Development of Chiral Bis(phosphoric Acid) and Chiral Pyrophosphoric Acid Catalysts for Enantioselective Aza-Friedel–Crafts Reaction

OKAMOTO Haruka

Development of Chiral Bis(phosphoric Acid) and Chiral Pyrophosphoric Acid Catalysts for Enantioselective Aza-Friedel–Crafts Reaction

OKAMOTO Haruka

Graduate School of Engineering, Nagoya University

Nagoya, 2018

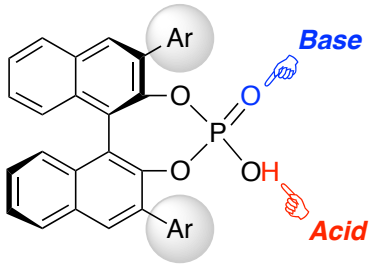
Contents

Chapter 1

Introduction and General Summary

1-1. Introduction

In modern organic synthesis, new methods are still needed for the more efficient synthesis of optically active compounds through asymmetric catalyses.[1] Recently, a variety of chiral organocatalysts have been developed, and they have already contributed to the development of environmentally-benign process chemistry in both the laboratory and industry.[2] In particular, chiral Brønsted acid organocatalysts are highly useful, and several efficient asymmetric reactions have been developed by many research groups. In this regard, BINOL (1,1'-bi-2-naphthol)-derived chiral phosphoric acid catalyst **1**, which was developed independently by Akiyama[3] and Terada,[4] is one of the most practical and accommodating chiral Brønsted acid catalysts.[5]

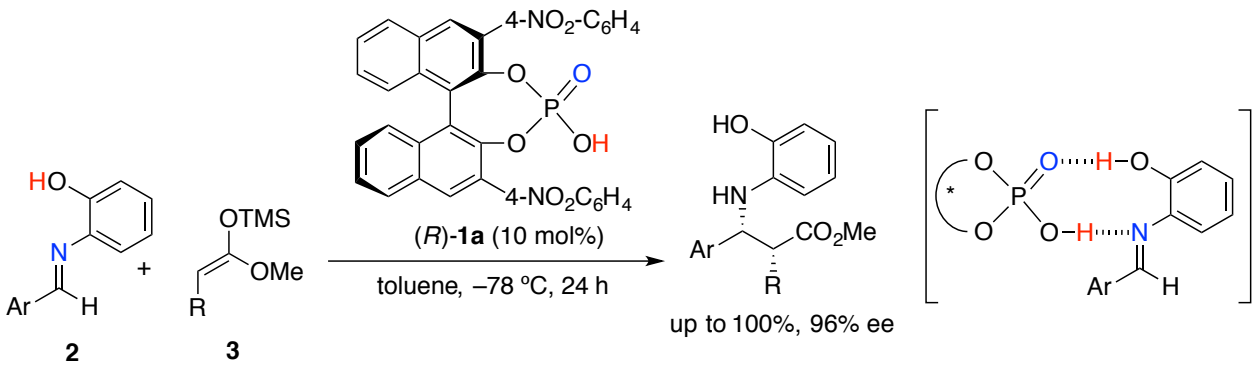


(*R*)-**1**

Figure 1. Chiral BINOL-derived phosphoric acid (*R*)-**1**

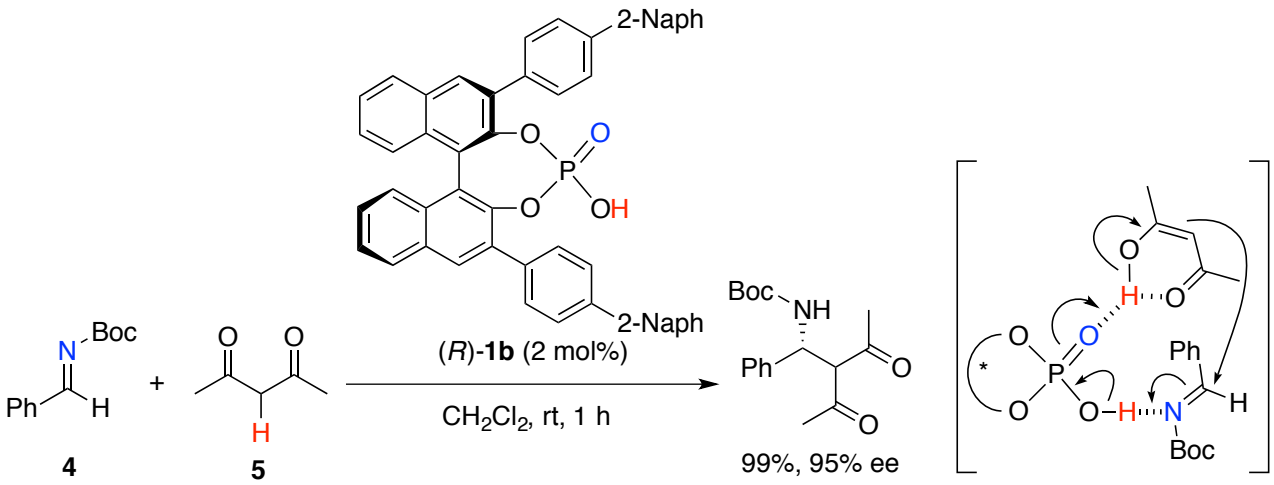
Chiral phosphoric acid (*R*)-**1** has a Brønsted acid function on the P-O*H* moiety (pK_a(DMSO) = 1.98–6.38)[6] as well as a base function on the P=*O* moiety. Therefore, (*R*)-**1** can act as an acid–base bifunctional catalyst.[5] For example, Akiyama reported that (*R*)-**1a** could activate *N*-(2-hydroxyphenyl)aldimines **2** through double hydrogen bonds in the enantioselective Mukaiyama–Mannich-type reaction of ketene silyl acetals **3** (Scheme 1).[3] Moreover, Terada reported that (*R*)-

Scheme 1. Mukaiyama–Mannich-type reaction by Akiyama[3]



2 **3** up to 100%, 96% ee

Scheme 2. Direct Mannich-type reaction by Terada[4]



1b could activate both *N*-Boc aldimine **4** and reagent **5** in the enantioselective direct Mannich-type reaction (Scheme 2).[4]

1-2 New Design of Chiral Bis(phosphoric Acid) Catalysts and Chiral Pyrophosphoric Acid Catalysts

The use of intramolecular hydrogen bonds in Brønsted acid catalysts is a practical method for increasing their acidity. For example, fumaric acid (*trans*-form) and maleic acid (*cis*-form) are geometric isomers with defferent acidities (Figure 2).[7] Maleic acid ($pK_a(H_2O)$ = 1.93) has an intramolecular hydrogen bond, and the acidity of one part of the carboxylic acids can increase (Figure 2a). On the other hand, fumaric acid ($pK_a(H_2O)$ = 30.3) cannot have an intramolecular hydrogen bond, and the acidity of each carboxylic acid cannot increase (Figure 2b). Therefore, the acidity of maleic acid is higher than that of fumaric acid.

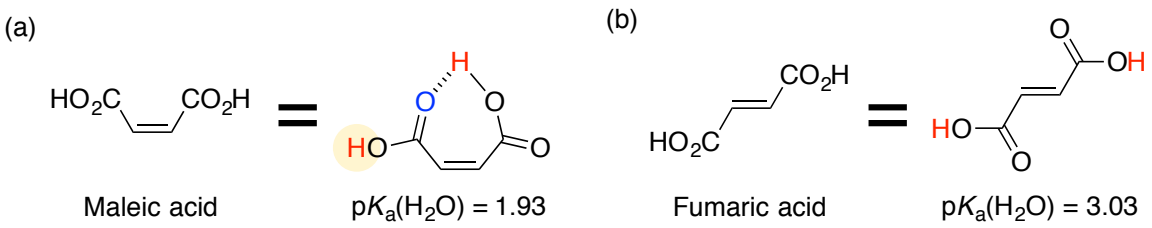


Figure 2. Effect of intramolecular hydrogen bonding on acidity

Indeed, a method based on such a combined acid system has already been used in the design of chiral catalysts. According to the general classification of the combined acid system described by Yamamoto,[8,9] maleic acid in Figure 2 is based on a Brønsted acid-assisted Brønsted acid (BBA) system. Some remarkable examples of chiral BBA catalysts are shown in Figure 3. Rawal reported the first example of chiral BBA catalysts by using chiral TADDOLs (α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol)s **6**[10] for the enantioselective hetero-Diels–Alder reaction.[11] Soon thereafter, Schaus developed chiral 3,3'-diaryl-BINOLs **7** for the enantioselective Morita–Baylis–Hillman reaction.[12] Moreover, chiral 1,1'-biaryl-2,2'-dimethanols **8** were developed by Yamamoto and Rawal,[13] chiral 2-bis(triflyl)methyl-2'-hydroxy-1,1'-binaphthyl **9** was developed by Ishihara and Yamamoto,[14] chiral binaphthyl dicarboxylic acids **10** were developed by Maruoka,[15] and chiral binaphthyl disulfonic acids (BINSA) **11** were developed by Ishihara.[16] These highly active chiral BBA catalysts have been used in a variety of asymmetric catalyses.

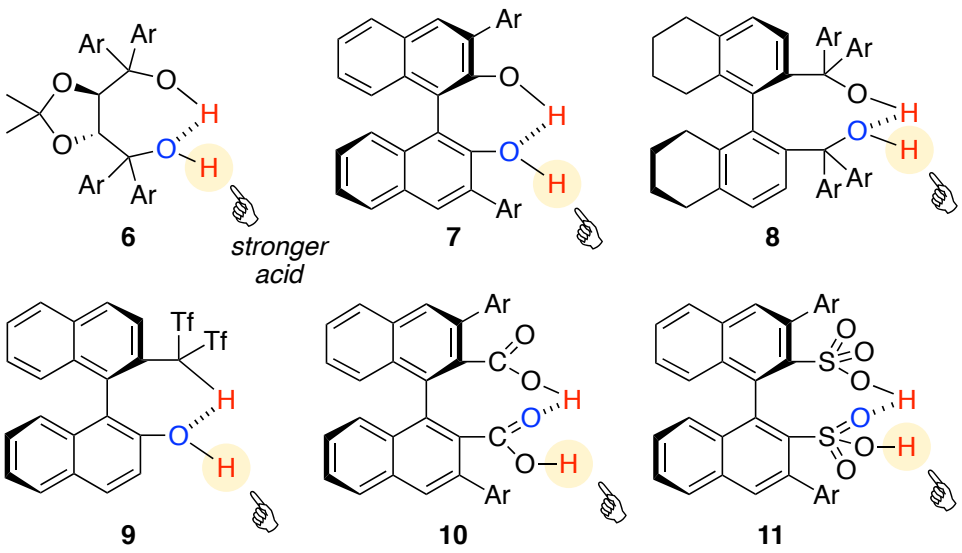
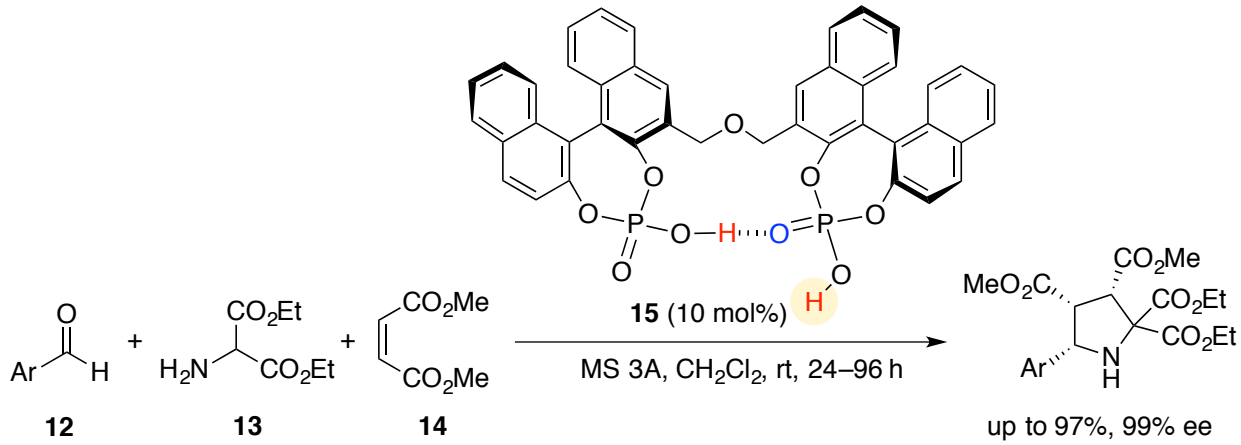


Figure 3. Chiral Brønsted acid-assisted Brønsted acid (BBA) catalysts

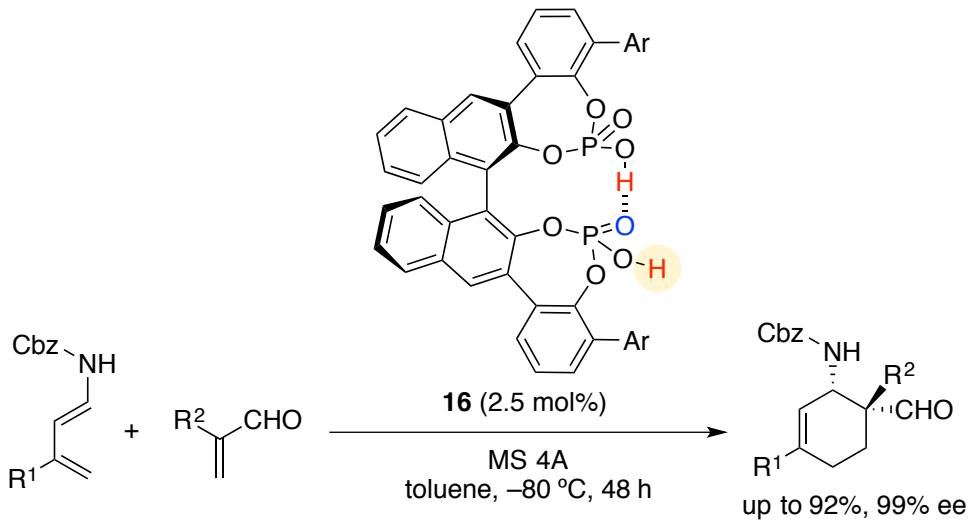
Chiral phosphoric acid catalysts can also provide a chiral BBA catalyst system by using two phosphoric acid units (Schemes 3 and 4). Gong reported the enantioselective three-component 1,3-dipolar addition reaction between aldehydes **12**, amino ester **13**, and maleic acid dimethyl ester **14** by using chiral linked-BINOL-derived bis(phosphoric acid) catalyst **15** (Scheme 3).[17] Later, Terada and Momiyama reported the enantioselective Diels–Alder reaction by using chiral

Scheme 3. Chiral bis(phosphoric acid) catalyst **15** for an enantioselective 1,3-dipolar addition reaction[17]



3,3'-di(2-hydroxy-3-arylphenyl)binaphthol-derived bis(phosphoric acid) catalysts **16** (Scheme 4).[18] These chiral bis(phosphoric acid)s **15** and **16** would have stronger Brønsted acidity than conventional chiral BINOL-derived phosphoric acids **1**. Therefore, these chiral bis(phosphoric acid)s might be effective for the activation of substrates that might be only barely activated by **1**.

Scheme 4. Chiral bis(phosphoric acid) catalyst **16** for an enantioselective hetero Diels–Alder reaction[18]



As shown in Figure 4a, chiral bis(phosphoric acid) catalysts **15** and **16**, which were developed by Gong and Terada, are chiral BBA catalysts **18** by virtue of the combined use of two units of

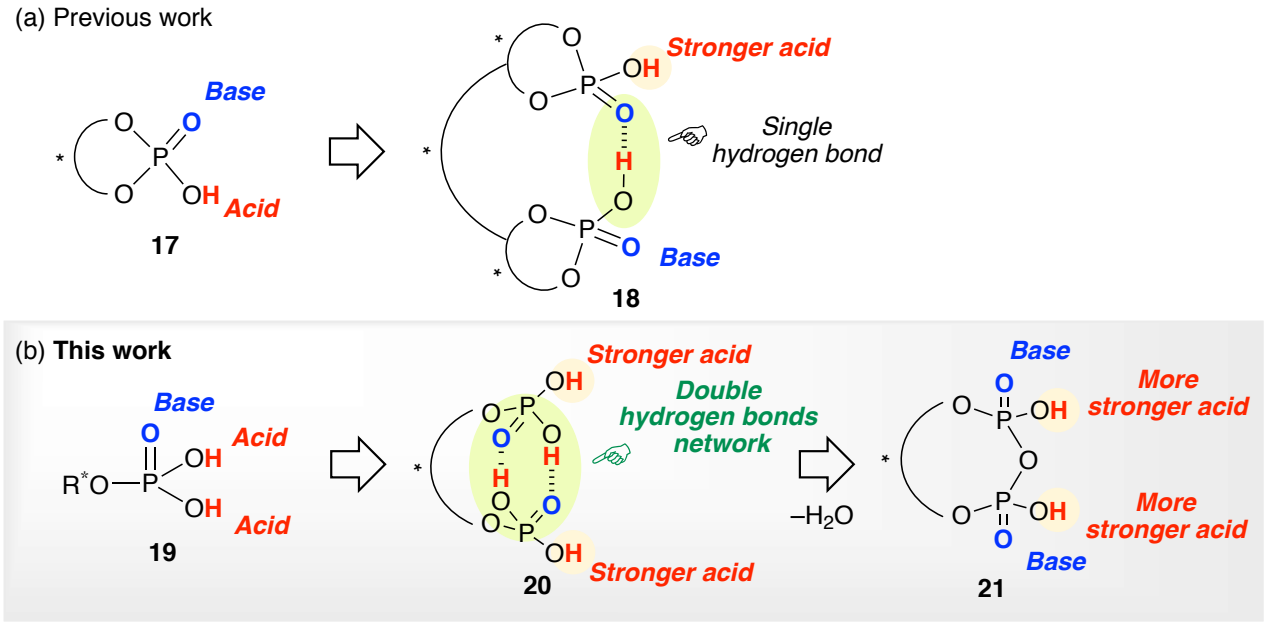
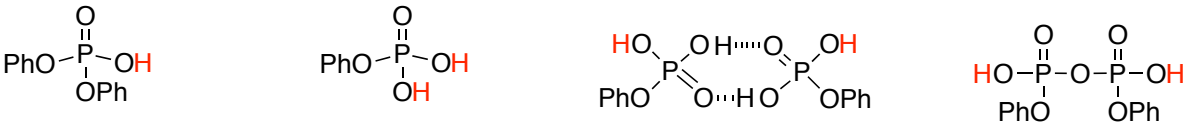


Figure 4. Design of chiral bis(phosphoric acid)s **20** and chiral pyrophosphoric acids **21**

phosphoric diesters **17**. Therefore, **18** can still act as acid–base catalyst beyond a single intramolecular hydrogen bond. In sharp contrast, the author focused on the units of phosphoric monoesters **19** instead of the units of phosphoric diesters **17** (Figure 4b). Accordingly, novel chiral bis(phosphoric acid) catalysts **20** have a double intramolecular hydrogen bonding network by virtue of the combined use of two units of phosphoric monoesters **19**. Since the two pairs of P-OH/P=O moieties in the catalysts **20** would be used in the cyclic structure of the double intramolecular hydrogen bonding network, catalysts **20** would act as a stronger Brønsted acid catalysts due to the two remaining P-OH moieties outside of the network. Moreover, novel chiral pyrophosphoric acid catalysts **21** would be prepared by the dehydrative condensation of catalysts **20**. Since the two pairs of P-OH/P=O moieties in the catalysts **21** are intact, catalysts **21** would act as novel double-acid–base bifunctional catalysts.

As shown in Figure 5, phosphoric diester **22** ($pK_a(H_2O)$ = 0.26) has stronger Brønsted acidity than phosphoric monoester **23** ($pK_a(H_2O)$ = 1.42). Therefore, in general, phosphoric monoesters would not have high catalytic activity as Brønsted acid catalysts. However, according to the author's preliminary DFT-calculation for molecular electrostatic potential (MEP, see Chapter 2 in detail), which shows a strong correlation between experimental pK_a values,[19] **24**, as a dimer of **23**, (MEP = 75.2 kcal/mol) with two hydrogen bonds between two molecules of **23** would have stronger Brønsted acidity than phosphoric diester **22** (MEP = 72.3 kcal/mol). In this regard, it is known

that a compound with multiple hydrogen bonds would show stronger Brønsted acidity than a compound with a single hydrogen bond.[20] Therefore, if novel chiral bis(phosphoric acid) catalysts **20** could be designed as shown in Figure 4b, they would provide higher catalytic activity than the conventional chiral phosphoric acid catalysts **1**. Moreover, pyrophosphoric acid **25**, which could be prepared through dehydration from two molecules of phosphoric monoester **23**, showed a much higher MEP value (78.4 kcal/mol) than **23**. Accordingly, if chiral pyrophosphoric acid catalysts **21** are designed as shown in Figure 4b, they should act as novel double-acid–base bifunctional catalysts with relatively high Brønsted acidity.



22 pK_a (H_2O) = 0.26, MEP = 72.3 kcal/mol

23 pK_a (H_2O) = 1.42, MEP = 69.0 kcal/mol

24 MEP = 75.2 kcal/mol

25 MEP = 78.4 kcal/mol

Figure 5. Estimated Brønsted acidity of phosphoric acids[21,22]

The aggregation of phosphoric acid catalysts sometimes reduces their catalytic activities. For example, the dimeric structures **26** of conventional chiral phosphoric acid catalysts **1** are relatively stable, and would decrease the catalytic activity (Figure 6a).[23] Moreover, X-ray analysis of Terada/Momiyama's chiral bis(phosphoric acid) catalysts **16** demonstrated the existence of polymeric structures **27** through hydrogen bonding,[18a] and thus the catalytic activity might be decreased (Figure 6b). In sharp contrast, the author developed chiral bis(phosphoric acid) catalysts **28**, which have two pairs of P-OH/P=O moieties in the cyclic structure of the double intramolecular hydrogen bonding network (Figure 6c). Accordingly, two active P-OH moieties are left outside after 'intramolecular dimerization', and the catalysts might act as highly active monomeric catalysts. On the other hand, chiral pyrophosphoric acid catalysts **29** have two pairs of P-OH/P=O moieties (Figure 6d). However, the author expected that they would hardly aggregate to polymeric structures, since these P-OH/P=O moieties would be so close to the sterically hindered substituents at the 3,3'-positions of the binaphthyl skeleton. Therefore, catalysts **29** might also act as highly active monomeric catalysts.

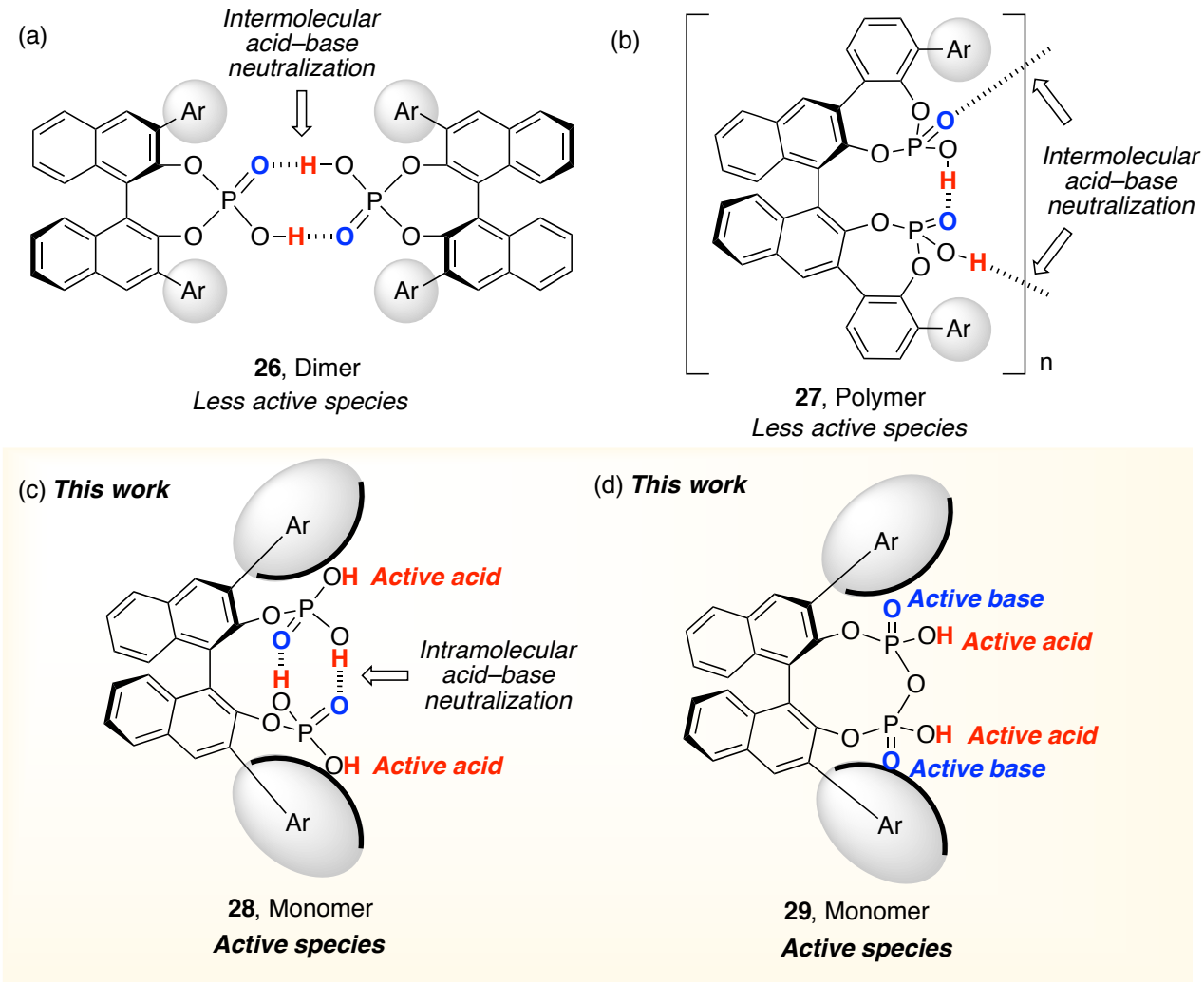


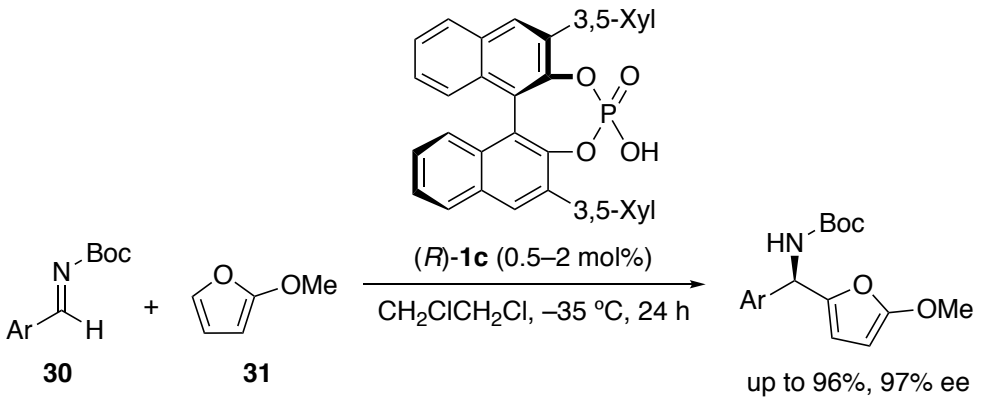
Figure 6. Effect of dimerization and/or oligomerization of chiral phosphoric acid catalysts

1-3. Enantioselective Aza-Friedel–Crafts Reaction of Furan with α-Ketimino Esters Catalyzed by Chiral Bis(phosphoric Acid) Catalysts

