated as a proof of concept in an asymmetric transformation. As a test reaction, the well-known asymmetric Friedel–Crafts reaction of indole and *N*-tosylimine was employed (Table 2).[48] Furthermore,

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Scheme 5. Deprotection of 16a and 16b

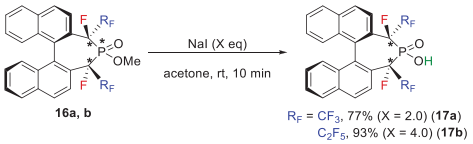
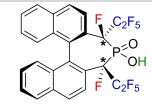
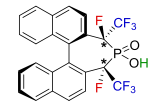
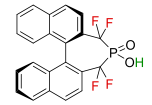
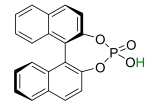
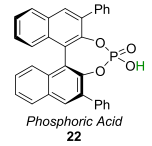


Table 2. Friedel–Crafts Reaction of *N*-Tosylimine 18 with Indole 19 Catalyzed by Chiral Brønsted Acids 8, 17a, 17b, 21, and 22

entry	cat.	yield (%)	*R* : *S*
1	 *[$(C_2F_5)_2F_2$]-Phosphinic Acid* **17b**	89 (60)[a]	76:24 (**82**:18)[a]
2	 *[$(CF_3)_2F_2$]-Phosphinic Acid* **17a**	63	66.5:33.5
3	 *[F_4]-Phosphinic Acid* **8**	56	54.5:45.5
4	 *Phosphoric Acid* **21**	42	44.5:**55.5**
5	 *Phosphoric Acid* **22**	80	25.5: 74.5

a : −78 °C, 48 h

[F_4]-Phosphinic acid **8** had a higher catalytic activity than phosphoric acid **21** (entry 3 vs 4) but surprisingly showed a changeover in the sense of enantioselectivity (*S* → *R*). Subsequently, when phosphinic acid **17a** substituted with CF_3 group was used, the enantioselectivity was dramatically improved along with the improvement of yield (entry 2). With phosphinic acid **17b** having a C_2F_5 group as a longer chain of the perfluoroalkyl group, further improvement in yield and enantioselectivity was achieved—up to 82% *R*-selectivity and 89% yield (entry 1). [C_2F_5]-Phosophinic acid **17b** had a higher catalytic activity than 3,3′-substituted phosphoric acid **22** (entry 1 vs 5).

In summary, we have designed and synthesized chiral C_2-phosphinic acids with chiral fluoroalkyl groups at the closest *α*-position for reaction field. In the synthesis of fluoroalkylated phosphinic acids, the stereoselective addition/cyclization sequence of methyl phosphinate can be achieved with excellent yield and diastereoselectivity. The relative configuration of fluoroalkylated products can also be determined by X-ray analysis to prove the fluoroalkyl groups in a pseudoequatorial orientation directed toward the active site. The new Brønsted acids provide high catalytic activity and enantioselectivity in the Friedel–Crafts reaction. These results indicate fluoroalkyl groups at the closest *α*-position for the active site are effective for asymmetric transformations. Further investigation along this line on the fluorinated functional groups at the closest *α*-position for active sites is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01131.

Experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1906829 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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