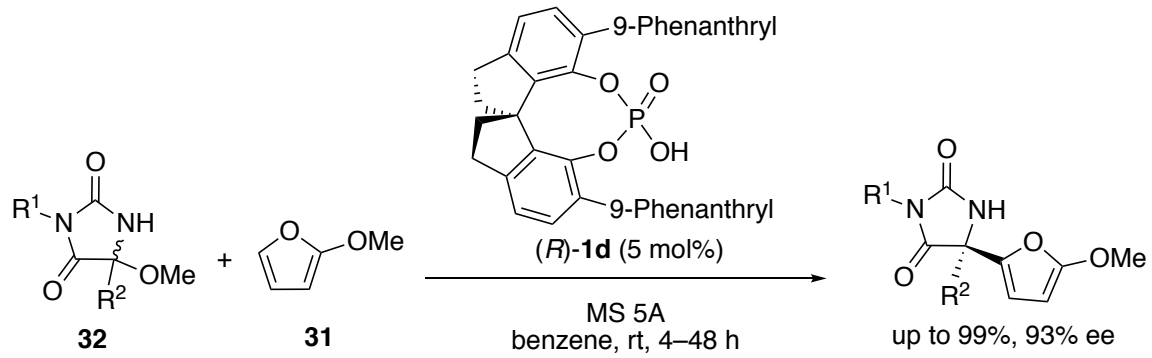
The author focused on the enantioselective aza-Friedel–Crafts reaction[24] with the use of novel chiral C_2-symmetric bis(phosphoric acid) catalysts **28**. In fact, the enantioselective aza-Friedel–Crafts reaction of hetero-aromatic compounds with imines provides highly versatile optically active heterocycles, which would be key intermediates of natural products and pharmaceuticals. [28,29] In particular, the corresponding products of the aza-Friedel–Crafts reaction of 2-methoxyfuran **31** might be transformed such a variety of compounds.[30] Nevertheless, there are still few examples of the enantioselective aza-Friedel Crafts reaction of **31**.[26] Terada reported, for the first time, the enantioselective aza-Friedel−Crafts reaction of **31** with simple and reactive *N*- Boc aldimine **30**

with the use of (*R*)-**1c** (Scheme 5).[25] Later, Terada reported the enantioselective aza-Friedel–Crafts reaction of **31** with reactive (thio)hydantoin-derived aliphatic cyclic ketimines, which can be

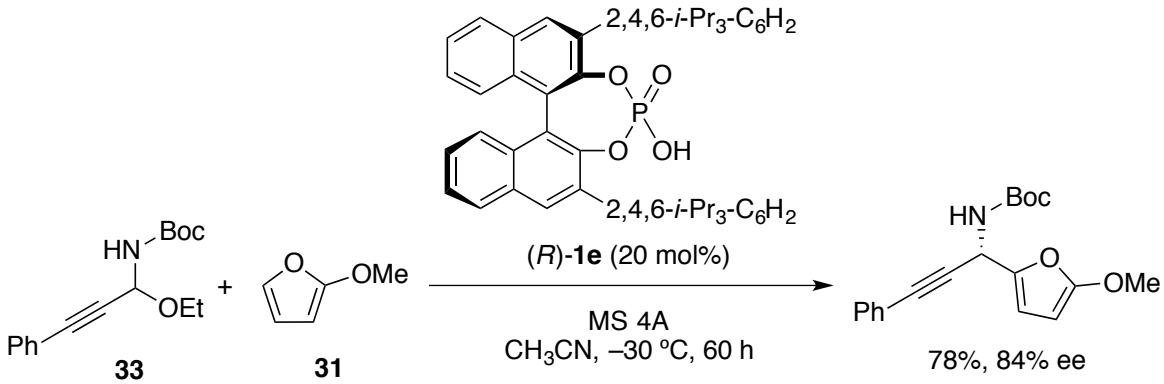
Scheme 5. Enantioselective aza-Friedel–Crafts reaction by Terada[25]



Scheme 6. Enantioselective aza-Friedel–Crafts reaction by Terada[26]



Scheme 7. Enantioselective aza-Friedel–Crafts reaction by Shao[27]

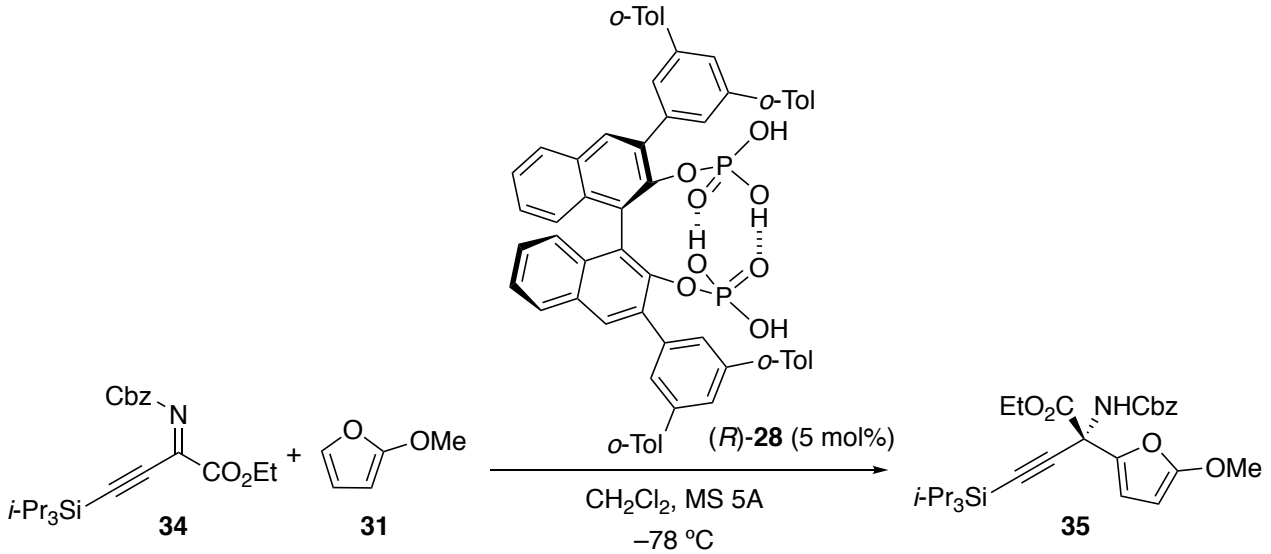


generated *in situ* from hemiaminal ethers **32**, with the use of (*R*)-**1d** (Scheme 6).[26] Very recently, Shao also reported the enantioselective aza-Friedel–Crafts reaction of **31** with highly reactive *C*-alkynyl imines, which would be generated *in situ* from *C*-alkynyl *N*-Boc-protected *N*,*O*-acetal **33**, with the use of as much as 20 mol% of (*R*)-**1e** (Scheme 7).[27] These three examples used reactive substrates, which might be suitable even for conventional chiral phosphoric acid catalysts with moderate Brønsted acidity. In contrast to these previous studies, the author decided to use less reactive acyclic ketimines, particularly such as β,γ-alkynyl-α-imino ester **34**[31], with the new C_2-symmetric catalysts (*R*)-**28**.

Chapter 2 describes a highly enantioselective aza-Friedel–Crafts reaction of 2-methoxyfuran **31** with β,γ-alkynyl-α-imino ester **34**, with the novel chiral C_2-symmetric BINOL-derived bis(phosphoric acid) catalyst (*R*)-**28**, which has two OP(=O)$(OH)_2$ moieties at the 2,2'-positions (Scheme 8).[32]

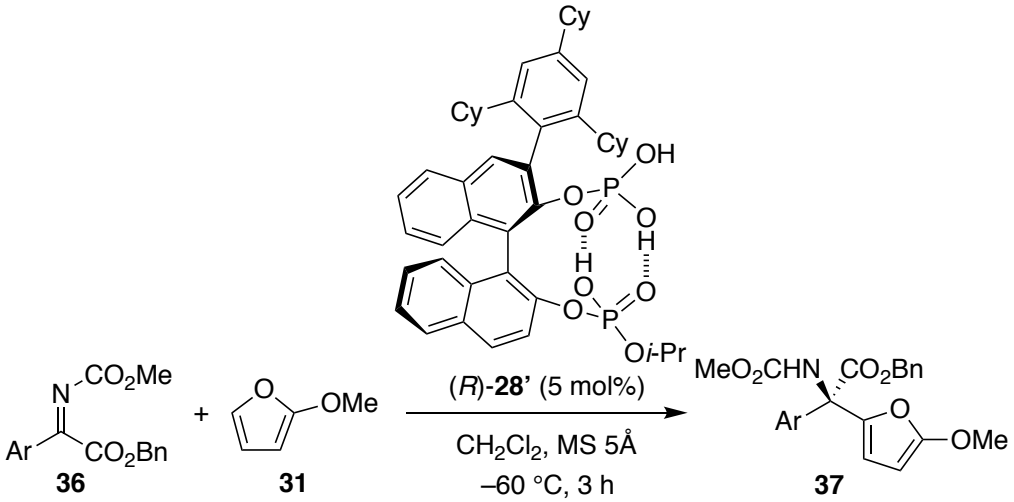
Through the reaction, highly functionalized optically active α-amino acid derivative **35**, which has acetylene, ester, carbamate, and furyl groups at a chiral quaternary carbon center, was successfully obtained in high yield with high enantioselectivities. Overall, C_2-symmetric catalyst (*R*)-**28** showed higher catalytic activity than conventional chiral phosphoric acids **1**, due to the stronger Brønsted acidity as well as the monomeric structure of (*R*)-**28**.

Scheme 8. Enantioselective aza-Friedel–Crafts reaction of 2-methoxyfuran **31** with imines **34** catalyzed by chiral C_2-symmetric bis(phosphoric acid) (*R*)-**28**[32]

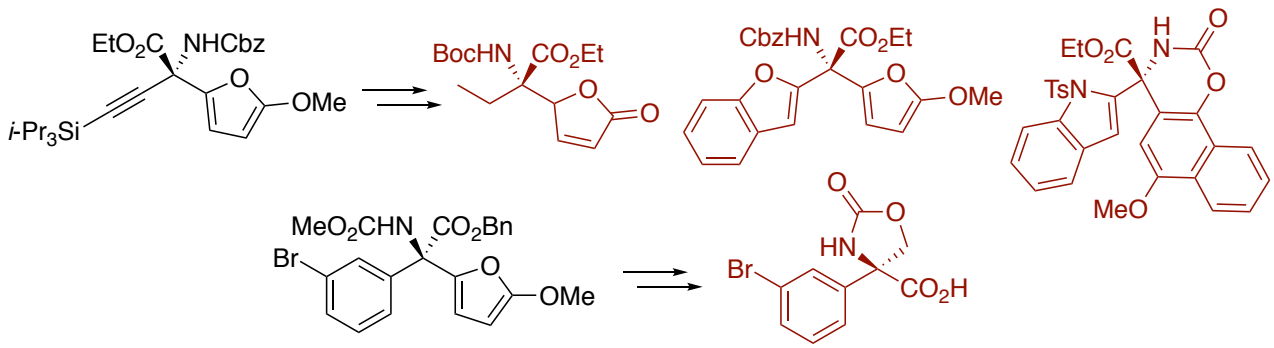


Based on full understanding the properties of C_2-symmetric catalyst (*R*)-**28**, we further disclosed that novel C_1-symmetric catalyst (*R*)-**28'** can achieve wide substrate scope of imines in Chapter 2 (Scheme 9).[32] C_1-symmetric catalyst (*R*)-**28'** has an extremely bulky 2,4,6-$Cy_3C_6H_2$ moiety at the 3-position, and thus one active H^+-site should be essential in the structure to avoid the unexpected reaction pathways. Ultimately, the novel C_1-symmetric catalyst (*R*)-**28'** could be used for the reaction of aromatic imines **36**, and the desired corresponding products **37** were successfully obtained in high yields with high enantioselectivities.

Scheme 9. Enantioselective aza-Friedel–Crafts reaction of 2-methoxyfuran **31** with aromatic imines **36** catalyzed by chiral C_1-symmetric bis(phosphoric acid) (*R*)-**28'**[32]



Scheme 10. Transformation to synthetically difficult optically active *N*- and *O*-heterocycles and α-aryl-substituted serine-derivative.[32]



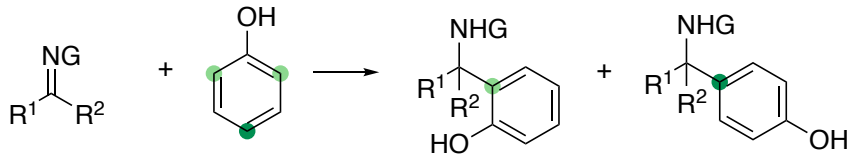
Both the reactions in Scheme 8 and 9 could be conducted on a practical >1 gram-scale. The functional groups of the obtained product **35** could be selectively transformed, and the

corresponding versatile and synthetically difficult optically active *N*- and *O*-heterocycles were obtained (Scheme 10).[32] Moreover, from the obtained product **37**, desired optically active α-aryl-substituted serine-derivative could be successfully transformed.

1-4 Chiral Pyrophosphoric Acid-Catalyzed Site- and Enantioselective Aza-Friedel–Crafts Reaction of Phenols with Aldimines

There have been no reports on asymmetric catalyses with the use of chiral pyrophosphoric acids. In this research, the author focused on a site- and enantioselective aza-Friedel–Crafts reaction of phenol **39** with aldimines **38** (Scheme 11). In general, simple phenols induce the *ortho*/*para*-orientation, and the corresponding *ortho*-adducts **40** and *para*-adducts **41** would be generated unselectively.[33] Therefore, the catalysts should control both the site-selectivity of **39** and the enantioface-selectivity of **38**.

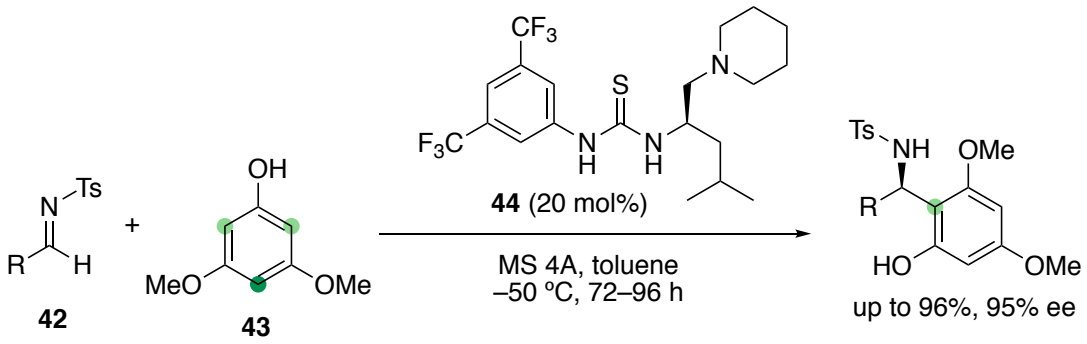
Scheme 11. Site-selectivity of phenols in aza-Friedel–Crafts reaction



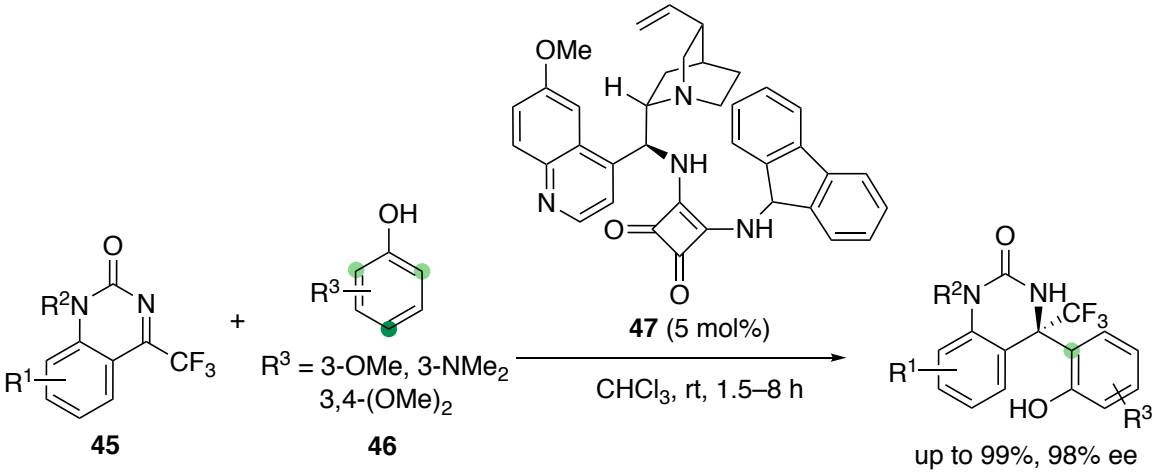
38 **39** **40** *ortho*-adduct **41** *para*-adduct

Several examples of the catalytic enantioselective aza-Friedel–Crafts reactions of naphthols and sesamols with imines have been reported.[34] The reaction sites of highly reactive naphthols and sesamols are completely dependent on these substrates, and usually one reaction site would be provided from each substrate.[34] In contrast, there have been only three examples of the catalytic enantioselective aza-Friedel–Crafts reaction of simple phenols with imines, probably due to the difficulty of site-selectivity (i.e., *ortho*- and *para*-selectivity) of simple phenols.[27,34j,35] Qu reported the enantioselective aza-Friedel–Crafts reaction of 3,5-dimethoxy phenol **43** with *N*-tosyl-aldimines **42** catalyzed by acid–base bifunctional thiourea catalyst **44** (Scheme 12).[35] Moreover, Wang and Xie reported the enantioselective aza-Friedel–Crafts reaction of phenols with electron-donating groups **46** with α-trifluoromethyl ketimines **45** catalyzed by cinchona alkaloid catalyst **47** (Scheme 13).[34j] Very recently, Shao reported the *ortho*- and enantioselective aza-Friedel–Crafts reaction of non-substituted phenol **39** with *N*-Boc-β,γ-alkynyl aldimines **49**, which would be

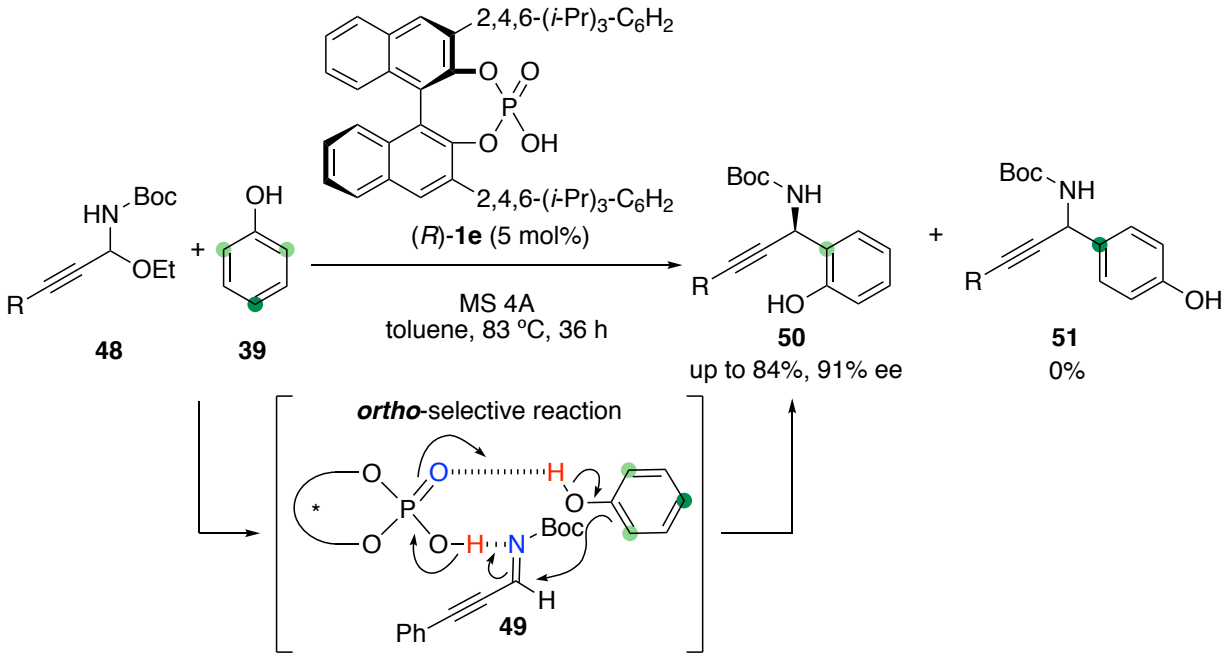
Scheme 12. Enantioselective aza-Friedel–Crafts reaction of phenols by Qu[35]



Scheme 13. Enantioselective aza-Friedel–Crafts reaction of phenols by Hui[34j]



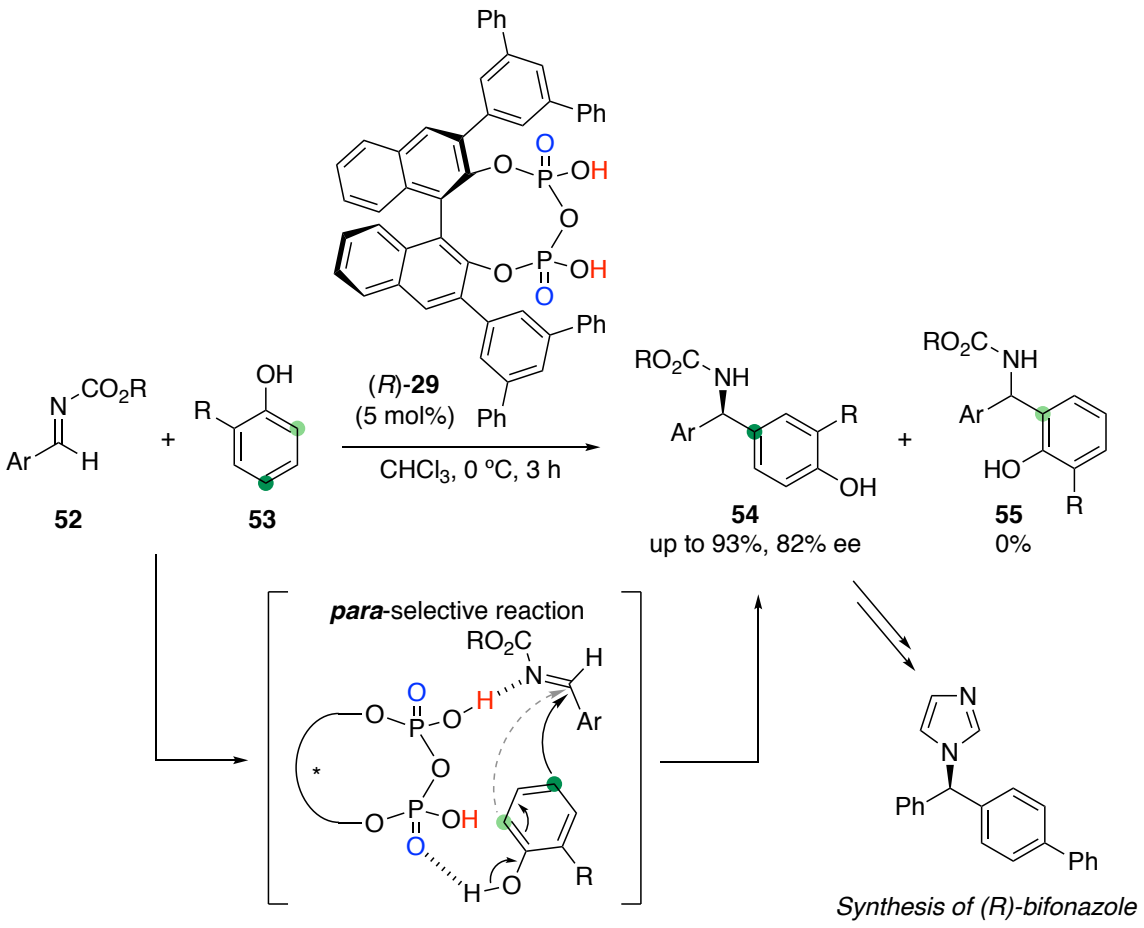
Scheme 14. *Ortho*- and enantioselective aza-Friedel–Crafts reaction of phenols by Shao[27]



generated *in situ* from *N,O*-acetals **48**, catalyzed by chiral phosphoric acid catalyst (*R*)-**1e** (Scheme 14).[27] In this reaction, the imine **49** would be activated by the P-OH moiety of the catalyst (*R*)-**1e**, whereas phenol would be activated by the P=O moiety of the catalyst (*R*)-**1e**. Overall, these three reports were limited to *ortho*-selective reactions, and a *para*-selective reaction has not yet been developed.

Chapter 3 describes the first catalytic site- and enantioselective aza-Friedel–Crafts reaction of phenols **53** with aldimines **52** with the use of novel chiral BINOL-derived pyrophosphoric acid catalyst (*R*)-**29** (Scheme 15).[36] Through this reaction, simple phenols **53** could react at an anomalous *para*-position exclusively, and the corresponding products **54** could be obtained with moderate to good enantioselectivities. Aldimines **52** and phenols **53** might be activated independently by two acid–base moieties of (*R*)-**29**, and thus the *para*-position of **53** would be close

Scheme 15. *Para*- and enantioselective aza-Friedel–Crafts reaction of phenols **54** with imines **53** catalyzed by chiral pyrophosphoric acid (*R*)-**29**[36]



to the imino-carbon of **52** due to geometric considerations. To demonstrate the synthetic utility of this catalysis, the transformation of a product into the key intermediate for (*R*)-bifonazole was demonstrated on an enlarged scale.

1-5. Summary

In summary, the author focused in this rescarch on phosphoric monoester units, which might be used in the design of a new type of novel chiral BINOL-derived phosphoric acid catalysts. First, the author developed novel chiral C_2-symmetric and C_1-symmetric bis(phosphoric acid) catalysts **28** and **28'**, which have a double intramolecular hydrogen bonding network. Since the two pairs of P-OH/P=O moieties in the catalyst would be used in the cyclic structure of the double intramolecular hydrogen bonding network, the catalyst would act as a stronger Brønsted acid catalyst due to the two remaining P-OH moieties. Indeed, the author successfully developed the enantioselective aza-Friedel–Crafts reaction of 2-methoxyfuran with α-ketimino esters with the use of **28** or **28'**. Second, the author developed novel chiral pyrophosphoric acid catalysts **29**, which were prepared through the dehydrative condensation of chiral bis(phosphoric acid)s. Remarkably, two pairs of free P-OH/P=O moieties are left in the catalyst, and it would act as a unique acid–base bifunctional catalyst. Indeed, the author successfully developed the catalytic site- and enantioselective aza-Friedel–Crafts reaction of phenols with aldimines with the use of **29**. Overall, the author developed a new methodology for molecular transformation through highly efficient catalytic systems using **28**, **28'** and **29**, which may have greater catalytic activeties than conventional chiral phosphoric acid catalysts. The catalytic systems described herein might be promising for the further development of a new strategy that uses a highly practical family of chiral pyrophosphoric acid catalysts, due to the much higher catalytic activities of the present catalysts.

1-6. References

1. (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Eds. Springer: Berlin, Germany, **1999**; Vol. 1. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Eds. Springer: Berlin, Germany, **1999**; Vol. 2. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Eds. Springer: Berlin, Germany, **1999**; Vol. 3. (d) *New Frontiers in Asymmetric Catalysis*; Mikami, K.; Lautens, M.; Eds.; Wiley-VCH: Weinheim, Germany, **2007**. (e) *Multicatalyst System in Asymmetric Catalysis*; Zhou, J., Ed.; Wiley-VCH: Weinheim, Germany, **2014**.
2. (a) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Macmillan, D.; Berkessel, A.; Gröger, H.; Wiley-VCH: Weinheim, Germany, **2005**. (b) *Asymmetric Organocatalysis: 291 (Topics in Current Chemistry)*; List, B.; Ed. Springer: Berlin, Germany, **2009**. (c) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications, 3 Volume Set*; Dalko, P. I.; Wiley-VCH: Weinheim, Germany, **2013**. (d) *Handbook of Reagents for Organic Synthesis: Reagents for Organocatalysis*; Rovis, T.; Wiley-VCH: Weinheim, Germany, **2016**.
3. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
4. Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
5. Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (d) Terada, M. *Synthesis* **2010**, *12*, 1929. (e) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem. Eur. J.* **2010**, *16*, 9350. (f) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (g) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.
6. Selected papers for p*K*a values of chiral phosphoric acids. (a) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J.-M.; Berkeddel, A.; O'Donoghue, A. C. *Chem. Eur. J.* **2011**, *17*, 8524. (b) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569. (c) Chen, Y.; Xue, X.-S.; Jin, J.-L.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2013**, *78*, 7076. (d) Yang, C.; Xue, X.-S.; Li, X.; Chen, J.-P. *J. Org. Chem.* **2014**, *79*, 4340.
7. Dawson, R. M. C. *Data for Biochemical Research*, Oxford, Clarendon Press, **1959**.
8. (a)*Main Group Metals in Organic Synthesis;* Yamamoto, H.; Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, **2004**. (b) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H.; Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, **2008**.
9. For reviews on classification of the combined acid system, see: (a) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Chem. Rec.* **2002**, *2*, 177. (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.*

2005, *44*, 1924.

10. For an excellent review on TADDOLs, see: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed*. **2001**, *40*, 92.
11. (a)Huang Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5846.
12. McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094.
13. Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.
14. Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175.
15. (a) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (b) Hashimoto, T.; Kimura, H.; Nakatsu, H.; Maruoka, K. *J. Org. Chem.* **2011**, *76*, 6030.
16. (a) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (b) Hatano, M.; Hattori, Y.; Furuya, Y.; Ishihara, K. *Org. Lett.* **2009**, *11*, 2321. (c) Hatano, M.; Sugiura, Y.; Ishihara, K. *Tetrahedron: Asymmetry* **2010**, *21*, 1311. (d) Hatano, M.; Sugiura, Y.; Akakura, M.; Ishihara, K. *Synlett* **2011**, *9*, 1247. (e) Hatano, M.; Ozaki, T.; Sugiura, Y.; Ishihara, K. *Chem. Commun*. **2012**, *48*, 4986. (f) Hatano, M.; Ozaki, T.; Nishikawa, K.; Ishihara, K. *J. Org. Chem.* **2013**, *78*, 10405. (g) Hatano, M.; Ishihara, K. *Asian J. Org. Chem.* **2014**, *3*, 352.
17. (a) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (b) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946. (c) Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 4050. (d) Guo, C.; Song, J.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 2676. (e) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504.
18. (a) Momiyama, N.; Konno, T.; Furiya, Y.; Iwamoto, T.; Terada, M. *J. Am. Chem. Soc.* **2011**, *133*, 19294. (b) Momiyama, N.; Narumi, T.; Terada, M. *Chem. Commun.* **2015**, *51*, 16976. (c) Momiyama, N.; Funayama, K.; Noda, H.; Yamanaka, M.; Akasaka, N.; Ishida, S.; Iwamoto, T.; Terada, M. *ACS Catal.* **2016**, *6*, 949.
19. Liu, S.; Pedersen, L. G. *J. Phys. Chem. A* **2009**, *113*, 3648.
20. Shokri, A.; Abedin, A.; Fattahi, A.; Kass, A. R. *J. Am. Chem. Soc.* **2012**, *134*, 10646.
21. Shamir, D.; Zilbermann, I.; Maimon, E.; Shames, A. I.; Cohen, H.; Meyerstein, D. *Inorg. Chim. Acta* **2010**, *363*, 2819.
22. Krašovec, F.; Jan, J. *Croat. Chem. Acta* **1963**, *35*, 183.
23. Selected papers on the aggregation of chiral phosphoric acid catalysts. (a) Li, N.; Chen, X.-H.;

Zhou, S.-M; Luo, S.-W.; Song, J.; Ren, L.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2010**, *49*, 6378. (b) Monaco, M. R.; Pupo, G.; List, B. *Synlett* **2016**, *27*, 1027.

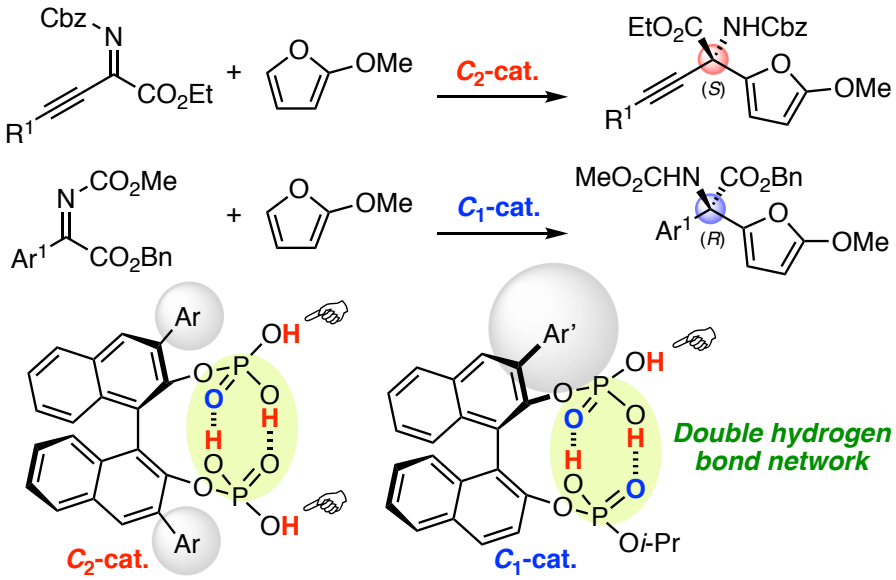
24. For reviews on enantioselective Friedel–Crafts reactions, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550. (b) Jørgensen, K. A. *Synthesis* **2003**, *2003*, 1117. (c) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, *2005*, 1199. (d) Poulsen, T. B.; Jøgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903.
25. Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.
26. Terada reported pioneering work on the enantioselective aza-Friedel–Crafts reaction of 2-methoxyfuran with aldimines and ketimines by chiral phosphoric acid catalysts. See: Kondoh, A.; Ota, Y.; Komuro, T.; Egawa, F.; Kanomata, K.; Terada, M. *Chem. Sci.* **2016**, *7*, 1057.
27. Wang, Y.; Jiang, L.; Li, L.; Dai, J.; Xiong, D.; Shao, Z. *Angew. Chem. Int. Ed.* **2016,** *55*, 15142.
28. Selected papers on bioactive compounds containing nitrogen atoms. (a) Nugent, T. C. *Chiral Amine Synthesis; Methods, Developments and Applications*, Wiley-VCH, Weinheim, **2010**. (b) Olah, G. A. *Friedel–Crafts Chemistry*, Wiley, New York, **1973**. (c) Badini, M.; Umani-Ronchi, A. *Catalytic Asymmetric Friedel–Crafts Alkylations*, Wiley-VCH, Weinheim **2009**. (d) Wright, J. L.; Gregory, T. F.; Kesten, S. P.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. T.; Wise, L. D.; Espitia, S. A.; Konkoy, C. S.; Whittemore, E. R.; Woodward, R. M. *J. Med. Chem*. **2000**, *43*, 3408. (e) Yu, P. H.; Davis, B.; Boulton, A. A. *J. Med. Chem.* **1992**, *35*, 3705.
29. (a) Sheng, Y.-F.; Zhang, A. J.; Zhang, X.-J, You, S.-L. Chin. *J. Org. Chem.* **2008**, *28*, 605. (b) Cai, Q.; Zhen, M.; You, S.-L. *Chem. Soc. Rev.* **2009**, *38*, 2190. (c) Eichholzer, A.; Bandimi, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608. (d) Nachtsheim, B. J.; Rueping, M. *Beilstein*. *J. Org. Chem.* **2010**, *6*, 6. (e) R. M. de Figueiredo.; Camoagne, J. M.; Terrason, V. *Eur. J. Org. Chem.* **2010**, 2635. (f) Zen, M.; You, S.-L. *Synlett* **2010**, *2010*, 1289.
30. Selected papers for a transformation of 2-methoxyfuran moiety. (a) Zhou, W. S.; Lu, Z. H.; Xu, Y. M.; Liao, L. Y.; Wang, Z. M. *Tetrahedron* **1999**, *55*, 11959. (b) Demir, A. S. *Pure Appl. Chem.* **1997**, *69*, 105. (c) Koulocheri, S. D.; Magiatis, P.; Haroutounian, S. A. *J. Org. Chem.* **2001**, *66*, 7915. (d) Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371.
31. (a) Kang, Q.; Zhao, Z.-A.;You, S.-L. *Org. Lett.* **2008**, *10*, 2031. (b) Hatano, M.; Yamashita, K.; Mizuno, M.; Ito, O.; Ishihara, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 2707.
32. Hatano, M.; Okamoto, H.; Kawakami, T.; Toh, K.; Nakatsuji, H.; Sakakura, A.; Ishihara, K. *Chem. Sci.* **2018**, *9*, 6361.
33. Gong, Y.; Kimoto, H.; Kato, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2637.
34. Selected papers for the aza-Friedel–Crafts reaction of naphthols and sesamol. (a) Niu, L.-F.;

Xin, Y.-C.; Wang, R.-L.; Jiang, F.; Xu, P.-F.; Hui, X.-P. *Synlett* **2010**, *5*, 765. (b) Chauhan, P.; Chimni, S. S. *Eur. J. Org. Chem.* **2011**, 1636. (c) Liu, G.; Zhang, S.; Li, H.; Zhang, T.; Wang, W. *Org. Lett.* **2011**, *13*, 828. (d) Chauhan, P.; Chimni, S. S. *Tetrahedron Lett.* **2013**, *54*, 4613. (e) Bai, S.; Liao, Y.; Lin, L.; Luo, W.; Liu, X.; Feng, X. *J. Org. Chem.* **2014**, *79*, 10662. (f) Takizawa, S.; Hirata, S.; Murai, K.; Fujiola, H.; Sasaki, H. *Org. Biomol. Chem.* **2014**, *12*, 5827. (g) Kato, M.; Hirao, S.; Nakano, K.; Sato, M.; Yamanaka, M.; Sohtome, Y.; Nagasawa, K. *Chem. Eur. J*. **2015**, *21*, 18606. (h) Montesinos-Magraner, M.; Cantón, R.; Vila, C.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *RSC Adv.* **2015**, *5*, 60101. (i) Kumari, P.; Barik, S.; Khan, N. H.; Ganguly, B.; Kureshy, R. I.; Abdi, S. H.R.; Bajaj, H. C. *RCS Adv.* **2015**, *5*, 69493. (j) Zhou, D.; Huang, Z.; Yu, X.; Wang, Y.; Li, J.; Wang, W. *Org. Lett.* **2015**, *17*, 5554. (k) Kumari, P.; Jakhar, A.; Khan, N. H.; Tak, R.; Kureshy, R. I.; Abdi, S. H. R.; Bajaj, H. C. *Catal. Commun.* **2015**, *69*, 138. (l) Montesinos-Magraner, M.; Vila, C.; Cantón, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 6320. (m) Montesios-Magranera, M.; Vila, C.; Blay, G.; Pedro, J. R. *Synthesis* **2016**, *48*, 2151.

35. (a) Li, G.-X.; Qu, J. *Chem. Commun.* **2012**, *48*, 5518.
36. Okamoto, H.; Toh, K.; Mochizuki, T.; Nakatsuji, H.; Sakakura, A.; Hatano, M.; Ishihara, K. *Synthesis* **2018**, accepted.

Chapter 2

Enantioselective Aza-Friedel–Crafts Reaction of Furan with α-Ketimino Esters Induced by a Conjugated Double Hydrogen Bond Network of Chiral Bis(phosphoric Acid) Catalysts



Abstract: Chiral C_2- and C_1-symmetric BINOL-derived bis(phosphoric acid) catalysts, which have OP(=O)(OH)$_2$/OP(=O)(OH)(OR) moieties at the 2,2'-positions, were developed and used for the enantioselective aza-Friedel–Crafts reaction of 2-methoxyfuran with α-ketimino esters for the first time. The intramolecular conjugated double hydrogen bond network is a key to increasing the Brønsted acidity and preventing deactivation of the catalysts. Highly functionalized α-amino acid derivatives with a chiral quaternary carbon center could be transformed into versatile optically active *N*- and *O*-heterocycles and an α-aryl-substituted serine.

2-1 Introduction

The hydrogen bond network of chiral multiprotic acid catalysts plays an important role in activating Brønsted acidity, controlling conformational flexibility, and producing high enantioselectivity.[1,2] According to the general classification of combined acid catalysts described by Yamamoto,[3] some chiral Brønsted acid catalysts $R^*(XH)_2$ with a hydrogen bond network could be considered part of a Brønsted acid-assisted Brønsted acid (BBA) catalyst system. In such a BBA system, one hydrogen atom of an XH group might participate in an intramolecular hydrogen bond with the other XH group, which might be activated and thus used for activation of the substrate. Since 2003, when Rawal reported the first example of an intramolecular single hydrogen bonding network in chiral TADDOLs (α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanols)[4a,c] for the enantioselective hetero-Diels–Alder reaction, and after Schaus developed chiral 3,3'-diaryl-BINOLs (1,1'-bi-2-naphthol)[4b] for the enantioselective Morita–Baylis–Hillman reaction, great effort has been devoted to this research area (Fig. 1a). Chiral 1,1'-biaryl-2,2'-dimethanol (Yamamoto/Rawal),[4d] chiral glycolic acid (Yamamoto),[5] chiral 2-bis(triflyl)methyl-2'-hydroxy-1,1'-binaphthyl (Ishihara/Yamamoto),[6] chiral binaphthyl di-carboxylic acids (Maruoka),[7] 3,3-linked-bis(BINOL)-derived bis(phosphoric acid)s

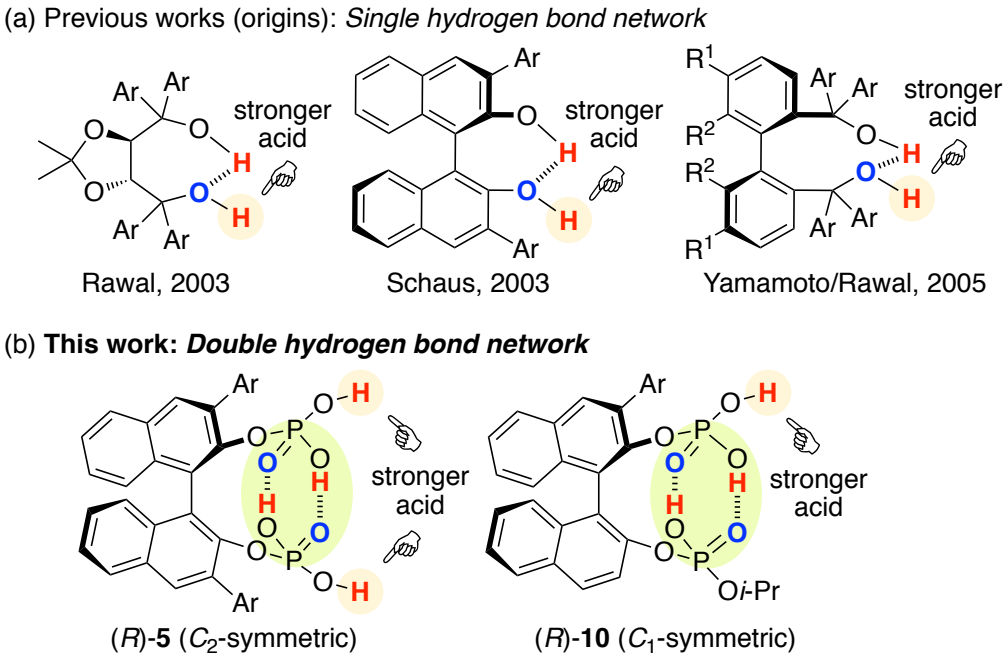


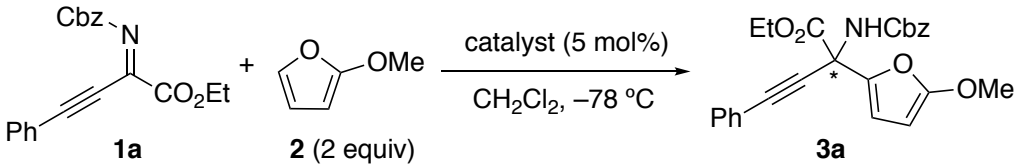
Fig. 1. Design of chiral BINOL-derived bis(phosphoric acid) catalysts.

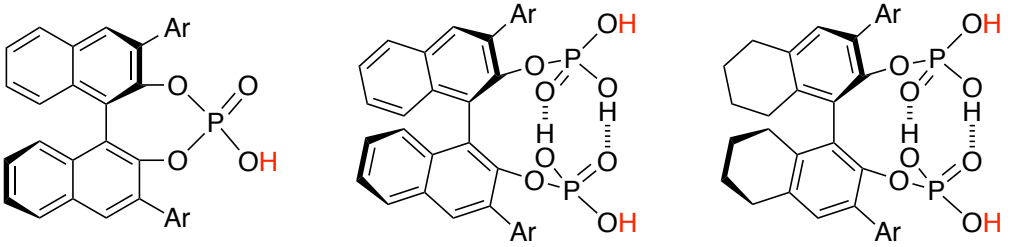
(Gong),[8] chiral binaphthyl disulfonic acids (BINSA) (our group),[9] and chiral 3,3'-di(2-hydroxy-3-arylphenyl)-BINOL-derived bis(phosphoric acid)s and chiral carboxylic acid–phosphoric acid combined catalysts (Momiyama/Terada)[10,11] have been developed for a variety of asymmetric catalyses. These outstanding chiral BBA catalysts might have an intramolecular single hydrogen bond network with the use of bis(monoprotic acid)s $R^*(XH)_2$. In sharp contrast, we envisioned that an intramolecular double hydrogen bond network may represent a new strategy for the design of chiral Brønsted acid catalysts. However, a simple and closed double hydrogen bond network, as seen in a dimeric structure of two molecules of carboxylic acids, would lose both the Brønsted acid- and base-functions upon neutralization. Therefore, here we developed chiral C_2-symmetric BINOL-derived bis(phosphoric acid) catalysts (*R*)-**5** as bis(diprotic acid)s $R^*(XH_2)_2$, which have two $OP(=O)(OH)_2$ moieties at the 2,2'-positions of the chiral binaphthyl backbone (Fig. 1b). Based on the essence of (*R*)-**5**, chiral C_1-symmetric catalysts (*R*)-**10**, which have $OP(=O)(OH)_2$/OP(=O)(OH)(O*i*-Pr) moieties, were also developed. Remarkably, outside of the conjugated intramolecular double hydrogen bond network, the Brønsted acid moiety would still exist and work as an active center by the BBA methodology.

2-2 Experimental investigation with chiral C_2-symmetric catalysts

We initially examined the aza-Friedel–Crafts (FC) reaction of 2-methoxyfuran **2**[12,13] with β,γ-alkynyl-α-imino esters **1a**[14] through the use of achiral Brønsted acid catalysts (5 mol%) in dichloromethane at –78 °C (Table 1 and also see the Experimental Section 9). As a result, suitable Brønsted acidity would be required for the reaction to proceed smoothly; catalysts that were too weakly acidic gave poor catalytic activity (entries 1 and 2) and catalysts that were too strongly acidic gave undesired byproducts due to the instability of **1a** and particularly **2** under acidic conditions (entries 4–6). Fortunately, phosphoric acids could be used without the serious generation of byproducts due to their suitable Brønsted acidity for this reaction, although the yields of product **3a** were moderate (entries 7 and 8). Next, we examined conventional chiral phosphoric acid (*R*)-**4a** (entry 9), which would be less aggregatable than the less bulky achiral phosphoric acids in entries 7 and 8. As a result, although the pK_a of (*R*)-**4a** would be similar to those of the achiral phosphoric acids in entries 7 and 8, the catalytic activity was greatly improved (see the Experimental Section 9 for details). Particularly, when (*R*)-**4b** with electron-withdrawing

Table 1. Screening of Brønsted acid catalysts[a]



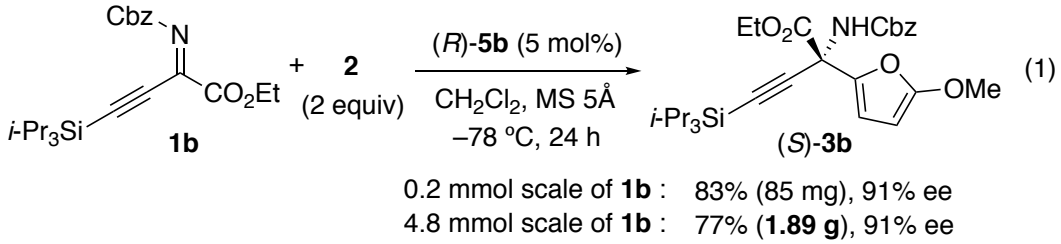


Entry	Catalyst	pK_a in H_2O[b]	pK_a in DMSO[b]	Reaction time (h)	Conversion (%) of **1a**	Yield (%) of **3a**	ee (%) of **3a**
1	CH_3CO_2H	4.76	12.3	24	0	0	–
2	CH_2BrCO_2H	2.86	–	24	13	13	–
3	CHF_2CO_2H	1.24	6.45	24	56	52	–
4	CCl_3CO_2H	0.65	2.5	24	>99	59	–
5	CF_3CO_2H	0.26	3.5	12	>99	53	–
6	*p*-$CH_3C_6H_4SO_3H$	–1.34	0.9	12	>99	34	–
7	$PhOP(=O)(OH)_2$	1.42	–	24	51	49	–
8	$(PhO)_2P(=O)OH$	0.26	3.7	24	60	60	–
9	(*R*)-**4a**	–	–	24	>99	87	26 (*S*)
10	(*R*)-**4b**	–	2.63	12	>99	73	40 (*S*)
11	(*R*)-**4c**	–	4.22	24	95	60	10 (*R*)
12	(*R*)-**5a**	–	–	5	>99	82	70 (*S*)
13	(*R*)-**5b**	–	–	8	>99	88	76 (*S*)
14	(*R*)-**5c**	–	–	24	>99	85	75 (*S*)

[a] The reaction was carried out with catalyst (5 mol%), **1a** (0.20 mmol, 1 equiv), and **2** (2 equiv) in dichloromethane (0.1 *M* based on **1a**) at –78 °C. Isolated yield of **3a** is shown. Cbz = CO_2CH_2Ph. [b] The pK_a value in the references. See the Experimental Section 9 for details.

CF_3 groups in its 3,3'-diaryl moieties was used, the reaction was accelerated, although the enantioselectivity was still low (40% ee) (entry 10). Moreover, well-acknowledged bulky (*R*)-**4c** was much less active than (*R*)-**4a** and (*R*)-**4b** (entry 11). In contrast, chiral C_2-symmetric bis(phosphoric acid) (*R*)-**5a**[15] was much more effective than (*R*)-**4a**–**c**, and

3a was obtained in 82% yield with 70% ee within 5 h (entry 12).[16] Slightly modified catalyst (*R*)-**5b** derived from (*R*)-3,3'-(3,5-(*o*-Tol)$_2$C$_6$H$_3$)$_2$-BINOL improved the enantioselectivity (76% ee) of **3a** (entry 13). (*R*)-**5c** with a 5,5',6,6',7,7',8,8'-H$_8$-binaphthyl backbone showed lower catalytic activity than (*R*)-**5a** and (*R*)-**5b**, and a prolonged reaction time (24 h) was needed (entry 14). Moreover, we optimized β,γ-alkynyl-α-imino esters **1** with the use of (*R*)-**5b** (see the Experimental Section 13 for details).[17] To avoid the effect of adventitious water, which might react with **1** and **2** to give undesired products, powdered MS 5Å was used as a drying agent. As a result, when we used **1b** with bulky *i*-Pr$_3$Si protection for the alkyne moiety, (*S*)-**3b** was obtained in 83% yield with 91% ee (Eq. 1). Remarkably, we could perform a 1.89 g-scale synthesis of (*S*)-**3b** (77% yield with 91% ee), and 99% of (*R*)-**5b** could be recovered.



We now turn our attention to mechanistic aspects. It is important to identify the intramolecular double hydrogen bond network in the catalysts. Fortunately, (*R*)-**5c**•(pyridine)$_2$ was crystallized, and the results of an X-ray analysis are shown in

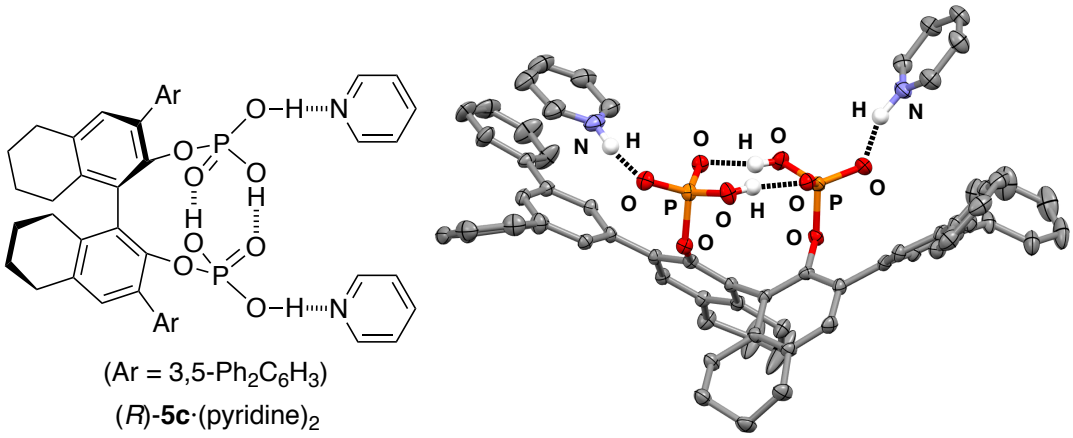
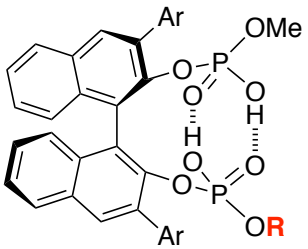


Fig. 2. X-ray analysis of (*R*)-**5c**•(pyridine)$_2$. Hydrogen atoms are partially omitted for clarity.

Fig. 2. As a result, two P(=O)(OH)$_2$ moieties at the 2,2'-positions of the H$_8$-binaphthyl backbone coordinate with each other, and the conjugated double hydrogen bond network is unambiguously formed at the center of the monomeric molecules. Pyridines are coordinated BBA-activated protons, which would be considered to activate the substrate in a similar way. In this regard, the role of the two outside protons was next examined with the use of monomethyl-protected (*R*)-**6a** and dimethyl-protected (*R*)-**6b** (Scheme 1). As a result, (*R*)-**6a** showed almost the same catalytic activity (81% yield and 91% ee of **3b**) as (*R*)-**5b**, whereas (*R*)-**6b** gave a poor result (22% yield and 34% ee of **3b**) in the reaction of **2** with **1b**. This result strongly suggests that two activated protons in (*R*)-**5b** should be independent of each other, although the absence of both protons results in a loss of catalytic activity. In contrast, the protons in the tight structure of a double hydrogen bond network might not be directly involved in promoting the reaction as possible Brønsted acids.

Scheme 1. Role of active H$^+$-centers in chiral C_2-symmetric catalysts (*R*)-**5b**.



(*R*)-**6a** (R = H, Ar = 3,5-(*o*-Tol)$_2$C$_6$H$_3$)
(*R*)-**6b** (R = Me, Ar = 3,5-(*o*-Tol)$_2$C$_6$H$_3$)

1b + **2** $\xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{MS 5Å}\\ -78\ ^\circ\text{C},\ 24\ \text{h}]{(R)\text{-}\mathbf{6a}\ \text{or}\ (R)\text{-}\mathbf{6b}\ (5\ \text{mol\%})}$ (*S*)-**3b**

(*R*)-**6a** (R = H)	81%, 91% ee
(*R*)-**6b** (R = Me)	22%, 34% ee
cf. (*R*)-**5b**	83%, 91% ee

Moreover, a non-linear effect was examined in the reaction of **2** with **1a** with the use of (*R*)-**5b** or (*R*)-**4a** (Fig. 3 and also see the Experimental Section 15). As expected from the X-ray structure of monomeric (*R*)-**5c**•(pyridine)$_2$, a linear relationship was observed for (*R*)-**5b**, and the yields were almost constant (71–75%) (Fig. 3a). In contrast, a positive non-linear effect was observed for (*R*)-**4a** (Fig. 3b).[18] This non-linear relationship strongly suggests that inactive dimeric species[19] might be involved under the reaction conditions for (*R*)-**4a** unlike (*R*)-**5b**. Indeed, although both (*R*)-**5b** and (*R*)-**4a** have almost the same sterically hindered 3,3'-diaryl moieties, the strongly Brønsted basic P=O moiety is still free in (*R*)-**4a**. It is quite unlike the situation in (*R*)-**5b**, which has a core hydrogen bond network through the "intramolecular dimerization" of two P(=O)(OH)$_2$ moieties. Thus, the much better catalytic activity of (*R*)-**5b** compared to (*R*)-**4a** might be

attributed to not only the stronger acidity of (*R*)-**5b** due to a BBA system but also the monomeric active species of (*R*)-**5b** due to the closed P=O moieties.[20]

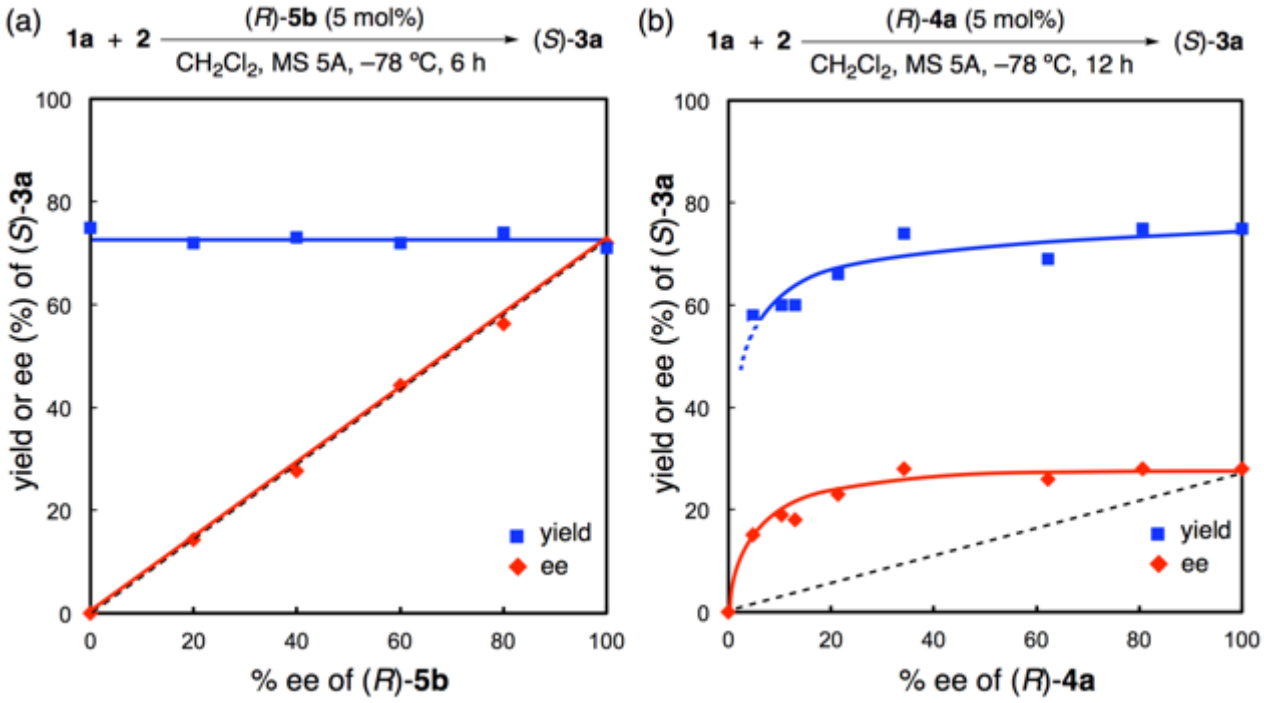
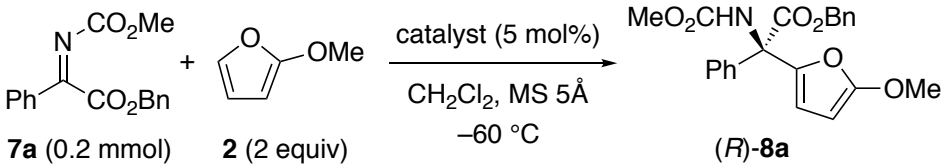


Fig. 3. Non-linear effects of (*R*)-**5b** and (*R*)-**4a**.

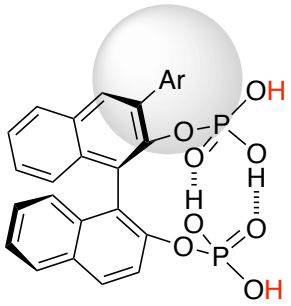
2-3 Experimental investigation with chiral C_1-symmetric catalysts

With the above understanding of the present catalyst system, we should expand the substrate scope of α-ketimino esters beyond the useful but specific substrates **1a** and **1b**. Due to their synthetic importance, we chose aryl α-ketimino esters, such as **7a** (Table 2). Unfortunately, however, (*R*)-**5b** was not effective for the reaction of less reactive **7a**, unlike more reactive **1a** and **1b**, and (*R*)-**8a** was barely obtained with 15% ee at slightly higher temperature (–60 °C) (entry 3). To improve the enantioselectivity, stereocontrol by more bulky substituents at the 3,3'-positions of the C_2-symmetric catalysts (*R*)-**5** should be needed. However, we could not introduce phosphoric acid moieties at the 2,2'-positions of the bulky 3,3'-Ar_2-BINOL-skeleton (e.g., Ar = 2,4,6-*i*-$Pr_3C_6H_2$). Instead, an extremely bulky C_1-symmetric catalyst (*R*)-**9c** with 2,4,6-$Cy_3C_6H_2$ at the 3-position could be readily prepared as well as (*R*)-**9a** (Ar = 3,5-$Ph_2C_6H_3$) and (*R*)-**9b** (Ar= 2,4,6-*i*-$Pr_3C_6H_2$). However, since two different active Brønsted acid centers would compete, the enantioselectivity was low (11–18% ee), as expected (entries 4–6). Based on the above consideration of C_2-symmetric catalysts (*R*)-**5**, we designed the

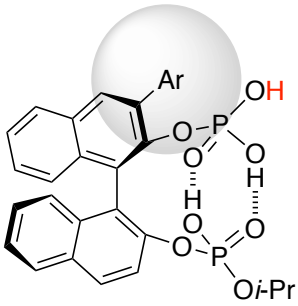
Table 2. Optimization of catalysts for the reaction of α-ketimino ester **7a**[a]



7a (0.2 mmol) **2** (2 equiv) (*R*)-**8a**



(*R*)-**9a** (Ar = 3,5-$Ph_2C_6H_3$)
(*R*)-**9b** (Ar = 2,4,6-*i*-$Pr_3C_6H_2$)
(*R*)-**9c** (Ar = 2,4,6-$Cy_3C_6H_2$)



(*R*)-**10a** (Ar = 3,5-$Ph_2C_6H_3$)
(*R*)-**10b** (Ar = 2,4,6-*i*-$Pr_3C_6H_2$)
(*R*)-**10c** (Ar = 2,4,6-$Cy_3C_6H_2$)

Entry	Catalyst	Reaction time (h)	Yield (%)	ee (%)
1	(*R*)-**4b** (Ar = 3,5-$(CF_3)_2C_6H_3$)	24	83	14
2	(*R*)-**4c** (Ar = 2,4,6-*i*-$Pr_3C_6H_2$)	24	79	0
3	(*R*)-**5b** (Ar = 3,5-(*o*-Tol)$_2C_6H_3$)	12	89	15
4	(*R*)-**9a** (Ar = 3,5-$Ph_2C_6H_3$)	3	51	11
5	(*R*)-**9b** (Ar = 2,4,6-*i*-$Pr_3C_6H_2$)	3	74	13
6	(*R*)-**9c** (Ar = 2,4,6-$Cy_3C_6H_2$)	3	82	18
7	(*R*)-**10a** (Ar = 3,5-$Ph_2C_6H_3$)	3	86	36
8	(*R*)-**10b** (Ar = 2,4,6-*i*-$Pr_3C_6H_2$)	3	96	91
9	(*R*)-**10c** (Ar = 2,4,6-$Cy_3C_6H_2$)	3	93	95

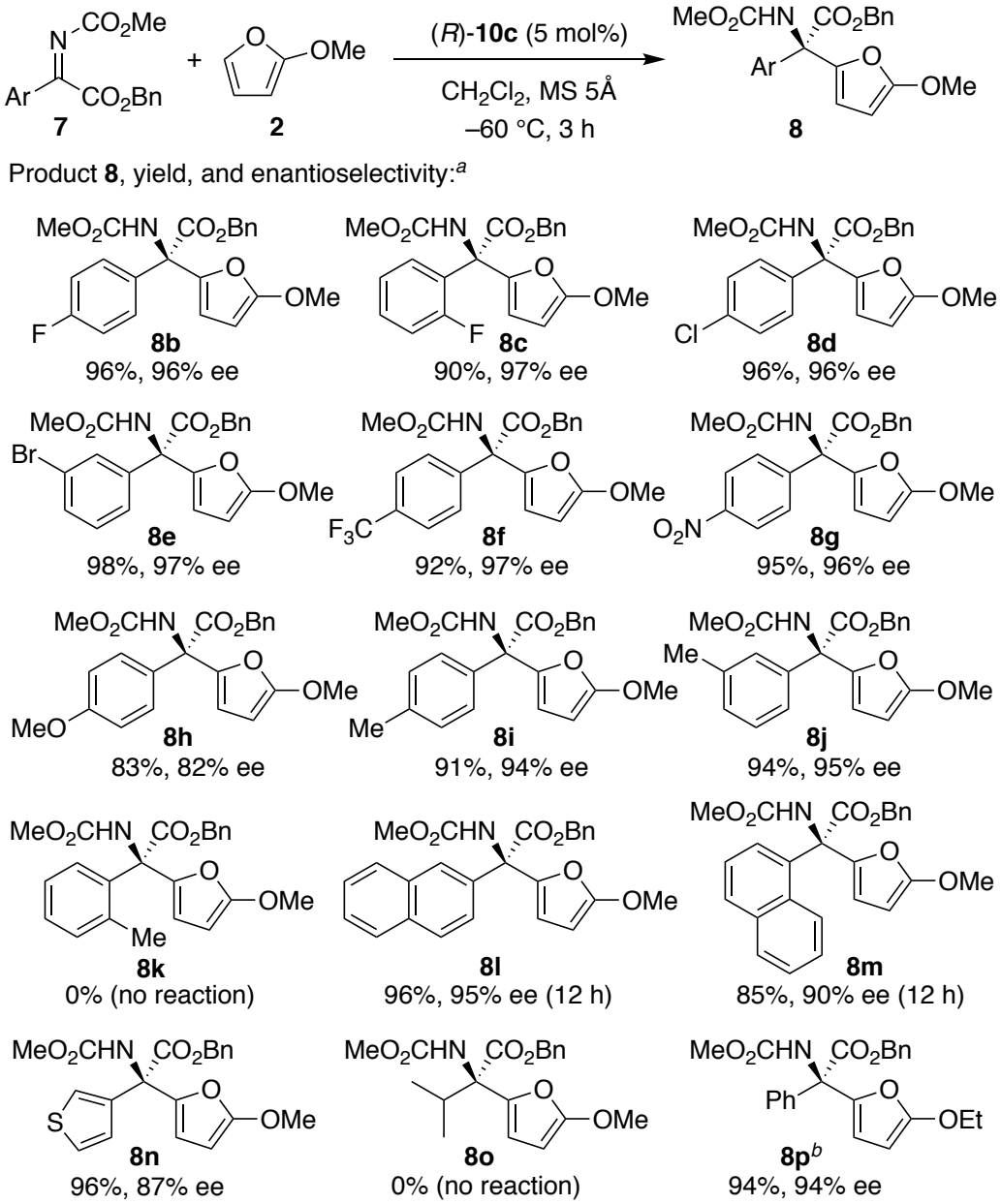
[a] The reaction was carried out with catalyst (5 mol%), **7a** (0.20 mmol, 1 equiv), **2** (2 equiv), and MS 5Å in dichloromethane (0.1 *M* based on **7a**) at –60 °C.

site-selectively mono-*i*-Pr-capped catalysts (*R*)-**10**.[21] As a result, when we use (*R*)-**10c** with extremely bulky 2,4,6-$Cy_3C_6H_2$ at the 3-position, the reaction proceeded smoothly, and (*R*)-**8a** was obtained in 93% yield with 95% ee (entry 9). The bulkiness of the aryl moiety at the 3-position is important, since slightly less hindered (*R*)-**10b** with 2,4,6-*i*-$Pr_3C_6H_2$ was less effective (entry 8), and much less hindered (*R*)-**10a** with 3,5-$Ph_2C_6H_3$ was entirely ineffective (entry 7). Conventional chiral phosphoric acids, such as (*R*)-**4b** and (*R*)-**4c**, were not effective (also see the Experimental Section 19 for

details): a prolonged reaction time (24 h) was needed and the enantioselectivity was low (entries 1 and 2).

With the optimized catalyst in hand, we next examined the scope of aryl α-ketimino esters **7** (Scheme 2). As a result, not only electron-withdrawing group- but also electron-donating group-substituted aryl substrates could be generally used (see **8b**–**j**, 83–

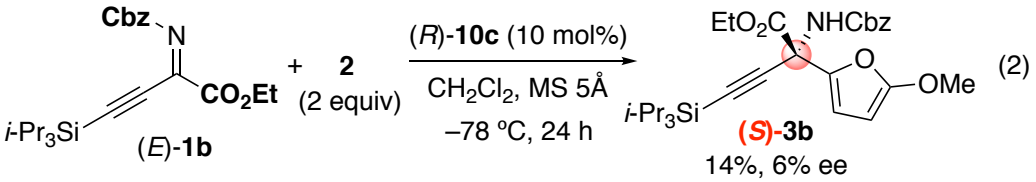
Scheme 2. Substrate scope in the enantioselective aza-FC reaction of 2-methoxyfuran **2** with aryl α-ketimino esters **7**.

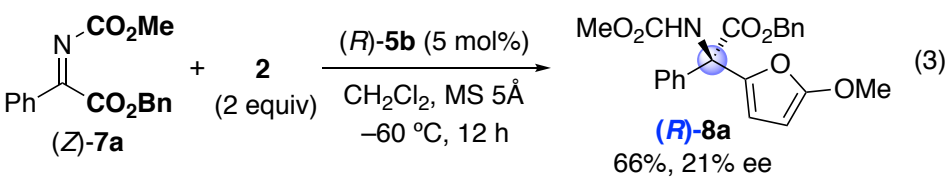


[a] The reaction was carried out with (*R*)-**10c** (5 mol%), **7** (0.20 mmol, 1 equiv), and **2** (2 equiv) in dichloromethane (0.1 *M* based on **7**) at –60 °C for 3 h. [b] 2-Ethoxyfuran was used instead of **2**.

98% yield with 82–97% ee). When we investigated simple *o*-, *m*-, and *p*-tolyl-substituted substrates (**7i**–**k**), *p*-tolyl **8i** and *m*-tolyl **8j** were obtained in high yields with high enantioselectivities (94% and 95% ee, respectively), whereas *o*-tolyl **8k** could not be obtained probably due to steric hindrance. Indeed, less sterically hindered *o*-F-C_6H_4 **8c** and 1-naphthyl **8m** were obtained with high enantioselectivities (97% and 90% ee, respectively). 2-Naphthyl **8l** and heteroaryl **8n** were also obtained successfully (95% and 87% ee, respectively). Unfortunately, however, a low-reactive aliphatic substrate **7o** could not be used, and no reaction proceeded. Moreover, instead of 2-methoxyfuran **2**, 2-ethoxyfuran[22] could be used, and the corresponding product **8p** was obtained in 94% yield with 94% ee.

To date, it has been difficult to consider the difference between the optimized C_2-symmetric (*R*)-**5b** and C_1-symmetric (*R*)-**10c**. As seen above, (*R*)-**5b**-catalysis of **1b** and **2** provided (*S*)-**3b**, and (*R*)-**10c**-catalysis of **7a** and **2** provided (*R*)-**8a**. Therefore, the observed absolute stereochemistries in **5b** and **8a** were opposite each other. This changeover might be caused by the geometry of α-ketimino esters (*E*)-**1b**[14] and (*Z*)-**7a**[23] (see the Experimental Section 27 for details). Moreover, (*S*)-**3b** was obtained in 14% yield with 6% ee by using (*R*)-**10c** (Eq. 2), whereas (*R*)-**8a** was obtained in 66% yield with 21% ee by using (*R*)-**5b** (Eq. 3). Overall, chiral C_2- and C_1-symmetric bis(phosphoric acid) catalysts were complementary, and either catalyst that was suitable for one reaction would not be suitable for the other reaction from the viewpoint of yield and enantioselectivity. Although preliminary possible transition states are considered as a working model (see the Experimental Section 28 for details), further investigations of the catalysts are still needed.[16,20]

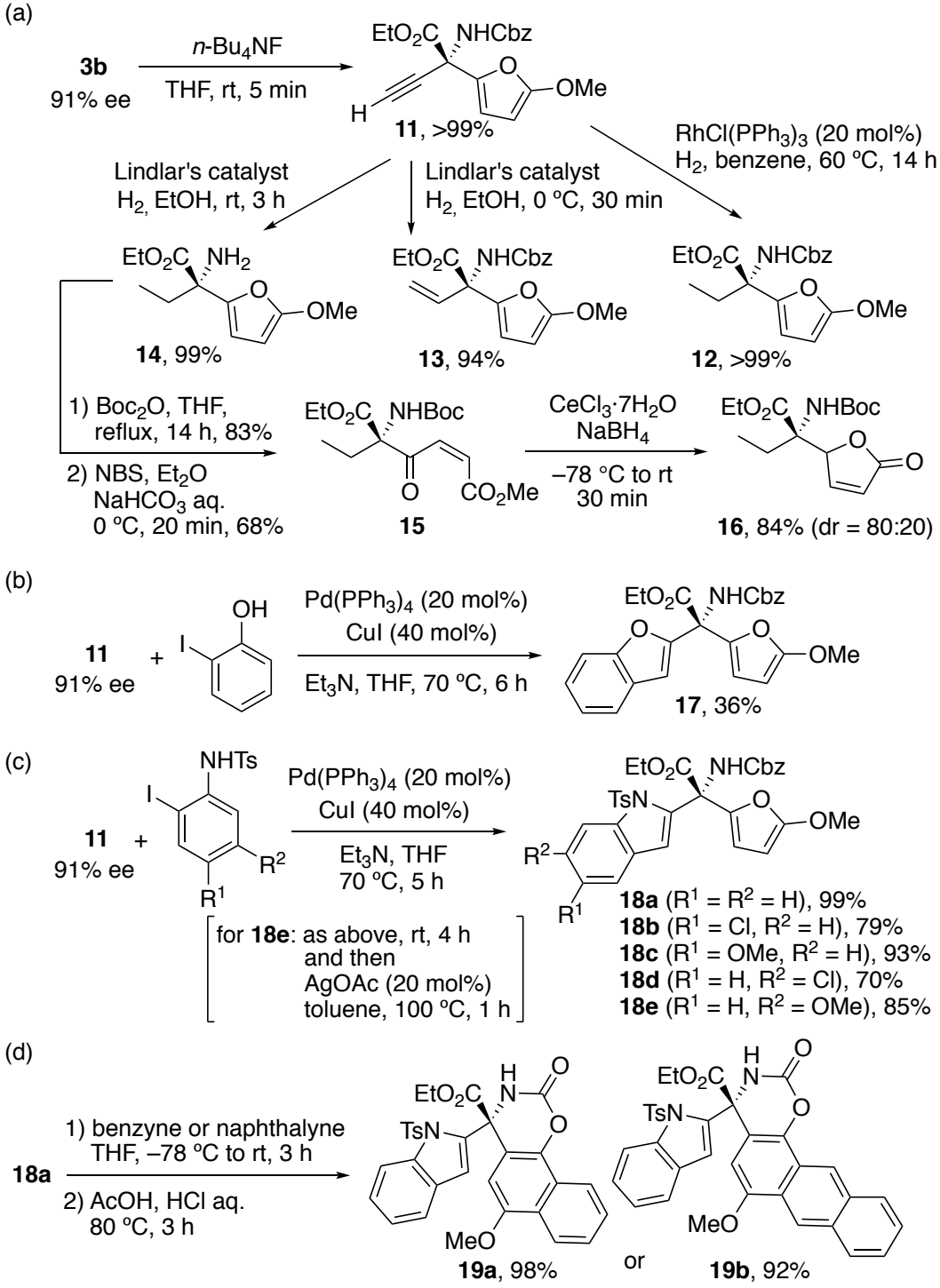




2-4 Transformation of products

Since optically active **3b** has four versatile and transferable functional groups, including acetylene, ester, carbamate, and furyl groups, at the chiral quaternary carbon, we chose to explore the transformations of these functional groups (Scheme 3a). First, the *i*-Pr_3Si

Scheme 3. Transformation of alkyne and furan moieties.

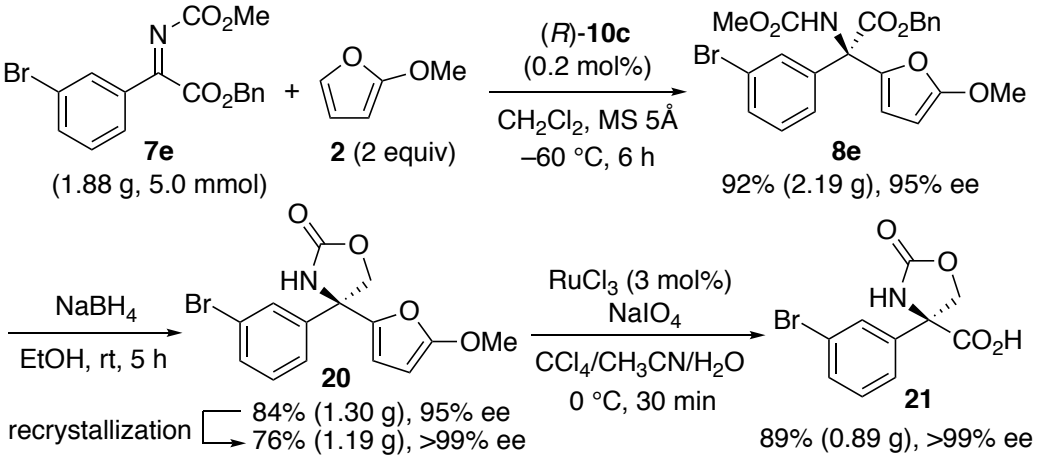


moiety of **3b** was removed by tetrabutylammonium fluoride (TBAF) to give **11** quantitatively. Next, **11** was reduced under typical reaction conditions. Wilkinson's catalyst completely reduced the acetylene moiety of **11**, and **12** was obtained quantitatively. Lindlar's catalyst facilitated the selective hydrogenation of acetylene at 0 °C to give vinyl compound **13** in 94% yield, whereas both acetylene and the Cbz moieties of **11** were reduced at room temperature and **14** was obtained quantitatively. Furthermore, the NH_2 moiety of **14** was protected by di-*tert*-butyl dicarbonate (Boc_2O) in 83% yield, and the corresponding product was consequently treated with *N*-bromosuccinimide (NBS) to give 1,4-dicarbonyl compound **15** in 68% yield *via* furan cleavage. Finally, chemoselective reduction of the keto moiety of **15** with the use of $CeCl_3/NaBH_4$ gave γ-butenolide **16** in 84% yield with a diastereomeric ratio of 80:20.[12]

We further explored the transformation of **11** to some optically active *N*- and *O*-heterocycles. Sonogashira coupling of **11** with 2-iodophenol proceeded in the presence of $Pd(PPh_3)_4$/CuI catalysts, and novel 2-substituted benzofuran **17**, which has a chiral quaternary carbon center with substitutions of furan, ester, and carbonate moieties, was obtained in 36% yield (Scheme 3b). A similar transformation of **11** with *N*-tosyl-2-iodoaniline proceeded, and novel 2-substituted indol **18a** with those functional groups was obtained quantitatively (Scheme 3c). Cl- or MeO-Substituted *N*-tosyl-2-iodoanilines were also tolerable, and **18b**–**e** were obtained in high yields (70–93%). Moreover, a Diels–Alder reaction of the furan moiety of **18a** with benzyne gave the corresponding adduct, which, without purification, was treated with HCl/acetic acid to give **19a** in 98% yield (Scheme 3d).[24] Naphthalyne in place of benzyne also gave the corresponding product **19b** in 92% yield. These indole-derived α-amino acid derivatives **18** and **19** with extraordinary structural diversities would facilitate the process of drug discovery.[25]

Since optically active α-aryl-substituted serines are synthetically useful,[26] we finally transformed the obtained product **8e** (Scheme 4). Before the transformation, we performed a >2 g-scale synthesis of **8e** (95% ee) with a catalyst loading as low as 0.2 mol%. The obtained **8e** was then reduced by $NaBH_4$, and compound **20** was obtained in 84% yield. Compound **20** was highly crystalline, and a single recrystallization increased the enantiopurity up to >99% ee. Finally, the 2-methoxyfuran moiety of **20** was oxidized by $RuCl_3$-catalyzed $NaIO_4$-oxidation,[27] and the corresponding desired optically active α-aryl-substituted serine-derivative **21** (0.89 g) was obtained in 89% yield.

Scheme 4. Transformation to optically active α-aryl-substituted serine **21**.



2-5 Conclusions

In summary, we have developed chiral BINOL-derived C_2- and C_1-symmetric bis(phosphoric acid) catalysts. The conjugated double hydrogen bond network was key to increasing the Brønsted acidity and preventing dimerization/deactivation of the catalysts. In particular, we developed a highly enantioselective aza-Friedel–Crafts reaction of 2-methoxyfuran with α-ketimino esters for the first time. By taking advantage of the highly functionalized products, some transformations to versatile *N*- and *O*-heterocycles and α-aryl-substituted serine with a chiral quaternary carbon center could be achieved. The further application of these catalysts in other asymmetric catalyses is underway.

2-6 Notes and Refrences

1. For reviews on asymmetric hydrogen bond network. (a) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.
2. For reviews on chiral Brønsted acids. (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Synthesis* **2010**, *2010*, 1929. (c) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (d) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (e) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277. (f) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2017**, *117*, 10608. (g) Merad, J.; Lalli, C.; Bernadat, G.; Maury, J. Masson, G. *Chem. Eur. J.* **2018**, *24*, 3925.
3. (a) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Chem. Rec.* **2002**, *2*, 177. (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.
4. (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094. (c) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5846. (d) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.
5. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080.
6. Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175.
7. (a) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (b) Hashimoto, T.; Kimura, H.; Nakatsu, H.; Maruoka, K. *J. Org. Chem.* **2011**, *76*, 6030.
8. (a) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (b) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946. (c) Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 4050. (d) Guo, C.; Song, J.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 2676. (e) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504.
9. Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858.
10. (a) Momiyama, N.; Konno, T.; Furiya, Y.; Iwamoto, T.; Terada, M. *J. Am. Chem. Soc.* **2011**, *133*, 19294. (b) Momiyama, N.; Narumi, T.; Terada, M.; *Chem. Commun.* **2015**, *51*, 16976. (c) Momiyama, N.; Funayama, K.; Noda, H.; Yamanaka, M.; Akasaka, N.; Ishida, S.; Iwamoto, T.; Terada, M. *ACS Catal.* **2016**, *6*, 949.

11. Momiyama, N.; Tabuse, H.; Noda, H.; Yamanaka, M.; Fujinami, T.; Yamanishi, K.; Izumiseki, A.; Funayama, K.; Egawa, F.; Okada, S.; Adachi, H.; Terada, M. *J. Am. Chem. Soc.* **2016**, *138*, 11353.
12. Terada reported a pioneering work on the enantioselective aza-FC reaction of 2-methoxyfuran with aldimines and ketimines by chiral phosphoric acid catalysts. See: (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (b) Kondoh, A.; Ota, Y.; Komuro, T.; Egawa, F.; Kanomata, K.; Terada, M. *Chem. Sci.* **2016**, *7*, 1057.
13. Shao recently reported catalytic enantioselective aza-FC-type reactions with alkynyl aldimines by using chiral phosphoric acid catalysts. Wang, Y.; Jiang, L.; Li, L.; Dai, J.; Xiong, D.; Shao, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 15142.
14. Substrates **1** would have an *E*-geometry. See the Experimental Section 27 for details. Also see our previous report: Hatano, M.; Yamashita, K.; Mizuno, M.; Ito, O.; Ishihara, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 2707.
15. The preparation of (*R*)-**5a** is described in detail in the Experimental Section 2.
16. To consider the acidity of the catalysts, we performed preliminary theoretical calculations in a working model by using molecular electrostatic potential (MEP). As a result, even among the same simple units, the conjugated double hydrogen bond network of bis(phosphoric acid)s showed higher acidity than the corresponding normal (phosphoric acid)s. See the Experimental Section 12 for details.
17. Other optimizations, such as for the solvent, reaction temperature, concentration, drying agents, etc., are shown in the Experimental Section 13.
18. A linear relationship was observed for less Brønsted-basic (*R*)-**4b**, which might act as a monomeric catalyst. See the Experimental Section 15 for details.
19. (a) Li, N.; Chen, X.-H.; Zhou, S.-M.; Luo, S.-W.; Song, J.; Ren, L.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2010**, *49*, 6378. (b) Monaco, M. R.; Pupo, G.; List, B. *Synlett* **2016**, *27*, 1027.
20. Indeed, ESI-MS analysis of (*R*)-**5b** showed an almost exclusive peak at *m/z* = 957.2763, which might be a monomer species as $[M–H]^-$. In contrast, achiral phosphoric acids and conventional chiral phosphoric acids showed some peaks, which might be monomer as well as dimer, trimer, tetramer, and so on. See the Experimental Section 16 for details.
21. The preparation of (*R*)-**10c** is described in detail in the Experimental Section 6.

22. Manly, D. G.; Amstutz, E. D. *J. Org. Chem.* **1956**, *21*, 516.
23. Hashimoto, T.; Yamamoto, K.; Maruoka, K. *Chem. Lett.* **2011**, *40*, 326.
24. The structure of **19a** was confirmed by X-ray analysis. A transformation of the Diels–Alder adduct to 1,4-naphthoquinol-derived 1,3-oxazinan-2-one **19a** involved a completely stereoselective H^+-promoted 1,2-migration. See the Experimental Section 25 for details.
25. (a) Saxton, J. E. *Nat. Prod. Rep.* **1993**, *10*, 349. (b) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532.
26. (a) Dirlam, N. L.; Moore, B. S.; Urban, F. J. *J. Org. Chem.* **1987**, *52*, 3587. (b) Küpfer, A.; Patwardhan, R.; Ward, S.; Schenker, S.; Preisig, R.; Branch, R. A. *J. Pharmacol. Exp. Ther.* **1984**, *230*, 28. (c) Olma, A.; *Polish J. Chem.* **1996**, *70*, 1442. (d) Marco, J. A.; Carda, M.; Murga, J.; González, F.; Falomir, E. *Tetrahedron Lett.* **1997**, *38*, 1841. Also see a review. (e) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.
27. (a) Köhler, F.; Gais, H.-J.; Raabe, G. *Org. Lett.* **2007**, *9*, 1231. (b) Liu, H.; Xu, J.; Du, D.-M. *Org. Lett.* **2007**, *9*, 4725.

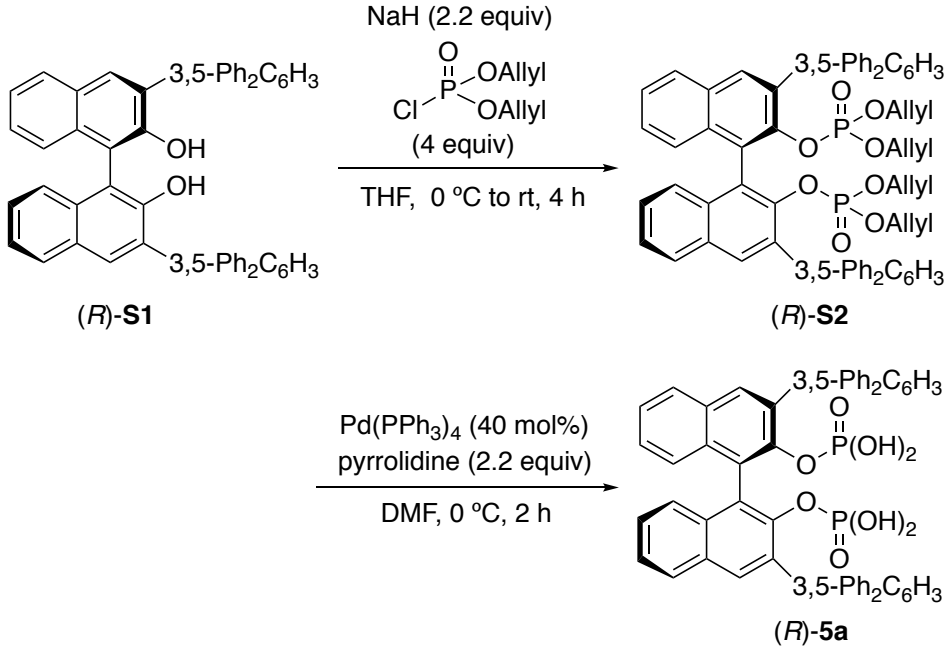
Experimental Section

Table of Contents:

1. General methods.

^{1}H NMR spectra were measured on a JEOL ECS400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.10 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). ^{31}P NMR spectra were measured on a JEOL ECS-400 (161 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard (H_3PO_4 at 0 ppm). High resolution mass spectral analyses were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700 (FAB), Bruker Daltonics micrOTOF-QII (ESI)). Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. *In situ*-IR analysis was performed by Mettler-Toledo ReactIR 15. High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-M20A and chiral column of Daicel CHIRALCEL, CHIRALPAK; AD-H, AS-H, OD-H, OD-3, IA-3, IC-3. Optical rotations were measured on Rudolph Autopol IV digital polarimeter. DFT calculation was performed by Spartan'10 for Macintosh from Wavefunction, Inc. X-ray analysis was performed by Rigaku PILATUS-200K. The products were purified by column chromatography on silica gel (E. Merck Art. 9385; Kanto Chemical Co., Inc. 37560). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. In experiments that required dry solvents such as chloroform, dichloromethane, methanol, acetonitrile, etc. were distilled in prior to use. 2-Methoxyfuran is commercially available, and 2-ethoxyfuran was prepared according to the literature procedure.[1]

2. Preparation of chiral C_2-symmetric bis(phosphoric acid)s (*R*)-5 (Method 1).

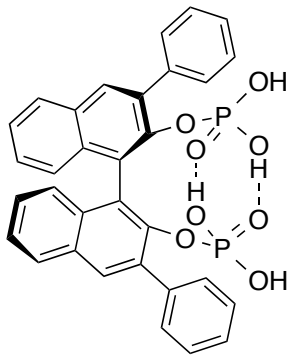


Preparation of (*R*)-S2: A solution of (*R*)-**S1** (4.05 g, 5.45 mmol) and sodium hydride (*ca.* 60%w/w oil dispersion, 480 mg, 12 mmol) in THF (55 mL) was stirred at 0 °C for 30 min under a nitrogen atmosphere. Diallyl chlorophosphate[2] (3.55 mL, 21.7 mmol) was slowly added at 0 °C, and the mixture was stirred at room temperature for 4 h. The resulting mixture was then cooled in ice bath, and diluted with ethyl acetate (40 mL) and water (20 mL). The product was extracted with ethyl acetate (20 mL × 2) and washed with brine (20 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give the product (*R*)-**S2** as colorless solid (4.05 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17-3.24 (m, 2H), 3.49-3.60 (m, 4H), 3.73-3.81 (m, 2H), 4.75-4.84 (m, 8H), 5.15-5.25 (m, 2H), 5.26-5.38 (m, 2H), 7.32-7.42 (m, 8H), 7.44-7.50 (m, 10H), 7.73 (d, J = 7.3 Hz, 8H), 7.84 (t, J = 1.4 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 1.4 Hz, 4H), 8.06 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) Many peaks overlapped. δ 67.4, 67.7, 124.7, 125.3, 126.1, 126.9, 127.5, 127.6, 127.7, 128.9, 131.3, 131.6, 132.0, 132.3, 133.7, 134.7, 139.3, 141.1, 145.4. ^{31}P NMR (160 MHz, $CDCl_3$) δ –5.8. HRMS (FAB+) calcd for $C_{68}H_{57}O_8P_2$ $[M+H]^+$ 1063.3529, found 1063.3527.

Preparation of (*R*)-3,3'-di(3,5-terphenyl)-1,1'-binaphthyl-2,2'-bis(phosphoric acid) ((*R*)-5a): Pyrrolidine (690 μL, 8.4 mmol) and tetrakis(triphenylphosphine)palladium (0) (1.76 g, 1.52 mmol) was added to a solution of (*R*)-**S2** (4.05 g, 3.80 mmol) in *N*,*N*-dimethylformamide (38 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The solution was put onto a column with the anion exchange resin (DOWEX Cl^- form), which was prepared in advance. The sample-mounted resin was washed with THF (300 mL). Then THF and 12 *M* HCl aqueous solution (v/v = 10/1, 500 mL) was passed through the resin, and the filtrate was collected. The

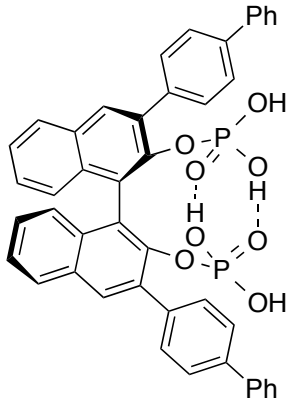
acidic layer was concentrated under reducued pressure, and extracted with dichloromethane (20 mL × 2) and washed with 1 *M* HCl aqueous solution (10 mL). The resulting organic layer was concentrated under reduced pressure. The obtained product was dissolved in toluene (20 mL), and the volatiles were thoroughly removed under reduce pressure. The product was dissolved in dichloromethane (10 mL), and the excess amount of *n*-hexane was added to give of (*R*)-**5a** as a white-yellow powder (3.02 g, 88% yield). A trace amount of Et_2O remained. ^{1}H NMR (400 MHz, THF-d_8) δ 3.50-5.00 (br, 4H), 7.30-7.37 (m, 4H), 7.38-7.51 (m, 12H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 8H), 7.88 (s, 2H), 8.00-8.04 (m, 6H), 8.23 (s, 2H). ^{13}C NMR (100 MHz, THF-d_8) δ 125.7 (2C), 126.1 (2C), 126.5 (2C), 126.7 (2C), 127.6 (2C), 128.0 (4C), 128.2 (8C), 129.0 (6C), 129.5 (8C), 132.4 (2C), 132.7 (2C), 133.6 (2C), 136.4 (2C), 140.4 (2C), 142.3 (4C), 142.4 (4C), 147.4 (2C) [Contamination of a trace amount of acetone (δ 30.2) through the ^{13}C NMR analysis.]. ^{31}P NMR (160 MHz, THF-d_8) δ –0.13. IR (KBr) 3423, 3058, 2924, 1595, 1400, 1239, 1190, 1151, 1034, 1002 cm^{-1}. $[\alpha]_D^{27}$ = +178.8 (*c* 1.00, THF). M.p. 218 °C (decomposition). HRMS (FAB–) calcd for $C_{56}H_{39}O_8P_2$ $[M–H]^-$ 901.2120, found 901.2138.

Preparation of anion exchange resin: Commercially available DOWEX Cl^- form ion-exchange resin (*ca.* 100 mL) in a column was washed with 1 *M* HCl aqueous solution (200 mL) until the yellow eluate would be colorless. The resin was washed with water (200 mL) until the acidic eluate would be neutral by monitoring with pH test paper. The resin was washed with 1 *M* NaOH aqueous solution (200 mL) and then water (500 mL) until the basic eluate would be neutral by monitoring with pH test paper.



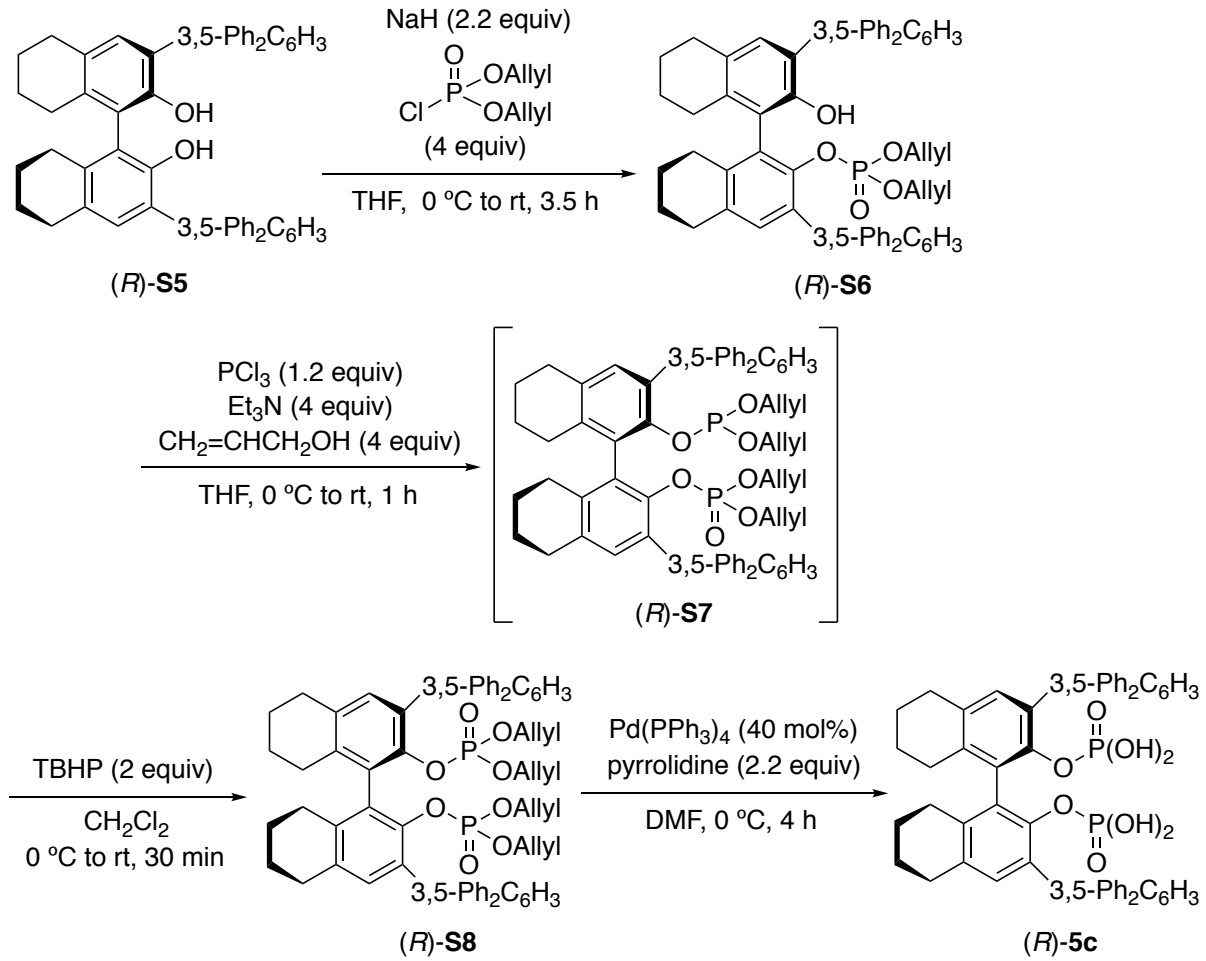
(*R*)-3,3'-Diphenyl-1,1'-binaphthyl-2,2'-bis(phosphoric acid) ((*R*)-S3): Prepared by Method 1. 83% yield for the first step and 97% yield for the second step. A trace amount of *n*-hexane remained. White-yellow soild. ^{1}H NMR (400 MHz, THF-d_8) δ 7.31 (t, *J* = 7.3 Hz, 2H), 7.37-7.41 (m, 6H), 7.47 (t, *J* = 6.9 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 6.9 Hz, 4H), 7.97 (d, *J* = 8.2 Hz, 2H), 8.02 (s, 2H) (Four P-OH moieties were not clearly observed.). ^{13}C NMR (100 MHz, THF-d_8) δ 125.5 (2C), 125.9 (2C), 126.2 (2C), 126.9 (2C), 127.5 (2C), 128.1 (4C), 128.6 (2C), 130.6 (4C), 131.6 (2C), 132.2 (2C), 133.0 (2C), 136.3 (2C), 139.1 (2C), 146.9 (2C). ^{31}P NMR (160 MHz, THF-d_8) δ –0.2. IR (KBr) 3448, 3052, 2890, 1496, 1423, 1359, 1246, 1194,

1149, 1033 cm^{-1}. M.p. 171 °C (decomposition). $[\alpha]_D^{27}$ = +174.7 (*c* 1.00, THF). HRMS (FAB–) calcd for $C_{32}H_{23}O_8P_2$ $[M–H]^-$ 597.0874, found 597.0891.



(*R*)-3,3'-Di(4-biphenyl)-1,1'-binaphthyl-2,2'-bis(phosphoric acid) ((*R*)-S4): Prepared by Method 1. 35% yield for the first step and 83% yield for the second step. A trace amount of DMF remained. White-yellow powder. ^{1}H NMR (400 MHz, THF-d_8) δ 4.50-5.02 (br, 4H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.39-7.46 (m, 6H), 7.48 (t, *J* = 6.9 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.66-7.76 (m, 8H), 7.82 (d, *J* = 8.2 Hz, 4H), 8.00 (d, *J* = 8.2 Hz, 2H), 8.10 (s, 2H). ^{13}C NMR (100 MHz, THF-d_8) δ 125.9 (2C), 126.3 (2C), 126.6 (2C), 127.0 (4C), 127.3 (2C), 127.6 (4C), 127.9 (2C), 128.9 (2C), 129.4 (4C), 131.4 (4C), 132.0 (2C), 132.6 (2C), 133.3 (2C), 136.2 (2C), 138.5 (2C), 140.6 (2C), 141.7 (2C), 147.2 (2C). ^{31}P NMR (160 MHz, THF-d_8) δ 0.1. IR (KBr) 3411, 3029, 1489, 1194, 1034 cm^{-1}. M.p. 206 °C (decomposition). $[\alpha]_D^{27}$ = +177.1 (*c* 1.00, THF). HRMS (FAB–) calcd for $C_{44}H_{31}O_8P_2$ $[M–H]^-$ 749.1494, found 749.1488.

3. Preparation of chiral C_2-symmetric bis(phosphoric acid)s (*R*)-5 (Method 2).



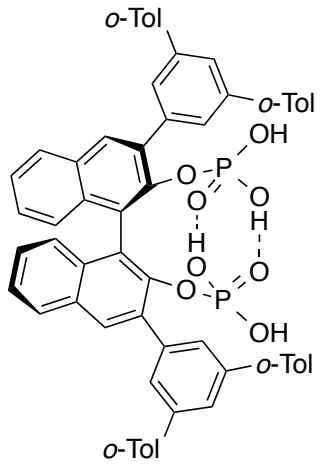
Preparation of (*R*)-S6: A solution of (*R*)-**S5** (2.27 g, 3.02 mmol) and sodium hydride (*ca.* 60%w/w oil dispersion, 266 mg, 6.65 mmol) in THF (30 mL) was stirred at 0 °C for 30 min under a nitrogen atmosphere. Diallyl chlorophosphate (1.97 mL, 12.0 mmol) was slowly added at 0 °C, and the mixture was stirred at room temperature for 4 h. The resulting mixture was then cooled in ice bath, and diluted with ethyl acetate (40 mL) and water (20 mL). The product was extracted with ethyl acetate (20 mL × 2) and washed with brine (20 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 20:1 to 10:1) to give the product (*R*)-**S6** as coloreless solid (2.39 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.92 (m, 8H), 2.09-2.23 (m, 2H), 2.51-2.66 (m, 2H), 2.73-2.95 (m, 4H), 3.50-3.59 (m, 1H), 3.64-3.73 (m, 1H), 3.74-3.87 (m, 2H), 4.83-4.90 (m, 2H), 4.99-5.07 (m, 2H), 5.27-5.39 (m, 1H), 5.48-5.59 (m, 1H), 6.61 (s, 1H), 7.22-7.26 (m, 2H), 7.32-7.51 (m, 12H), 7.65-7.72 (m, 8H), 7.72-7.77 (m, 4H), 7.82-7.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) Many peaks overlapped. δ 22.7, 23.0, 23.2, 23.4, 27.1, 27.4, 29.6, 29.8, 67.5 (d, J_{C-P} = 5.7 Hz), 68.2 (d, J_{C-P} = 5.7 Hz), 117.5, 117.6, 124.7, 125.2, 127.2, 127.4, 127.5, 127.6, 127.7, 128.7, 128.9, 129.8, 130.4, 130.8, 131.0, 131.6, 131.8, 131.9 (d, J_{C-P} = 7.6 Hz), 132.3 (d, J_{C-P} = 8.6 Hz), 135.7, 136.0, 138.0,

139.2, 139.7, 141.1, 141.6, 141.8, 144.0 (d, J_{C-P} = 8.6 Hz), 149.0. ^{31}P NMR (160 MHz, $CDCl_3$) δ –3.99. IR (KBr) 3268, 3033, 2927, 2856, 1594, 1497, 1450, 1410, 1250, 1030 cm^{-1}. M.p. 122 °C (decomposition). $[\alpha]_D^{26}$ = –40.7 (*c* 1.00, $CHCl_3$). HRMS (ESI+) calcd for $C_{62}H_{56}O_5P$ $[M+H]^+$ 911.3860, found 911.3860.

Preparation of (*R*)-S7: To a solution of (*R*)-**S6** (2.20 g, 2.41 mmol) and triethylamine (1.34 mL, 9.6 mmol) in THF (6 mL) was added phosphorus trichloride (255 μL, 2.92 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 min, and then allyl alcohol (670 μL, 9.85 mmol) was slowly added at 0 °C. The mixture was stirred at room temperature for 1 h. The resulting mixture was diluted with ethyl acetate (40 mL) and water (20 mL). The product was extracted with ethyl acetate (20 mL × 2) and washed with brine (20 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure to give a coloreless solid mixture of products (*R*)-**S7** and its partially air-oxidized compound (i.e., (*R*)-**S8**), which were used for the next step without the further purification.

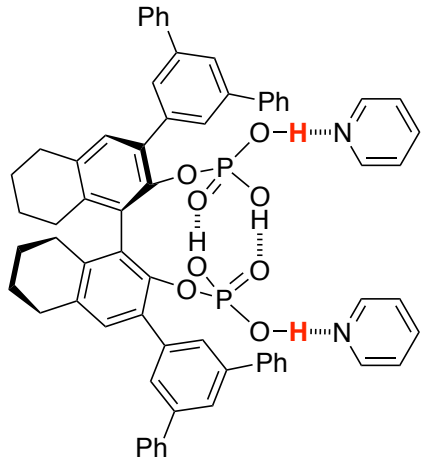
Preparation of (*R*)-S8: A solution of the obtained (*R*)-**S7** (and (*R*)-**S8**) (2.41 mmol based on (*R*)-**S6**) in dichloromethane (24 mL) was added *tert*-butyl hydroperoxide (TBHP, *ca.* 5.5 *M* in nonane solution, 870 μL, 4.79 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. The resulting mixture was diluted with ethyl acetate (40 mL) and saturated $Na_2S_2O_3$ aqueous solution (10 mL). The product was extracted with ethyl acetate (20 mL × 2) and washed by brine (20 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 2:1) to give the desired product (*R*)-**S8** as coloreless solid (1.41 g, 55% yield based on 2.41 mmol of (*R*)-**S6**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.86 (m, 8H), 2.31-2.45 (m, 2H), 2.70-2.91 (m, 6H), 3.52-3.61 (m, 2H), 3.70-3.88 (m, 6H), 4.83-4.91 (m, 4H), 4.95-5.07 (m, 4H), 5.34-5.45 (m, 2H), 5.48-5.59 (m, 2H), 7.16 (s, 2H), 7.37 (t, *J* = 7.3 Hz, 4H), 7.46 (t, *J* = 7.3 Hz, 8H), 7.69 (d, *J* = 7.3 Hz, 8H), 7.72-7.78 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8 (2C), 23.0 (2C), 27.6 (2C), 29.6 (2C), 67.4 (d, J_{C-P} = 5.7 Hz, 2C), 67.5 (d, J_{C-P} = 5.7 Hz, 2C), 117.2 (2C), 117.5 (2C), 125.0 (2C), 127.4 (8C), 127.5 (4C), 128.0 (4C), 128.9 (8C), 129.1 (2C), 131.9 (2C), 132.1 (2C), 132.4 (d, J_{C-P} = 7.6 Hz, 2C), 132.6 (d, J_{C-P} = 8.5 Hz, 2C), 134.9 (2C), 138.5 (2C), 139.5 (2C), 141.1 (4C), 141.6 (4C), 144.1 (d, J_{C-P} = 7.6 Hz, 2C). ^{31}P NMR (160 MHz, $CDCl_3$) δ –6.12. IR (KBr) 3448, 3059, 3033, 2935, 2860, 1734, 1594, 1498, 1452, 1423, 1409, 1278, 1196, 1031 cm^{-1}. M.p. 238-240 °C. $[\alpha]_D^{27}$ = –87.2 (*c* 1.00, $CHCl_3$). HRMS (ESI+) calcd for $C_{68}H_{65}O_8P_2$ $[M+H]^+$ 1071.4149, found 1071.4138.

Preparation of (*R*)-3,3'-di(3,5-terphenyl)-1,1'-(5,5',6,6',7,7',8,8'-octahydro-binaphthyl)-2,2'-bis(phosphoric acid) ((*R*)-5c): (*R*)-**S8** was used for the next step with the same procedure described above, and (*R*)-**5c** was obtained as a white-yellow powder (0.937 g, 78% yield). A small amount (4%) of inseparable *n*-hexane remained, and the purity of (*R*)-**5c** was 95% (i.e., 74% yield equivalent). ^{1}H NMR (400 MHz, THF-d_8) δ 1.60-1.91 (m, 8H), 2.10-2.20 (m, 2H), 2.75-2.98 (m, 6H), 7.27 (s, 2H), 7.32 (t, J = 7.3 Hz, 4H), 7.44 (t, J = 7.3 Hz, 8H), 7.74-7.85 (m, 14H), 9.01 (br, 4H). ^{13}C NMR (100 MHz, THF-d_8) δ 23.8 (2C), 24.1 (2C), 28.1 (2C), 30.4 (2C), 125.2 (2C), 127.9 (4C), 128.1 (8C), 128.8 (4C), 129.4 (8C), 130.8 (2C), 132.7 (2C), 133.9 (2C), 135.1 (2C), 137.1 (2C), 140.9 (2C), 142.0 (4C), 142.5 (4C), 146.2 (2C). ^{31}P NMR (160 MHz, THF-d_8) δ 0.32. IR (KBr) 3621, 3419, 2928, 2857, 1594, 1497, 1449, 1409, 1035 cm^{-1}. M.p. 194 °C (decomposition). $[\alpha]_D^{23}$ = –99.2 (*c* 1.00, THF). HRMS (FAB–) calcd for $C_{56}H_{47}O_8P_2$ $[M–H]^-$ 909.2746, found 909.2729.



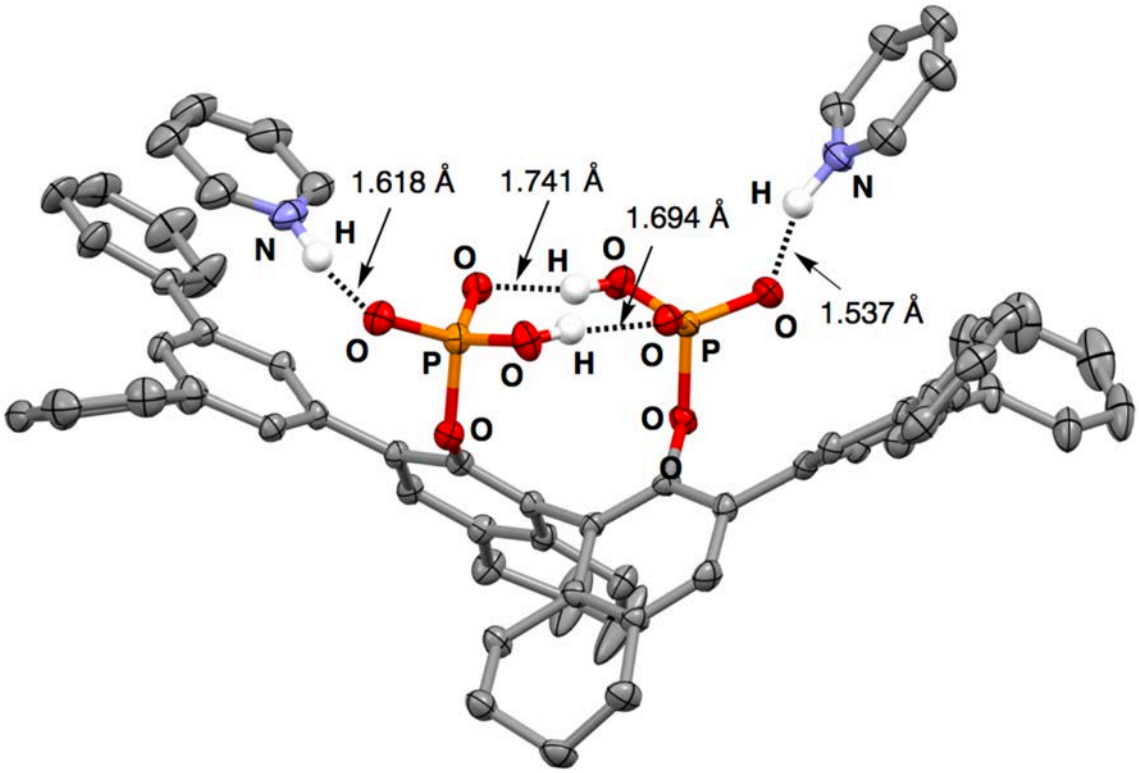
(*R*)-3,3'-Di(3,5-di(*o*-tolyl)phenyl)-1,1'-binaphthyl-2,2'-bis(phosphoric acid) ((*R*)-5b): Prepared by Method 2. A trace amount of *n*-hexane, DMF, and EtOAc remained. A white-yellow powder. ^{1}H NMR (400 MHz, THF-d_8) δ 2.39 (s, 12H), 7.18-7.64 (m, 26H), 7.56 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 1.8 Hz, 4H), 7.98 (d, J = 8.2 Hz, 2H), 8.14 (s, 2H). ^{13}C NMR (100 MHz, THF-d_8) δ 20.9 (4C), 125.8 (2C), 126.4 (6C), 126.6 (2C), 127.5 (2C), 127.9 (4C), 128.9 (2C), 129.7 (2C), 130.6 (8C), 131.0 (4C), 132.0 (2C), 132.6 (2C), 133.5 (2C), 136.4 (4C), 136.8 (2C), 139.3 (2C), 142.2 (4C), 143.0 (4C), 147.4 (2C). ^{31}P NMR (160 MHz, THF-d_8) δ –0.08. IR (KBr) 3057, 2923, 2237, 1594, 1493, 1451, 1399, 1239, 1189, 1151, 1097, 1042 cm^{-1}. M.p. 223 °C (decomposition). $[\alpha]_D^{28}$ = +242.3 (*c* 1.00, $CHCl_3$). HRMS (ESI–) calcd for $C_{60}H_{47}O_8P_2$ $[M–H]^-$ 957.2752, found 952.2756.

4. X-ray analysis of (*R*)-5c•(pyridine)$_2$ (Fig. 2).



Crystal data of (*R*)-5c·(pyridine)$_2$ (Fig. S1): Compound (*R*)-**5c**·(pyridine)$_2$ was recrystallized in benzene for X-ray analysis. Formula $C_{67}H_{60}Cl_2N_2O_8P_2$, colorless, crystal dimensions 0.20 × 0.20 × 0.20 mm^3, orthorhombic, space group $P2_12_12_1$ (#19), a = 11.4778(15) Å, b = 13.6448(18) Å, c = 36.849(5) Å, α = 90.00 °, β = 90.00 °, γ = 90.00 °, V = 5771.0(13) Å^3, Z = 4, ρ_{calc} = 1.328 g cm^{-3}, F(000) = 2416, μ(MoKα) = 0.228 mm^{-1}, T = 123 K. 39877 reflections collected, 12226 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.53 °), and 746 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Flack x = –0.001(17). R_1 = 0.0374 and wR_2 = 0.0884. GOF =1.017. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1520625. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Web page: http://www.ccdc.cam.ac.uk/].

(a) Side view



(b) Top view

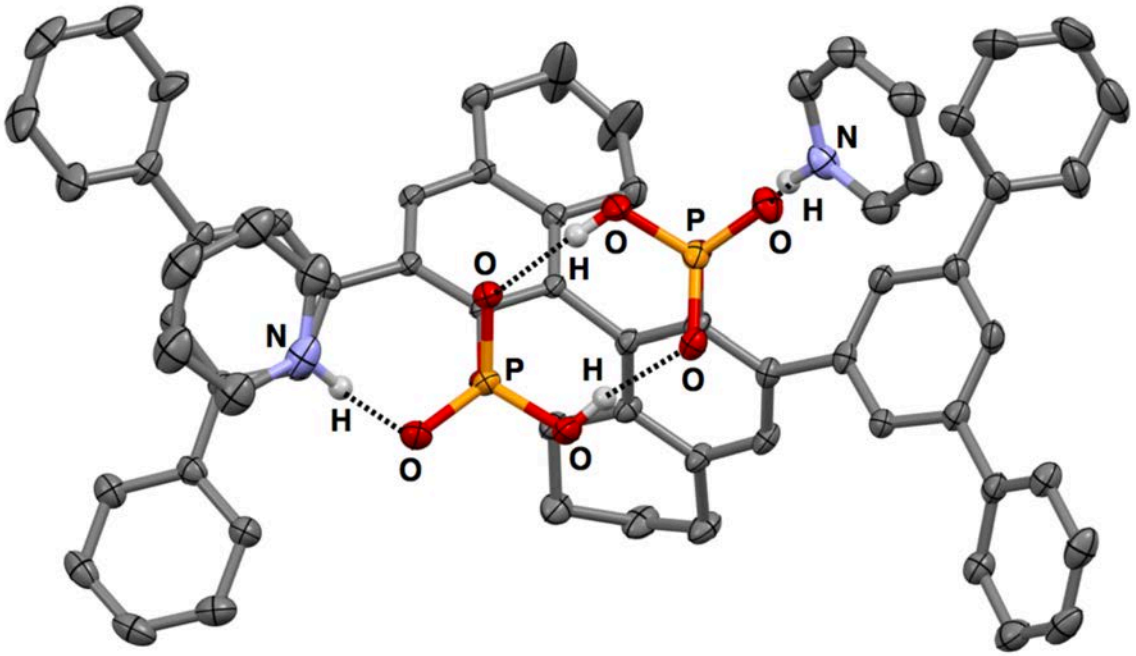
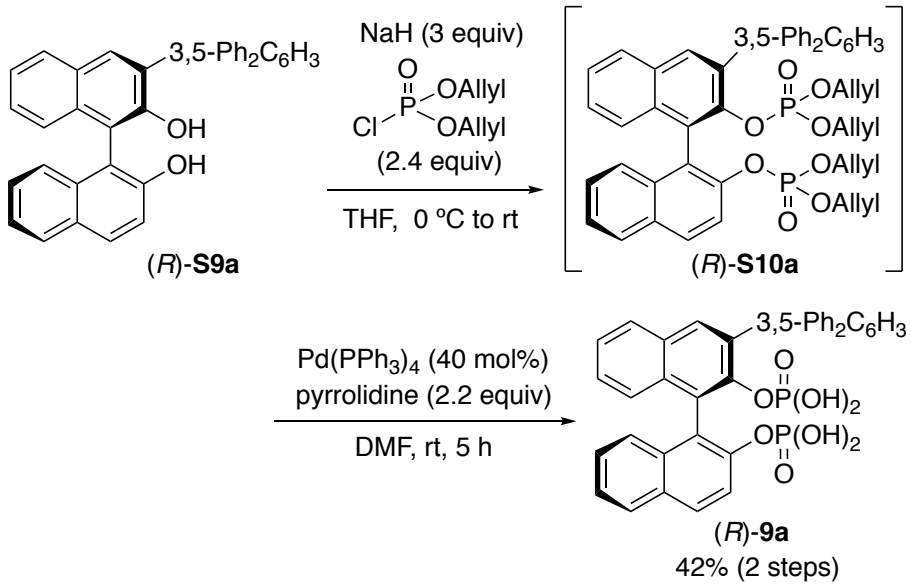


Fig. S1 ORTEP drawing of (*R*)-**5c**•(pyridine)$_2$. (a) Side view. (b) Top view. Some hydrogen atoms were omitted for clarity.

5. Preparation of chiral C_1-symmetric bis(phosphoric acid)s (*R*)-9.

Method A

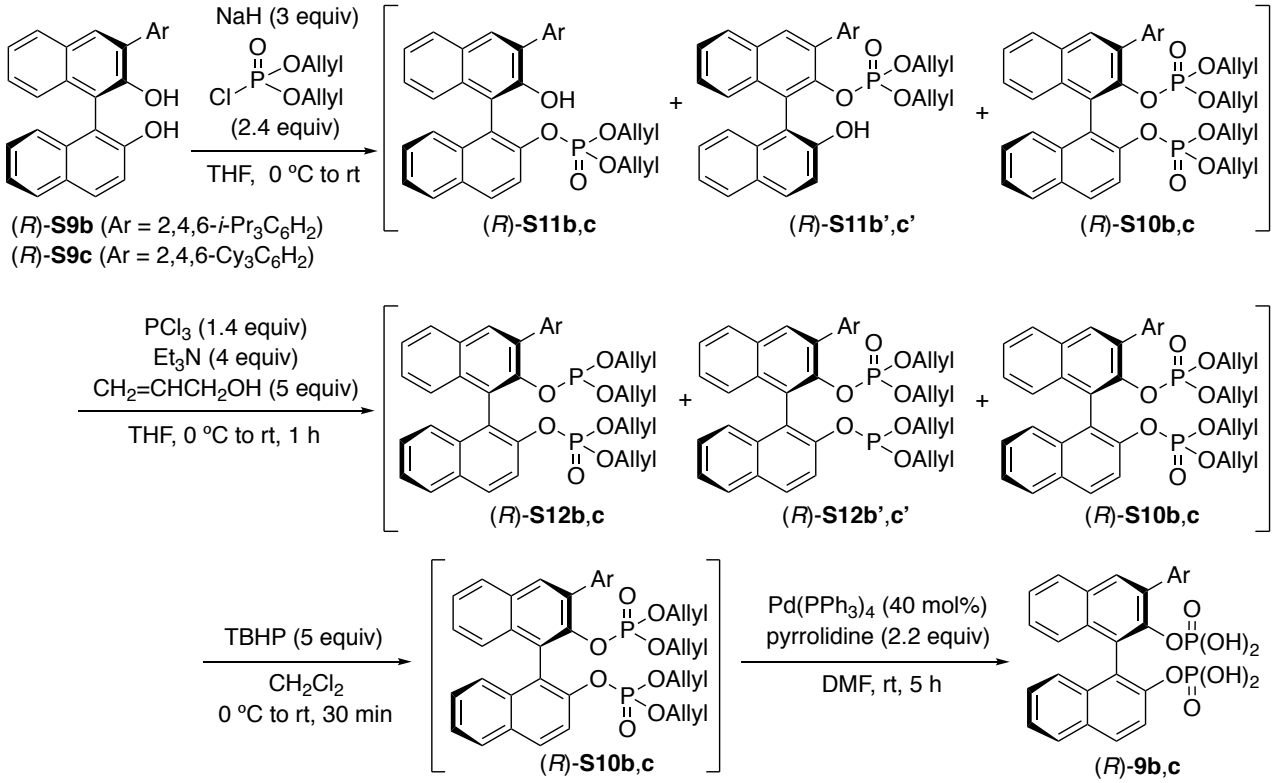


Preparation of (*R*)-S10a: A solution of chiral diol (*R*)-**S9a**[3] (1.67 g, 3.25 mmol) and sodium hydride (*ca.* 60%w/w oil dispersion, 400 mg, 9.9 mmol) in THF (33 mL) was stirred at 0 °C for 3 h under a nitrogen atmosphere. Diallyl chlorophosphate[2] (1.30 mL, 7.9 mmol) was slowly added at 0 °C, and the mixture was stirred at room temperature for 9 h. The resulting mixture was then cooled in ice bath, and diluted with ethyl acetate (20 mL) and water (10 mL). The product was extracted with ethyl acetate (10 mL × 2) and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude was roughly purified by short silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1). Impure (*R*)-**S10a** was obtained in ca. 75% yield (2.0 g).

Preparation of (*R*)-9a: Pyrrolidine (430 μL, 5.3 mmol) and tetrakis(triphenylphosphine)palladium (0) (1.1 g, 0.96 mmol) was added to a solution of (*R*)-**S10a** (impure, 2.0 g, 2.4 mmol) in *N*,*N*-dimethylformamide (24 mL) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. The solution was put onto a column with the anion exchange resin (DOWEX Cl^- form. See below for the preparation of the resin), which was prepared in advance. The sample-mounted resin was washed with THF (300 mL). Then THF and 12 *M* HCl aqueous solution (v/v = 10/1, 500 mL) was passed through the resin, and the filtrate was collected. The acidic layer was concentrated under reduced pressure, and extracted with dichloromethane (20 mL × 2) and washed with 1 *M* HCl aqueous solution (10 mL). The resulting organic layer was concentrated under reduced pressure. The obtained product was dissolved in toluene (20 mL), and the volatiles were thoroughly removed under reduced pressure. The product was dissolved in dichloromethane (10 mL), and the excess amount of *n*-hexane was added to give pure (*R*)-**9a** as a white-yellow powder (0.924 g, 42% yield in two steps).

(*R*)-3-(3,5-Terphenyl)-1,1'-binaphthyl-2,2'-bis(phosphoric acid) ((*R*)-9a): Light brown solid. ^{1}H NMR (400 MHz, THF-d_8) δ 7.18 (d, J = 8.7 Hz, 1H), 7.23-7.50 (m, 11H), 7.59 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 7.3 Hz, 4H), 7.87 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.95-8.05 (m, 4H), 8.19 (s, 1H), 9.81 (brs, 4H). ^{13}C NMR (100 MHz, THF-d_8) Peaks are overlapped. δ 122.4, 124.0 (d, J_{C-P} = 5.7 Hz), 125.6, 125.9, 126.4, 126.5, 127.4, 127.6, 128.0, 128.1, 128.9, 129.0, 129.5, 130.6, 132.2, 132.5, 133.9, 134.4, 136.2, 140.3, 142.2, 142.3, 147.2 (d, J_{C-P} = 6.7 Hz), 149.2 (d, J_{C-P} = 5.7 Hz). ^{31}P NMR (160 MHz, THF-d_8) δ –2.07, 1.27. IR (KBr) 3058, 2923, 2851, 2240, 1595, 1404, 1237, 1032, 998 cm^{-1}. M.p. was not available due to decomposition. $[\alpha]_D^{27}$ = +186.8 (*c* 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{38}H_{29}O_8P_2$ $[M+H]^+$ 675.1338, found 675.1326.

Method B



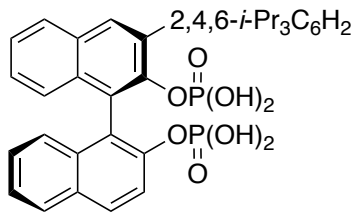
Preparation of (*R*)-S11b, (*R*)-S11b', and (*R*)-S10b (or (*R*)-S11c, (*R*)-S11c', and (*R*)-S10c): A solution of chiral diol (*R*)-**S9b** (or (*R*)-**S9c**) (3.8 mmol) and sodium hydride (*ca.* 60%w/w oil dispersion, 440 mg, 11 mmol) in THF (38 mL) was stirred at 0 °C for 3 h under a nitrogen atmosphere. Diallyl chlorophosphate (1.8 mL, 9.1 mmol) was slowly added at 0 °C, and the mixture was stirred at room temperature for 7 h. The resulting mixture was then cooled in ice bath, and diluted with ethyl acetate (20 mL) and water (10 mL). The product was extracted with ethyl acetate (10 mL × 2) and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1) to give the

mixture of (*R*)-**S11b**, (*R*)-**S11b'**, and (*R*)-**S10b** (or (*R*)-**S11c**, (*R*)-**S11c'**, and (*R*)-**S10c**) which was used for the next step without the further purification.

Preparation of (*R*)-S12b, (*R*)-S12b', and (*R*)-S10b (or (*R*)-S12c, (*R*)-S12c', and (*R*)-S10c): To a solution of the mixture of (*R*)-**S11b**, (*R*)-**S11b'**, and (*R*)-**S10b** (or (*R*)-**S11c**, (*R*)-**S11c'**, and (*R*)-**S10c**) (based on 3.8 mmol of starting (*R*)-**S9b** (or (*R*)-**S9c**)) and triethylamine (2.6 mL, 19 mmol) in THF (38 mL) was added phosphorus trichloride (460 μL, 5.3 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 min, and then allyl alcohol (1.6 mL 19 mmol) was slowly added at 0 °C. The mixture was stirred at room temperature for 1 h. The resulting mixture was diluted with ethyl acetate (40 mL) and water (20 mL). The product was extracted with ethyl acetate (20 mL × 2) and washed with brine (20 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude products (*R*)-**S12b**, (*R*)-**S12b'**, and (*R*)-**S10b** (or (*R*)-**S12c**, (*R*)-**S12c'**, and (*R*)-**S10c**) were used for the next step without the further purification.

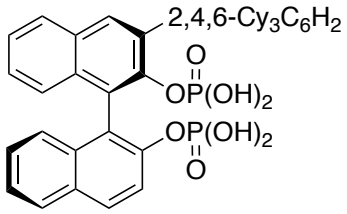
Preparation of (*R*)-S10b or (*R*)-S10c: A solution of the obtained crude products **S12b**, **S12b'**, and (*R*)-**S10b** (or (*R*)-**S12c**, (*R*)-**S12c'**, and (*R*)-**S10c**) (based on 3.8 mmol of starting (*R*)-**S9b** (or (*R*)-**S9c**)) in dichloromethane (38 mL) was added *tert*-butyl hydroperoxide (TBHP, *ca.* 5.5 *M* in nonane solution, 3.5 mL, 19 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. The resulting mixture was diluted with ethyl acetate (40 mL) and saturated $Na_2S_2O_3$ aqueous solution (10 mL). The product was extracted with ethyl acetate (20 mL × 2) and washed by brine (20 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude was roughly purified by short silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1) to give (*R*)-**S10b** (or (*R*)-**S10c**) (impure).

Preparation of (*R*)-9b or (*R*)-9c: (*R*)-**9b** and (*R*)-**9c** were prepared by the similar procedure for (*R*)-**9a** described above.



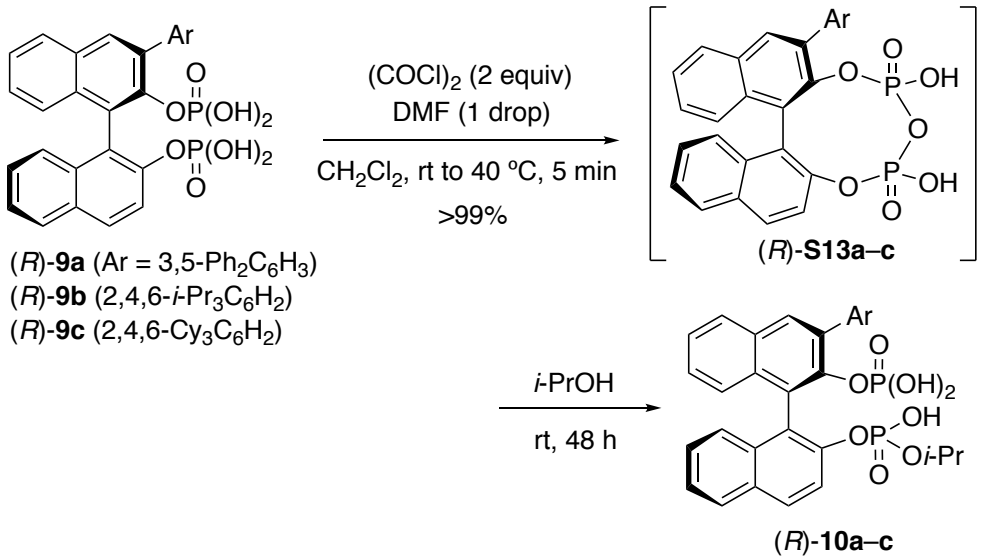
(*R*)-3-(2,4,6-Triisopropylphenyl)-1,1'-binaphthyl-2,2'-bis(phosphoric acid) ((*R*)-9b): Prepared by **Method B** (Typically 45–55% yield in four steps from (*R*)-**S9b**). Light brown solid. ^{1}H NMR (400 MHz, THF-d_8) δ 1.00 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.27 (d, *J* = 6.9 Hz, 9H), 2.84 (septet, *J* = 6.9 Hz, 1H), 2.91 (septet, *J* = 6.9 Hz, 1H), 2.97 (septet, *J* = 6.9 Hz, 1H), 7.03 (d, *J* = 1.4 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 7.22-7.31 (m, 2H), 7.34-7.45 (m, 2H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.80 (brs,

4H), 7.84-7.95 (m, 3H), 7.98 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, THF-d_8) Peaks are overlapped. δ 23.6, 23.8, 24.5, 24.6, 25.5, 27.4, 31.9, 32.0, 35.4, 120.7, 121.7, 122.6, 123.7 (d, J_{C-P} = 6.7 Hz), 125.4 (d, J_{C-P} = 3.8 Hz), 125.7, 126.3, 126.7, 127.0, 128.7, 128.8, 130.4, 132.0, 132.2, 132.5, 133.1, 133.9, 134.5, 134.7, 148.2, 148.3 (d, J_{C-P} = 6.7 Hz), 148.9, 149.0, 149.3 (d, J_{C-P} = 5.7 Hz). ^{31}P NMR (160 MHz, THF-d_8) δ –3.42, 0.78. IR (KBr) 3462, 2961, 2869, 1603, 1509, 1466, 1415, 1362, 1210, 1001 cm^{-1}. M.p. was not available due to decomposition. $[\alpha]_D^{24}$ = +257.2 (*c* 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{35}H_{39}O_8P_2$ $[M+H]^+$ 649.2120, found 649.2119.



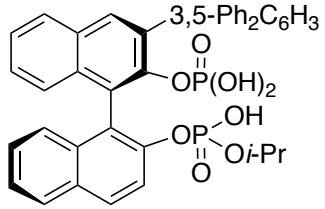
(*R*)-3-(2,4,6-Tricyclohexylphenyl)-1,1'-binaphthyl-2,2'-bis(phosphoric acid) ((*R*)-9c): Prepared by **Method B** (Typically 25–35% yield in four steps from (*R*)-**S9c**). Light brown solid. ^{1}H NMR (400 MHz, THF-d_8) δ 1.01-2.00 (m, 28H), 2.11 (d, J = 12.4 Hz, 2H), 2.38-2.61 (m, 3H), 6.90 (br, 4H), 6.99 (s, 1H), 7.07 (s, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.21-7.34 (m, 3H), 7.36-7.48 (m, 2H), 7.57 (d, J = 9.2 Hz, 1H), 7.83 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, THF-d_8) Peaks are overlapped. δ 27.2, 27.3, 27.5, 27.8, 28.0, 28.2, 33.4, 34.1, 35.5, 35.6, 36.5, 38.3, 42.7, 42.9, 45.9, 122.0, 122.8, 123.2, 124.0 (d, J_{C-P} = 6.7 Hz), 125.2 (d, J_{C-P} = 4.8 Hz), 125.8, 126.2, 126.5, 126.7, 127.0, 127.3, 128.7, 128.9, 130.3, 131.9, 132.2, 132.9, 133.5, 133.9, 134.5, 147.0, 147.7, 148.2, 148.3 (d, J_{C-P} = 6.7 Hz), 149.3 (d, J_{C-P} = 6.7 Hz). ^{31}P NMR (160 MHz, THF-d_8) δ –2.83, 1.64. IR (KBr) 3457, 2925, 2850, 1602, 1448, 1228, 1148, 1035, 1001 cm^{-1}. M.p. was not available due to decomposition. $[\alpha]_D^{25}$ = +213.6 (*c* 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{44}H_{51}O_8P_2$ $[M+H]^+$ 769.3059, found 769.3081.

6. Preparation of chiral C_1-symmetric bis(phosphoric acid)s (*R*)-10.



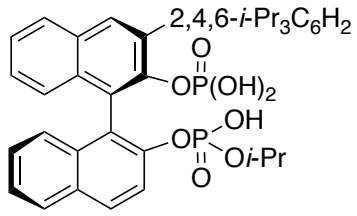
(*R*)-**9a** (Ar = 3,5-$Ph_2C_6H_3$)
(*R*)-**9b** (2,4,6-*i*-$Pr_3C_6H_2$)
(*R*)-**9c** (2,4,6-$Cy_3C_6H_2$)

To a solution of (*R*)-**9** (0.030 mmol) in dichloromethane (2 mL), one drop of *N*,*N*-dimethylformamide was added at room temperature. Then oxalyl chloride (5.1 μL, 0.060 mmol) was added at room temperature, and the mixture was warmed to 40 °C. The mixture was stirred at 40 °C for 5 min. Toluene (2 mL) was then added to the resulting mixture, and the volatiles were removed *in vacuo* under heat conditions (ca. 40–50 °C). The obtained product (*R*)-**S13** was used in the next step without further purification. Compound (*R*)-**S13** was dissolved in 2-propanol (2 mL) and the solution was stirred at room temperature for 48 h. 2-Propanol was then removed *in vacuo*. (*R*)-**10** was separated by silica gel column chromatography (eluent: $CHCl_3$:MeOH = 9:1 to 4:1). The isolated (*R*)-**10** was dissolved in chloroform (10 mL), and washed with 1 *M* HCl aqueous solution (10 mL). The resulting organic layer was concentrated under reduced pressure. The obtained compound was dissolved in toluene (2 mL), and the volatiles were thoroughly removed under reduced pressure to give pure (*R*)-**10** as light brown solid.

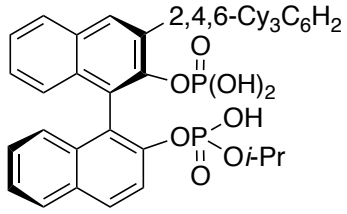


(1*R*)-3-([1,1':3',1''-Terphenyl]-5'-yl)-2'-((hydroxy(isopropoxy)phosphoryl)oxy)-[1,1'-binaphthalen]-2-yl dihydrogen phosphate ((*R*)-10a): 17% yield in 2 steps. Light brown solid. ^{1}H NMR (400 MHz, THF-d_8) δ 0.99 (d, J = 6.0 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 4.39 (m, 1H), 7.03 (br, 3H), 7.24 (d, J = 8.7 Hz, 1H), 7.27-7.37 (m, 4H), 7.38-7.49 (m, 7H), 7.72-7.83 (m, 5H), 7.85-7.91 (m, 1H), 7.92-8.06 (m, 5H), 8.19 (s, 1H). ^{13}C NMR (100 MHz, THF-d_8) Peaks are overlapped. δ 23.5 (d, J_{C-P} = 4.8 Hz), 23.7 (d, J_{C-P} = 5.7 Hz), 73.6 (d, J_{C-P} = 5.7 Hz), 121.4, 123.6 (d, J_{C-P} = 7.6 Hz), 125.6, 125.8, 126.5, 126.6, 127.4, 127.5, 128.0, 128.1, 128.9, 129.5, 130.8,

132.2, 132.5, 133.9, 134.5, 136.0, 140.4, 142.3, 142.4, 146.9 (d, J_{C-P} = 6.7 Hz), 149.1 (d, J_{C-P} = 5.7 Hz). ^{31}P NMR (160 MHz, THF-d_8) δ –3.37, –3.04. IR (KBr) 3450, 3059, 2925, 2853, 1595, 1498, 1467, 1405, 1237, 1149, 1001 cm^{-1}. M.p. was not available due to decomposition. $[\alpha]_D^{29}$ = +184.3 (*c* 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{41}H_{35}O_8P_2$ $[M+H]^+$ 717.1807, found 717.1789.



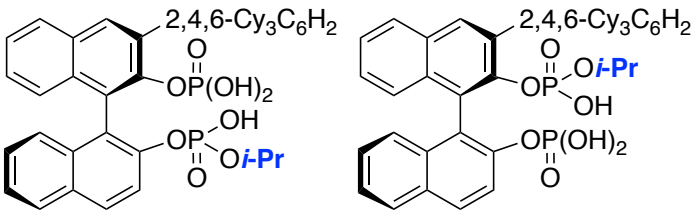
(*R*)-2'-((Hydroxy(isopropoxy)phosphoryl)oxy)-3-(2,4,6-triisopropylphenyl)-[1,1'-binaphthalen]-2-yl dihydrogen phosphate ((*R*)-10b): 50% yield in 2 steps. Light brown solid. ^{1}H NMR (400 MHz, THF-d_8) δ 0.70 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.19-1.35 (m, 15H), 2.74-2.99 (m, 3H), 4.20 (m, 1H), 6.72 (br, 3H), 7.05 (d, *J* = 1.4 Hz, 1H), 7.12 (d, *J* = 1.4 Hz, 1H), 7.22-7.49 (m, 6H), 7.83-7.96 (m, 4H), 7.99 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, THF-d_8) Peaks are overlapped. δ 23.1 (d, J_{C-P} = 4.8 Hz), 23.6, 23.8, 24.5, 27.0, 31.9, 32.0, 35.3, 72.8 (d, J_{C-P} = 6.7 Hz), 120.7, 121.2, 121.6, 122.9 (d, J_{C-P} = 8.6 Hz), 125.3, 125.6, 126.3, 126.4, 126.8, 127.1, 127.2, 128.7, 128.8, 130.7, 132.1, 132.2, 132.4, 133.2, 133.9, 134.4, 134.5, 147.9 (d, J_{C-P} = 7.6 Hz), 148.1, 148.8, 148.9, 149.1 (d, J_{C-P} = 5.7 Hz). ^{31}P NMR (160 MHz, THF-d_8) δ –4.96, –4.88. IR (KBr) 3451, 2959, 2927, 2869, 1626, 1467, 1415, 1362, 1230, 1033, 999 cm^{-1}. M.p. was not available due to decomposition. $[\alpha]_D^{28}$ = +254.3 (*c* 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{38}H_{45}O_8P_2$ $[M+H]^+$ 691.2590, found 691.2599.



(*R*)-2'-((Hydroxy(isopropoxy)phosphoryl)oxy)-3-(2,4,6-tricyclohexylphenyl)-[1,1'-binaphthalen]-2-yl dihydrogen phosphate ((*R*)-10c): 58% yield in 2 steps. Light brown solid. ^{1}H NMR (400 MHz, THF-d_8) δ 0.97-1.80 (m, 23H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.80-1.96 (m, 5H), 1.98-2.13 (m, 2H), 2.39-2.57 (m, 3H), 4.41 (m, 1H), 7.00 (d, *J* = 1.4 Hz, 1H), 7.08 (d, *J* = 1.4 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.24-7.35 (m, 3H), 7.35-7.45 (m, 2H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.83 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 9.54 (br, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) Peaks are overlapped. δ 23.5 (d, J_{C-P} = 4.8 Hz), 23.7 (d, J_{C-P} = 4.8 Hz), 27.1, 27,2, 27.4, 27.8, 28.0, 28.1, 33.7, 33.9, 35.5, 35.6, 36.3, 38.2, 42.7, 45.9, 73.4 (d, J_{C-P} = 5.7 Hz), 121.7, 122.0, 123.1, 123.3 (d, J_{C-P} = 6.7 Hz), 125.1 (d, J_{C-P} =

3.8 Hz), 125.7, 126.3, 126.6, 126.7, 127.2, 127.3, 128.7, 129.0, 130.6, 132.0, 132.2, 132.7, 133.5, 133.9, 134.3, 134.6, 147.0, 147.8, 147.9 (d, J_{C-P} = 6.7 Hz), 148.1, 149.2 (d, J_{C-P} = 5.7 Hz). ^{31}P NMR (160 MHz, DMSO-d_6) δ –4.04, –2.88. IR (KBr) 3448, 2925, 2850, 1626, 1448, 1231, 1147, 1033, 999 cm^{-1}. M.p. was not available due to decomposition. $[\alpha]_D^{26}$ = 193.6 (*c* 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{47}H_{57}O_8P_2$ $[M+H]^+$ 811.3529, found 811.3523.

We tried to crystallize (*R*)-**10c**, but we could not obtain a suitable crystalfor X-ray analysis. Instead, we obtained a suitable crystal of *racemic*-**10c**. By X-ray analysis, we unambiguously confirmed the structure of **10c** (Fig. S3), in particular, the position of the *i*-Pr moiety. The other possible isomer (*R*)-**10c'** was not obtained in our preparation, probably due to steric constraints of the bulky aryl moiety at the 3-position of the binaphthyl of (*R*)-**S13c** (Fig. S2). *Racemic*-**10c** does not have a conjugated intramolecular double hydrogen bond network as seen for (*R*)-**5c**•(pyridine)$_2$ in Fig. S1. Indeed, *racemic*-**10c** formed a dimer due to an intermolecular hydrogen bond network as shown in Fig. S4. The dimer structure is symmetric: one is (*R*)-**10c** and the other is (*S*)-**10c**. Intramolecular hydrogen bonds are not observed among dimers. (*R*)-**10c** and (*S*)-**10c** have one intramolecular hydrogen bond (1.696 Å), respectively, and four hydrogen bonds (1.576–1.848 Å) are observed between (*R*)-**10c** and (*S*)-**10c**. This dimerization of *racemic*-**10c** might disturb the formation of a conjugated intramolecular double hydrogen bond network. To date, it is still unclear whether or not optically pure (*R*)-**10c** would form a dimer. However, by the ESI-MS analysis of (*R*)-**10c** (Fig. S7f), (*R*)-**10c** might be a monomer as a major species.



(*R*)-**10c** (*R*)-**10c**' (Not obtained)

Fig. S2 (*R*)-**10c** and a possible isomer (*R*)-**10c'**. (*R*)-**10c'** was not obtained in our preparation.

Crystal data of *racemic*-10c (Figs. S3 and S4): *Racemic*-**10c** was recrystallized in chloroform–*n*-hexane for X-ray analysis. Formula $C_{47}H_{56}O_8P_2$, colorless, crystal dimensions 0.15 × 0.13 × 0.12 mm^3, monoclinic, space group *P–1* (#2), *a* = 12.7831(18) Å, *b* = 14.6459(16) Å, *c* = 14.800(2) Å, α = 116.231(11) °, β = 101.896(13) °, γ = 102.26(2) °, *V* = 2282.1(6) Å^3, *Z* = 2, ρ_{calc} = 1.180 g cm^{-3}, F(000) = 864, μ(MoKα) = 0.145 mm^{-1}, *T* = 93 K. 19527 reflections collected, 9800 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.55 °), and 532 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0477 and wR_2 = 0.1472. GOF = 1.091. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC- 1834632.

Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Web page: http://www.ccdc.cam.ac.uk/].

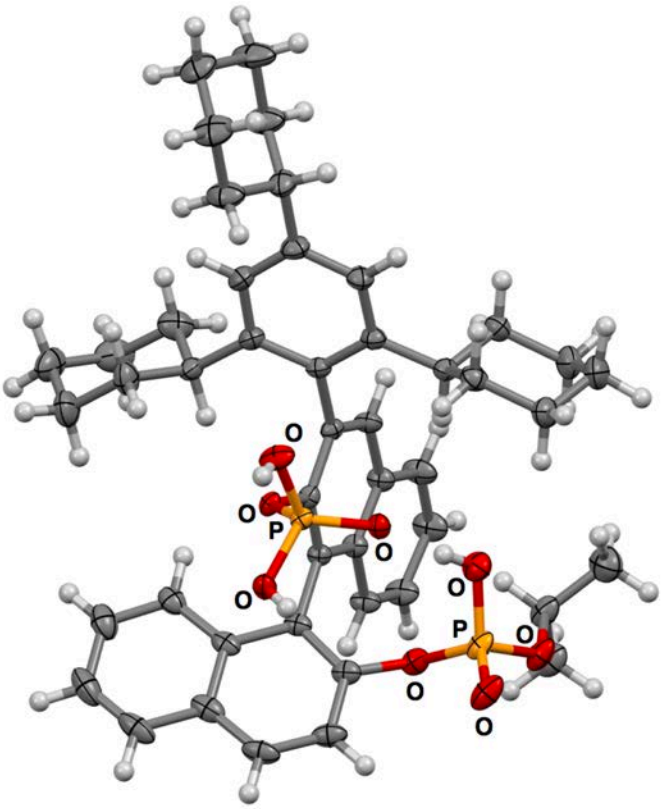


Fig. S3 ORTEP drawing of *racemic*-**10c**.

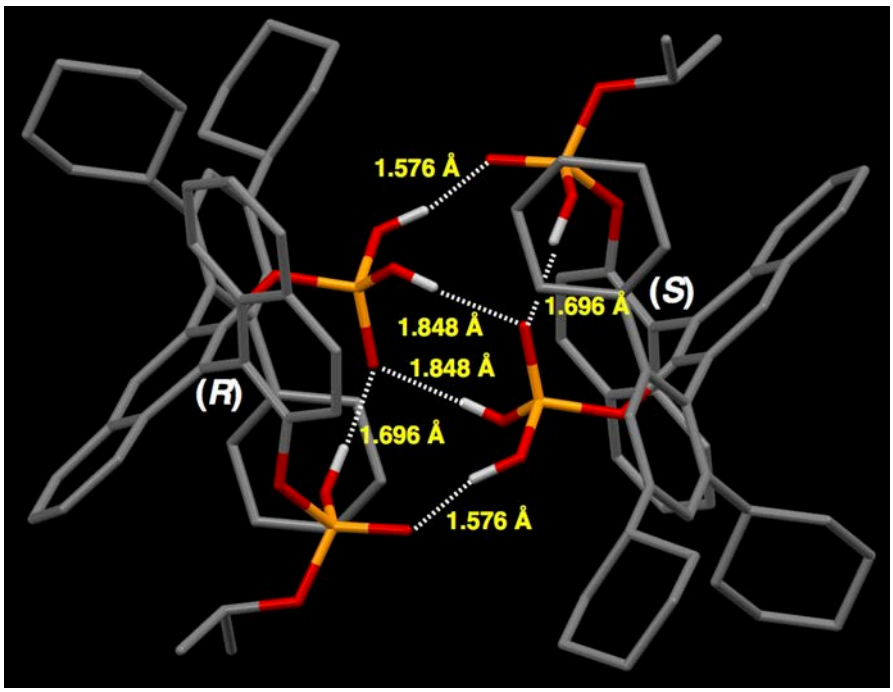
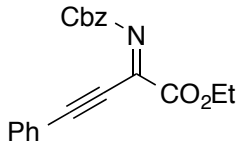


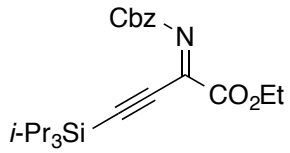
Fig. S4 Dimer structure of *racemic*-**10c** (*R*/*S*-pair).

7. Preparation of α-ketimino esters 1.

β,γ-Alkynyl-α-imino esters 1: Ketoesters **S14** were prepared based on the reported procedures.[4–6] Compounds **1** were prepared on the basis of a literature procedure.[7] To a well-dried round bottom two necks flask (50 mL) with ketoester **S14** (5.0 mmol) and *N*-Cbz-triphenyliminophosphorane[8] (2.06 g, 5.0 mmol) was added toluene (10 mL). The mixture was heated to 120 °C and stirred for 6 h. After cooling to room temperature, volatiles were removed under reduced pressure. The resultant residue was purified by MPLC (eluent: *n*-hexane:EtOAc = typically 100:0 to 80:20) to give the desired product **1**.

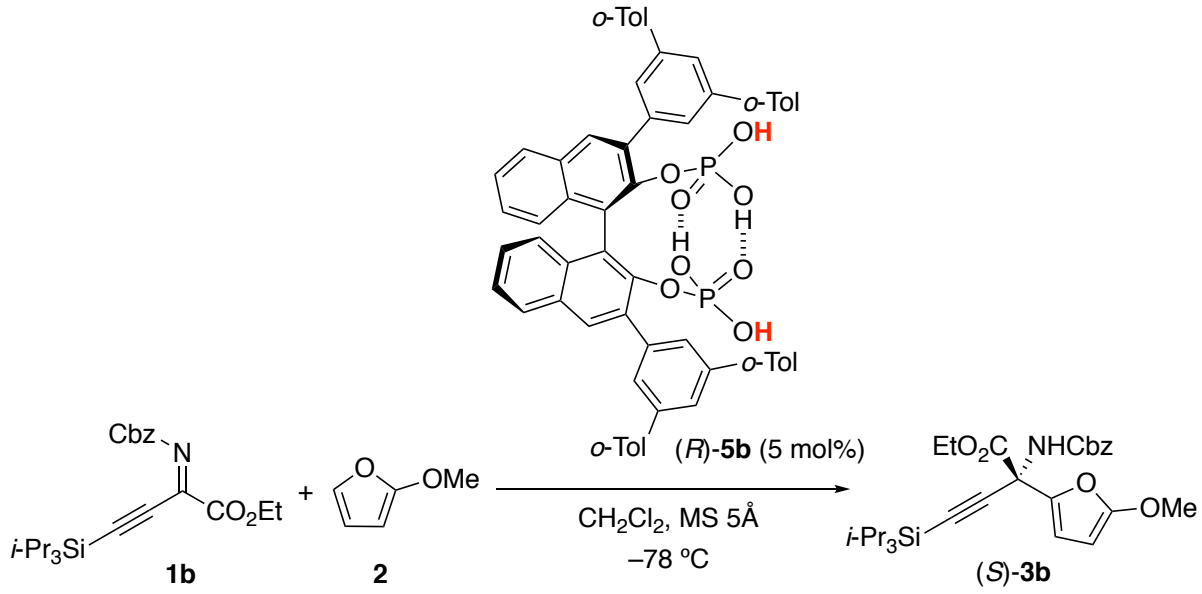


Ethyl 2-(((benzyloxy)carbonyl)imino)-4-phenylbut-3-ynoate (1a): 37% yield. Yellow-orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 6.9 Hz, 3H), 4.42 (q, J = 6.9 Hz, 2H), 5.35 (s, 2H), 7.27-7.50 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 63.4, 68.8, 81.0, 102.5, 119.4, 128.5 (7C) 131.1, 132.9 (2C), 134.9, 146.0, 160.7, 161.1. IR (neat) 3456, 2983, 2198, 1733, 1615, 1490, 1444, 1373, 1216, 1101, 1021 cm^{-1}. HRMS (FAB+) calcd for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1236, found 336.1241.



Ethyl 2-(((benzyloxy)carbonyl)imino)-4-(triisopropylsilyl)but-3-ynoate (1b): 78% yield. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04-1.15 (m, 21H), 1.37 (t, J = 6.9 Hz, 3H), 4.37 (q, J = 6.9 Hz, 2H), 5.27 (s, 2H), 7.33-7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (3C), 13.8, 18.3 (6C), 63.1, 68.8, 96.5, 108.5, 128.3 (2C), 128.4 (3C), 134.5, 145.4, 160.1, 160.7. IR (neat) 3461, 2944, 2866, 2152, 1748, 1618, 1462, 1370, 1220, 1132, 1021 cm^{-1}. HRMS (FAB+) calcd for $C_{23}H_{34}NO_4Si$ $[M+H]^+$ 416.2257, found 416.2265.

8. Representative procedures for the enantioselective aza-Friedel–Crafts reaction of 2 with 1 (Table 1 and Eq. 1).

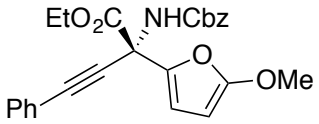


0.20 mmol scale: 85.3 mg, 83%, 91% ee (24 h)
4.80 mmol scale: 1.89 g, 77%, 91% ee (36 h)

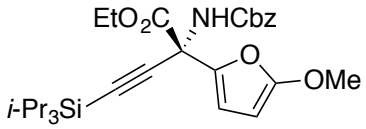
Standard conditions (0.20 mmol scale): To a well-dried pyrex Schlenk tube charged with activated MS 5Å (50 mg) under a nitrogen atmosphere were added catalyst (*R*)-**5b** (9.6 mg, 0.010 mmol) in dichloromethane (1.0 mL) and α-ketimino ester **1b** (83 mg, 0.20 mmol). The mixture was diluted with dichloromethane (1.0 mL) and cooled to –78 °C. 2-Methoxyfuran **2** (37 μL, 0.40 mmol) was added and the mixture was stirred at –78 °C for 24 h. To quench the reaction, silica gel (4 mL) was added to the mixture at –78 °C. The resultant silica gel was thoroughly washed with *n*-hexane and ethyl acetate (3:1, 200 mL) at room temperature. The filtrate was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give the product **3b** (85.3 mg, 83% yield). The catalyst could be recovered as some metal (Li, Na, K, Ca, etc.) salts of (*R*)-**5b** through the same silica gel column chromatography (eluent: $CHCl_3$:MeOH = 3:1) quantitatively. When the catalyst would be reused for the catalysis, the further purification with washing by 1 *M* HCl aqueous solution is necessary (>99% recovery). The enantiomeric purity of **3b** was determined by chiral HPLC analysis (91% ee).

Gram-scale synthesis: To a well-dried pyrex Schlenk tube charged with activated MS 5Å (50 mg) under a nitrogen atmosphere were added catalyst (*R*)-**5b** (230 mg, 0.24 mmol) in dichloromethane (14 mL) and α-ketimino ester **1b** (2.00 g, 4.8 mmol). The mixture was diluted with dichloromethane (34 mL) and cooled to –78 °C. 2-Methoxyfuran **2** (880 μL, 9.6 mmol) was added and the mixture was stirred at –78 °C for 36 h. To quench the reaction, silica gel (100 mL) was added to the mixture at –78 °C. The resultant silica gel was thoroughly washed with

n-hexane and ethyl acetate (3:1, 400 mL) at room temperature. The filtrate was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give the product **3b** (1.89 g, 77% yield). The catalyst could be recovered as some metal salts of (*R*)-**5b** through the same silica gel column chromatography (eluent: $CHCl_3$:MeOH = 3:1) quantitatively. When the catalyst would be reused for the catalysis, the further purification with washing by 1 *M* HCl aqueous solution is necessary (>99% recovery). The enantiomeric purity of **3b** was determined by chiral HPLC analysis (91% ee).



Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(5-methoxyfuran-2-yl)-4-phenylbut-3-ynoate (3a): 88% yield, 76% ee. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 6.8 Hz, 3H), 3.82 (s, 3H), 4.22-4.38 (m, 2H), 5.09 (d, *J* = 12.1 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.15 (d, *J* = 3.6 Hz, 1H), 6.21 (br, 1H), 6.60 (br, 1H), 7.28-7.39 (m, 8H), 7.46 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 56.6, 57.8, 63.6, 67.0, 80.8, 83.6, 84.6, 111.7, 122.1, 128.1 (3C), 128.2 (2C), 128.5 (2C), 128.8, 132.1 (2C), 136.2, 138.5, 154.0, 161.6, 167.0. IR (neat) 3409, 2979, 2936, 2906, 1734, 1615, 1576, 1490, 1369, 1260, 1022 cm^{-1}. $[\alpha]_D^{26}$ = –2.8 (*c* 1.00, $CHCl_3$, 76% ee (*S*)). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 1.0 mL/min, t_R = 15.9 min (major, *S*), 32.4 min (minor, *R*). HRMS (FAB+) calcd for $C_{25}H_{23}NNaO_6$ $[M+Na]^+$ 456.1423, found 456.1418.

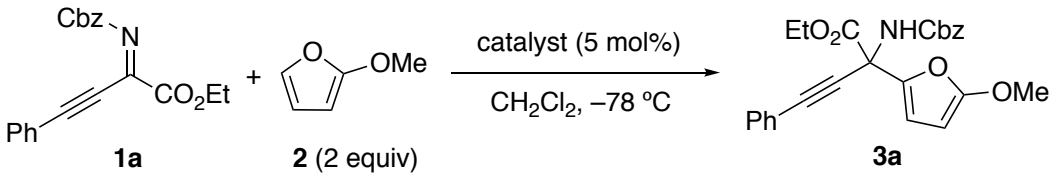


Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(5-methoxyfuran-2-yl)-4-(triisopropylsilyl)but-3-ynoate (3b): 83% yield, 91% ee. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 21H), 1.23 (t, *J* = 6.9 Hz, 3H), 3.80 (s, 3H), 4.15 (br, 1H), 4.31 (br, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 2.8 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 6.11 (br, 1H), 6.54 (br, 1H), 7.25-7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (3C), 13.9, 18.6 (6C), 56.5, 57.8, 63.4, 66.8, 80.8, 86.3, 100.7, 111.8, 128.0 (3C), 128.4 (2C), 136.4, 138.7, 153.6, 161.4, 166.9. IR (neat) 3418, 2943, 2176, 1746, 1614, 1574, 1470, 1369, 1257, 1019 cm^{-1}. $[\alpha]_D^{24}$ = –2.8 (*c* 1.00, $CHCl_3$, 91% ee (*S*)). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 9/1, 254 nm, 0.6 mL/min, t_R = 10.3 min (major, *S*), 12.0 min (minor, *R*). HRMS (FAB+) calcd for $C_{28}H_{39}NNaO_6Si$ $[M+Na]^+$ 536.2444, found 536.2437.

9. Screening of achiral catalysts in the probe reaction of 2 with 1a.

The screening of achiral catalysts in the probe reaction of **2** with **1a** is summarized in Table S1. The pK_a values of the acid compounds used here are generally available in the literature. The desired product **3a** was obtained in better yield and chemoselectivity by catalysts, particularly some carboxylic acids such as CHF_2CO_2H and CCl_3CO_2H (entries 3 and 4), with pK_a values of 2.5–6.5 in DMSO and 0.65–1.24 in H_2O. The pK_a range was comparable to the pK_a values of phosphoric acids (entries 10 and 11).

Table S1 Screening of the achiral catalysts in the probe reaction of **2** with **1a**.

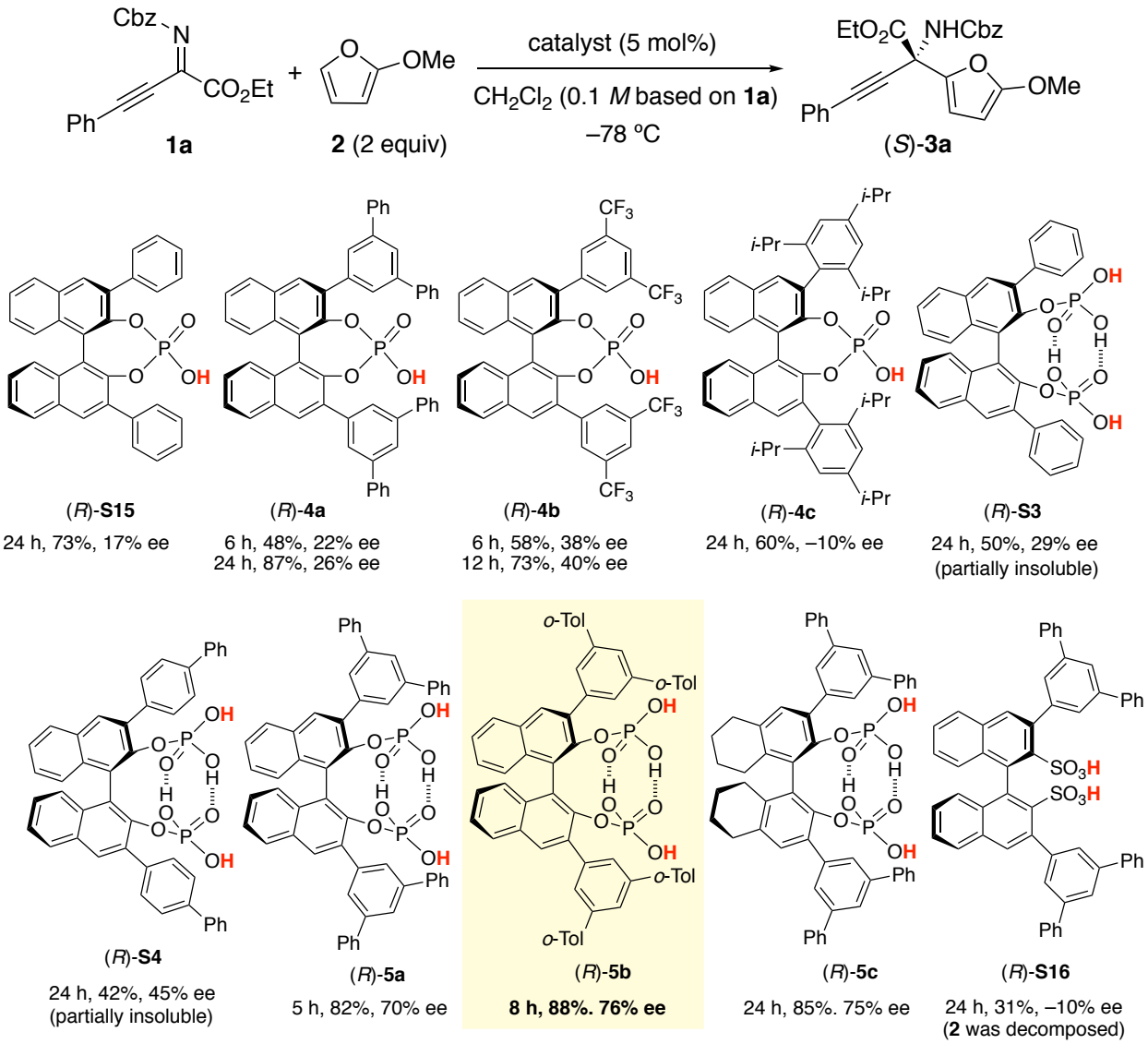


Entry	Catalyst	pK_a (calcd)[a]	pK_a in H_2O[b]	pK_a in DMSO	Reaction time (h)	Conversion (%)	Yield (%)
1	CH_3CO_2H	4.79	4.76	12.3[c]	24	0	0
2	CH_2BrCO_2H	2.73	2.86	–	24	13	13
3	CHF_2CO_2H	1.32	1.24	6.45[d]	24	56	52
4	CCl_3CO_2H	0.09	0.65	2.5[e]	24	>99	59
5	CF_3CO_2H	0.05	0.26	3.5[c]	12	>99	53
6	HCl[f]	–	–8.00	1.8[c]	3	>99	59
7	*p*-$CH_3C_6H_4SO_3H$	–0.43	–1.34	0.9[g]	12	>99	34
8	CF_3SO_3H	–3.91	–13.0	0.3[c]	6	>99	0
9	$(CF_3SO_2)_2NH$	–10.42	–	2.4[h]	3	>99	0
10	**$PhOP(=O)(OH)_2$**	1.25	1.42[i]	–	24	**51**	**49**
11	**$(PhO)_2P(=O)OH$**	1.12	0.26[j]	3.7[k]	24	**60**	**60**

[a] Data in SciFinder. Calculated using ACD/Labs Software V11.02. [b] D. Gryko, M. Zimnicka and R. Lipiński, *J. Org. Chem.*, 2007, **72**, 964. [c] F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456. [d] C. D. Ritchie and S. Lu, *J. Am. Chem. Soc.*, 1990, **112**, 7748. [e] H.-s. Kim, T. D. Chung and H. Kim, *J. Electroanal. Chem.*, 2001, **498**, 209. [f] 1 *M* HCl in diethyl ether was used as HCl source. [g] H. Kim, J. Gao and D. Burgessa, *J. Int. J. Pharm.*, 2009, **377**, 105. [h] C. Yang, X.-S. Xue, X. Li and J.-P. Cheng, *J. Org. Chem.*, 2014, **79**, 4340. [i] D. Shamir, I. Zilbermann, E. Maimon, A. I. Shames, H. Cohen and D. Meyerstein, *Inorg. Chim. Acta*, 2010, **363**, 2819. [j] F. Krašovec and J. Jan, *Croat. Chem. Acta*, 1963, **35**, 183. [k] P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Neudröfl, A. Berkessel and A. M. C. O'Donoghue, *Chem. Eur. J.*, 2011, **17**, 8524.

10. Screening of chiral catalysts in the probe reaction of 2 with 1a.

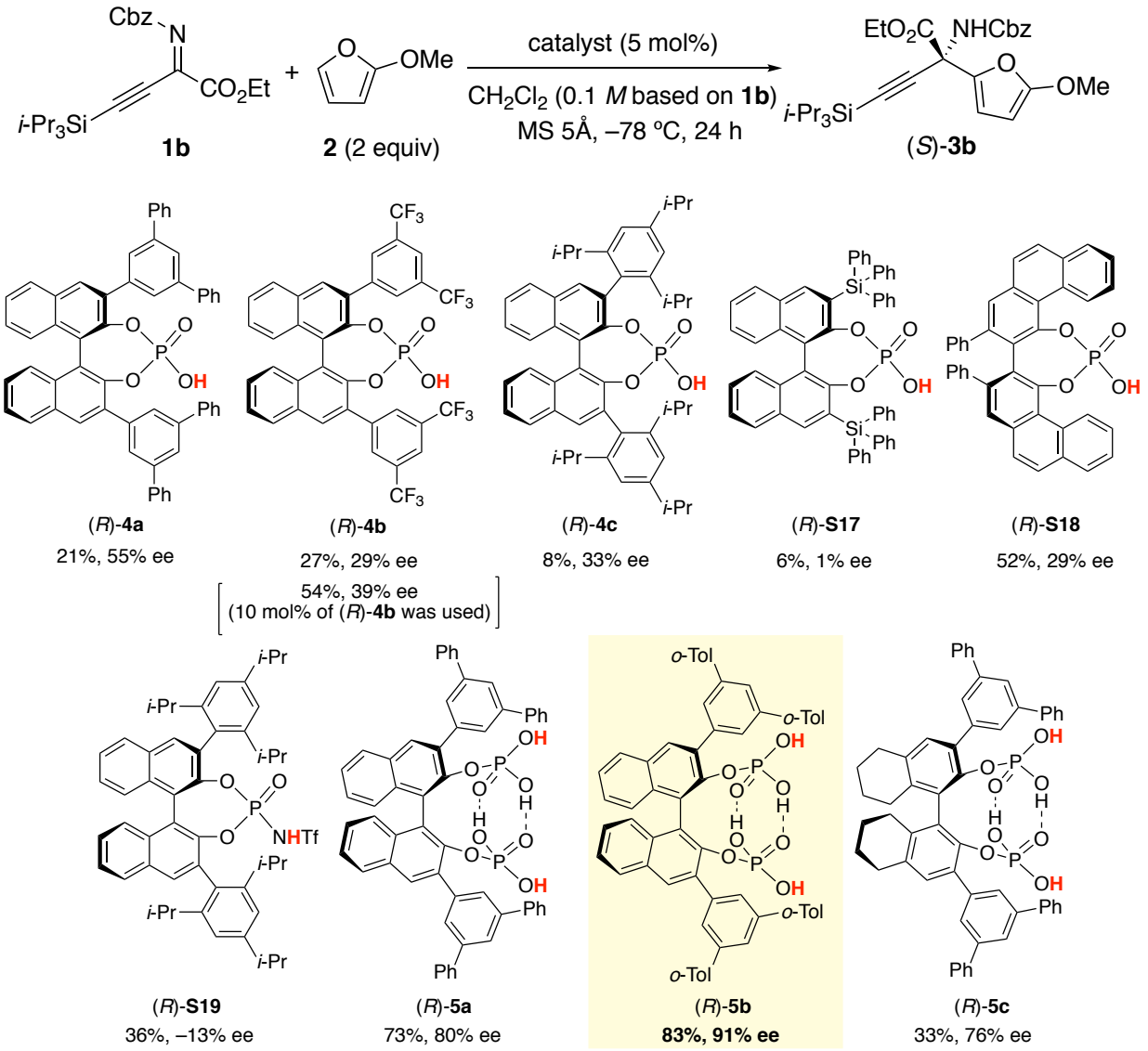
Screening of chiral catalysts in the probe reaction of **2** with **1a** is summarized in Scheme S1. The catalytic activities of conventional chiral phosphoric acids, such as (*R*)-**S15**,[9] (*R*)-**4a**,[10] and (*R*)-**4b**,[11] and (*R*)-**4c**[12] were moderate, but the enatio-induction were low. In contrast, bis(phosphoric acid)s (*R*)-**5a** and (*R*)-**5b** showed higher catalytic reactivities with high enantioselectivities, although sterically less hindered (*R*)-**S3** and (*R*)-**S4** showed low catalytic activities due to their low solubility. Less acidic (*R*)-**5c** did not provide better reactivity than (*R*)-**5a** or (*R*)-**5b**. Highly acidic chiral 3,3'-Ar_2-BINSA (*R*)-**S16**[13] gave a poor result, since significant amounts of byproducts were obtained due to the strong acidity of (*R*)-**S16**.



Scheme S1 Screening of the catalysts in the probe reaction of **2** with **1a**.

11. Screening of chiral catalysts in the probe reaction of 2 with 1b.

Substrate **1b** was much less reactive than **1a**. Therefore, the screening of chiral catalysts in the probe reaction of **2** with **1b** was examined again (Scheme S2). As a result, the catalytic activities of conventional chiral phosphoric acids (*R*)-**4a** and (*R*)-**4b** were low. An increase in the amount of (*R*)-**4b** from 5 mol% to 10 mol% slightly improved both the yield and the enantioselectivity. Moreover, chiral BINOL-derived phosphoric acids (*R*)-**4c** (i.e., TRIP) and (*R*)-**S17** were also quite inactive (<10% conversion). Chiral VAPOL-derived phosphoric acid (*R*)-**S18** moderately promoted the reaction but with low enantioselectivity. Chiral phosphoramide (*R*)-**S19** was also ineffective. Byproducts were obtained in the catalysis of (*R*)-**S18** (ca. 15% based on **1b**) and (*R*)-**S19** (ca. 20% based on **1b**). In contrast, bis(phosphoric acid)s (*R*)-**5a** and (*R*)-**5b** showed high yields with high enantioselectivities (up to 91% ee). In this reaction, less acidic (*R*)-**5c** gave a much lower yield and lower enantioselectivity (76% ee) than (*R*)-**5a** or (*R*)-**5b**. Based on these results, we selected (*R*)-**5b** as an optimized catalyst for this reaction.



Scheme S2 Screening of the catalysts in the probe reaction of **2** with **1b**.

12. Calculation of the electrostatic potential of phosphoric acids.

An effective approach to estimating molecular pK_a values from simple density functional calculations has been developed by Liu.[14] Various compounds show a strong correlation between experimental pK_a values and molecular electrostatic potential (MEP). As a result of their research, a linear relationship between the MEP and experimental pK_a values has been established. Therefore, we performed preliminary theoretical calculations using Spartan'10 for Macintosh from Wavefunction, Inc. (Fig. S5 and Table S2). The geometries of **S20–S26** were optimized with gradient-corrected density functional theory (DFT) calculations with B3LYP using the 6-31+G* basis set, after MMFF (molecular mechanics) and HF/3-21G (*ab initio* molecular orbital method) calculations. We first investigated the MEP values of simple compounds **S20** and **S21**, which have known pK_a values (pK_a = 0.26[15] for **S20** and 1.42[16] for **S21**). As a result, a higher MEP value was observed in **S20** than in **S21**, and our preliminary calculations for these model compounds may support a relationship between pK_a and MEP values.

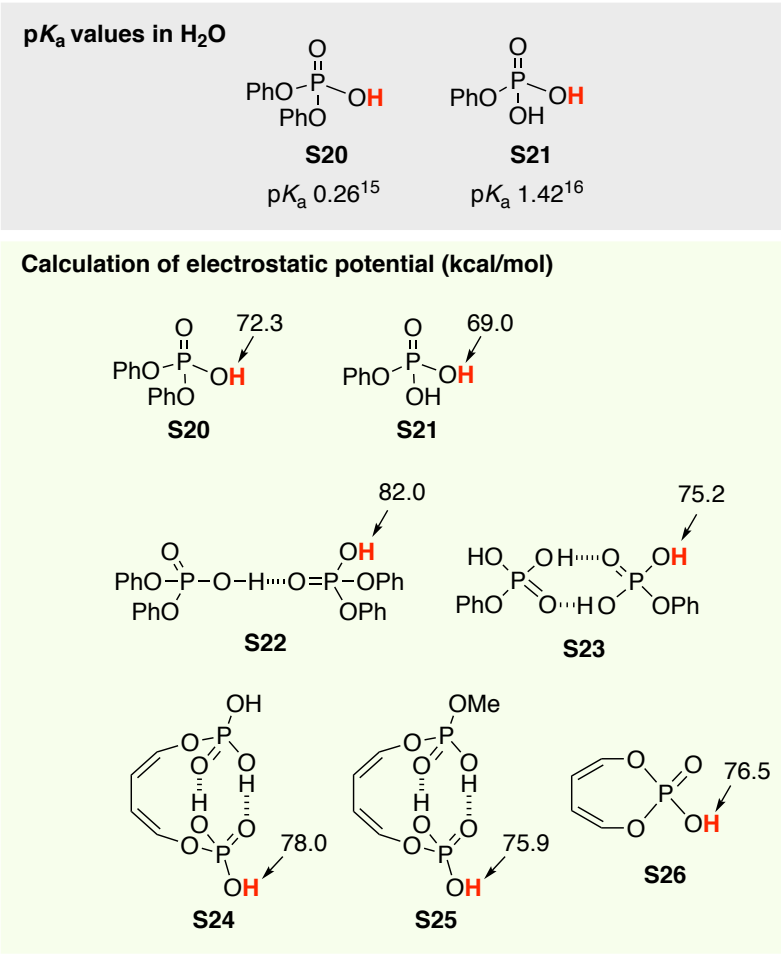


Fig. S5 Calculation of electrostatic potential (kcal/mol).

First, we investigated the effect of external hydrogen bonding in **S22** and **S23**, which involves one hydrogen bonding between two molecules of **S20** and two hydrogen bondings between two molecules of **S21**, respectively. Also, we observed a higher value of MEP (75.2 kcal/mol) for **S23** than for **S21** (69.0 kcal/mol). These results should clearly support the idea that appropriate hydrogen bonding between two molecules of phosphoric acids would increase the Brønsted acidity.

Next, we investigated the effect of two internal hydrogen bondings in **S24** as a simple model of (*R*)-**5**. As a result, we observed a higher value of MEP (78.0 kcal/mol) for cyclic **S24** than for acyclic **S23** (75.2 kcal/mol), although **S23** and **S24** have different ester moieties. Moreover, the MEP value for **S25** (75.9 kcal/mol) as a model of (*R*)-**10** was lower than that for **S24**. Moreover, the MEP value for **S26** (76.5 kcal/mol) as a model of (*R*)-**4** was lower than that for **S24** (78.0 kcal/mol). Accordingly, (*R*)-**5** might be expected to be more acidic than (*R*)-**4**, and (*R*)-**10** might be expected to be less acidic than (*R*)-**4** as shown in Fig. S6. It should be noted that the estimated order in Fig. S6 does not involve steric factors of the catalysts (also see Fig. S9).

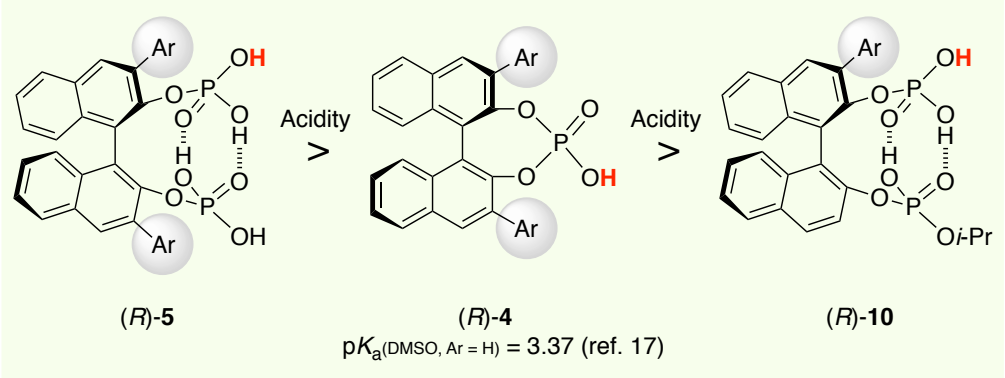


Fig. S6 Possible order of the strength of Brønsted acidity of (*R*)-**5**, (*R*)-**4**, and (*R*)-**10**.

Table S2 Summary of DFT calculation of **S20**–**S26** by using B3LYP/6-31+G*.

S20

```
Job type: Single point.
Method: RB3LYP
Basis set: 6-31+G*
Number of shells: 108
Number of basis functions: 349
Multiplicity: 1
Parallel Job: 4 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
SCF total energy:   -1106.2565201 hartrees
------------------------------------------------------------
Number   Atom     Charge   X(A)     Y(A)     Z(A)
1        P        0        -0.1230  -1.9290  0.0840
2        O        0        -1.0150  -2.7570  0.9210
3        O        0        0.7820   -2.7490  -0.9730
4        H        0        0.4900   -3.6740  -1.0280
5        O        0        -0.8030  -0.8630  -0.9230
```

6	O	0	0.9300	-1.0820	0.9590
7	C	0	-1.6920	0.1460	-0.5180
8	C	0	-3.4510	2.2030	0.1120
9	C	0	-2.7580	-0.1150	0.3430
10	C	0	-1.4910	1.4090	-1.0730
11	C	0	-2.3790	2.4380	-0.7550
12	C	0	-3.6340	0.9290	0.6570
13	H	0	-2.8950	-1.1080	0.7590
14	H	0	-0.6490	1.5710	-1.7390
15	H	0	-2.2290	3.4250	-1.1840
16	H	0	-4.4660	0.7380	1.3290
17	H	0	-4.1390	3.0070	0.3590
18	C	0	1.7690	-0.0460	0.5320
19	C	0	3.4810	2.0440	-0.1290
20	C	0	1.9280	1.0150	1.4220
21	C	0	2.4550	-0.0880	-0.6820
22	C	0	3.3100	0.9700	-1.0060
23	C	0	2.7890	2.0610	1.0860
24	H	0	1.3790	1.0090	2.3590
25	H	0	2.3310	-0.9280	-1.3560
26	H	0	3.8470	0.9450	-1.9510
27	H	0	2.9160	2.8910	1.7760
28	H	0	4.1510	2.8600	-0.3880

S21

Job type: Single point.
Method: RB3LYP
Basis set: 6-31+G*
Number of shells: 65
Number of basis functions: 208
Multiplicity: 1
Parallel Job: 4 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
SCF total energy: -799.9624168 hartrees

Number	Atom	Charge	X(A)	Y(A)	Z(A)
1	H	0	2.9260	-2.1460	0.0000
2	C	0	2.4020	-1.2080	0.0000
3	C	0	1.0520	1.2170	0.0000
4	C	0	1.0200	-1.1910	0.0000
5	C	0	3.1100	-0.0130	0.0000
6	C	0	2.4390	1.1960	0.0000
7	C	0	0.3400	0.0250	0.0000
8	H	0	0.4730	-2.1160	0.0000
9	H	0	4.1860	-0.0300	0.0000
10	H	0	2.9890	2.1200	0.0000
11	H	0	0.5220	2.1520	0.0000
12	P	0	-1.4480	0.1060	0.0000
13	O	0	-2.0390	1.4380	0.0000
14	O	0	-1.8790	-0.7790	-1.2560
15	H	0	-2.5920	-0.3810	-1.7420
16	O	0	-1.8790	-0.7790	1.2560
17	H	0	-2.5920	-0.3810	1.7420

S22

Job type: Single point.
Method: RB3LYP
Basis set: 6-31+G*
Number of shells: 216
Number of basis functions: 698
Multiplicity: 1
Parallel Job: 4 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
SCF total energy: -2212.5169304 hartrees

Number	Atom	Charge	X(A)	Y(A)	Z(A)
1	P	0	2.6350	1.0200	0.1910
2	O	0	1.2380	0.9950	-0.1950
3	O	0	3.5540	0.7700	-1.0590

4	O	0	3.0820	0.0130	1.3200
5	C	0	4.9370	0.7760	-1.0970
6	C	0	7.6870	0.7430	-1.2990
7	C	0	5.6210	1.9700	-1.0960
8	C	0	5.5960	-0.4310	-1.2100
9	C	0	6.9800	-0.4420	-1.3100
10	C	0	7.0050	1.9450	-1.1940
11	H	0	5.0790	2.8930	-1.0250
12	H	0	5.0300	-1.3390	-1.2280
13	H	0	7.5010	-1.3770	-1.4010
14	H	0	7.5470	2.8690	-1.1930
15	H	0	8.7600	0.7310	-1.3770
16	C	0	2.8490	-1.3630	1.3760
17	C	0	2.4940	-4.0830	1.5970
18	C	0	3.9450	-2.1660	1.6700
19	C	0	1.5790	-1.8820	1.2010
20	C	0	1.4110	-3.2560	1.3080
21	C	0	3.7580	-3.5340	1.7810
22	H	0	4.9150	-1.7190	1.8080
23	H	0	0.7370	-1.2560	0.9820
24	H	0	0.4240	-3.6600	1.1630
25	H	0	4.6020	-4.1680	2.0110
26	H	0	2.3550	-5.1470	1.6810
27	O	0	3.1360	2.3680	0.8330
28	H	0	3.4640	2.2820	1.7290
29	P	0	-2.1720	-0.2450	-0.3530
30	O	0	-1.5590	-1.4360	0.2070
31	O	0	-2.7930	0.6400	0.8100
32	O	0	-3.3570	-0.4720	-1.3760
33	C	0	-4.4310	-1.3140	-1.1620
34	C	0	-6.6250	-2.9570	-0.8600
35	C	0	-5.6940	-0.7540	-1.1310
36	C	0	-4.2420	-2.6820	-1.0460
37	C	0	-5.3500	-3.4990	-0.8920
38	C	0	-6.7930	-1.5840	-0.9800
39	H	0	-5.8050	0.3110	-1.2270
40	H	0	-3.2490	-3.0860	-1.0680
41	H	0	-5.2120	-4.5630	-0.8000
42	H	0	-7.7790	-1.1550	-0.9570
43	H	0	-7.4800	-3.5980	-0.7420
44	C	0	-3.4230	1.8580	0.7920
45	C	0	-4.7220	4.2930	0.9770
46	C	0	-3.8920	2.2970	2.0220
47	C	0	-3.5950	2.6230	-0.3510
48	C	0	-4.2480	3.8400	-0.2440
49	C	0	-4.5380	3.5130	2.1110
50	H	0	-3.7410	1.6780	2.8880
51	H	0	-3.2230	2.2910	-1.3010
52	H	0	-4.3800	4.4360	-1.1300
53	H	0	-4.8990	3.8510	3.0680
54	H	0	-5.2250	5.2400	1.0460
55	O	0	-1.2800	0.7000	-1.2110
56	H	0	-0.3690	0.7970	-0.9080

S23

Job type: Single point.
Method: RB3LYP
Basis set: 6-31+G*
Number of shells: 140
Number of basis functions: 454
Multiplicity: 1
Parallel Job: 4 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
SCF total energy: -1750.4488325 hartrees

Number	Atom	Charge	X(A)	Y(A)	Z(A)
1	P	0	1.5770	-1.9200	-0.4720
2	O	0	0.4630	-2.5520	-1.2420
3	O	0	1.8260	-0.4240	-0.9930
4	O	0	3.0190	-2.5960	-0.6880
5	H	0	3.0550	-3.4960	-0.3260
6	O	0	1.4060	-1.9070	1.1020
7	H	0	0.4680	-1.6450	1.3590

8	C	0	2.5410	0.5420	-0.2660
9	C	0	3.9180	2.5380	1.0700
10	C	0	1.8620	1.3210	0.6670
11	C	0	3.8890	0.7390	-0.5500
12	C	0	4.5770	1.7470	0.1280
13	C	0	2.5640	2.3230	1.3370
14	H	0	0.8100	1.1370	0.8580
15	H	0	4.3780	0.1110	-1.2870
16	H	0	5.6290	1.9120	-0.0840
17	H	0	2.0480	2.9370	2.0700
18	H	0	4.4570	3.3220	1.5950
19	P	0	-2.2670	-1.3620	0.5890
20	O	0	-1.0600	-1.0710	1.4150
21	O	0	-3.2200	-2.4420	1.2970
22	H	0	-3.8800	-2.8080	0.6850
23	O	0	-2.0180	-1.8620	-0.8900
24	O	0	-3.2780	-0.1140	0.4320
25	C	0	-2.8180	1.1150	-0.0700
26	C	0	-2.0290	3.5920	-1.0320
27	C	0	-2.6640	1.2900	-1.4430
28	C	0	-2.5880	2.1510	0.8320
29	C	0	-2.1920	3.3960	0.3410
30	C	0	-2.2640	2.5400	-1.9190
31	H	0	-2.8490	0.4590	-2.1140
32	H	0	-2.7220	1.9720	1.8940
33	H	0	-2.0100	4.2120	1.0340
34	H	0	-2.1350	2.6870	-2.9880
35	H	0	-1.7190	4.5630	-1.4090
36	H	0	-1.0600	-2.1530	-1.0730

S24

Job type: Single point.
Method: RB3LYP
Basis set: 6-31+G*
Number of shells: 88
Number of basis functions: 290
Multiplicity: 1
Parallel Job: 4 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
SCF total energy: -1441.9200909 hartrees

Number	Atom	Charge	X(A)	Y(A)	Z(A)
1	C	0	-1.5540	-0.3740	1.9070
2	H	0	-2.4840	-0.9310	1.9650
3	C	0	-0.6370	-0.3640	2.8830
4	H	0	-0.8950	-0.9190	3.7830
5	C	0	0.6370	0.3640	2.8830
6	H	0	0.8950	0.9190	3.7830
7	C	0	1.5540	0.3740	1.9070
8	H	0	2.4840	0.9310	1.9650
9	O	0	1.4150	-0.4330	0.7910
10	O	0	-1.4150	0.4330	0.7910
11	P	0	1.8230	-0.0380	-0.7180
12	O	0	1.2420	1.2490	-1.2150
13	P	0	-1.8230	0.0380	-0.7180
14	O	0	-1.2420	-1.2490	-1.2150
15	O	0	-1.4370	1.3560	-1.4980
16	H	0	-0.4420	1.4850	-1.4950
17	O	0	-3.4310	0.0260	-0.6950
18	H	0	-3.7890	-0.6530	-1.2920
19	O	0	3.4310	-0.0260	-0.6950
20	H	0	3.7890	0.6530	-1.2920
21	O	0	1.4370	-1.3560	-1.4980
22	H	0	0.4420	-1.4850	-1.4950

S25

Job type: Single point.
Method: RB3LYP
Basis set: 6-31+G*
Number of shells: 97
Number of basis functions: 313

```
Multiplicity: 1
Parallel Job: 4 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
SCF total energy:   -1481.2250368 hartrees
```

Number	Atom	Charge	X(A)	Y(A)	Z(A)
1	C	0	-0.2400	2.9900	0.4210
2	H	0	-0.1970	3.8860	1.0390
3	C	0	-1.4760	2.7510	-0.3360
4	H	0	-1.9010	3.5910	-0.8840
5	C	0	0.8700	2.2430	0.3970
6	H	0	1.7550	2.4700	0.9840
7	C	0	-2.1880	1.6190	-0.3600
8	H	0	-3.1030	1.4990	-0.9320
9	O	0	1.0000	1.1770	-0.4760
10	O	0	-1.8500	0.5440	0.4450
11	P	0	1.6700	-0.2480	-0.1260
12	O	0	1.2040	-0.8530	1.1630
13	P	0	-1.9250	-1.0170	0.0580
14	O	0	-1.2860	-1.3760	-1.2480
15	O	0	-3.5000	-1.3450	0.0880
16	H	0	-3.7390	-2.0100	-0.5800
17	O	0	-1.3420	-1.6860	1.3620
18	H	0	-0.3650	-1.4740	1.4510
19	O	0	1.3850	-1.0810	-1.4430
20	H	0	0.4100	-1.2960	-1.5260
21	O	0	3.2340	0.0700	-0.1680
22	C	0	4.1870	-0.9160	0.2930
23	H	0	3.9330	-1.2420	1.3060
24	H	0	5.1550	-0.4160	0.2840
25	H	0	4.2000	-1.7690	-0.3910

S26

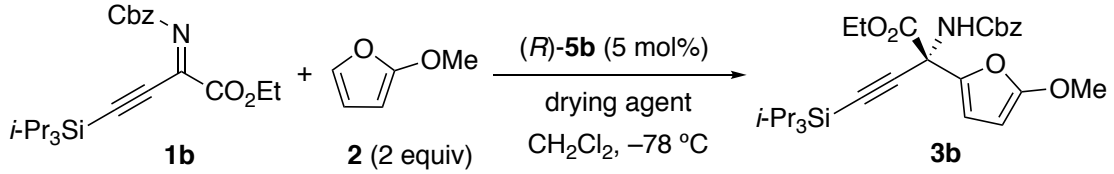
```
Job type: Single point.
Method: RB3LYP
Basis set: 6-31+G*
Number of shells: 56
Number of basis functions: 185
Multiplicity: 1
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
SCF total energy:    -797.7340994 hartrees
```

Number	Atom	Charge	X(A)	Y(A)	Z(A)
1	C	0	-2.1770	0.7520	-0.1110
2	H	0	-3.0770	1.2520	-0.4610
3	C	0	-2.2210	-0.6930	0.0810
4	H	0	-3.1650	-1.1450	0.3760
5	C	0	-1.1090	1.5270	0.1290
6	H	0	-1.0900	2.6000	-0.0280
7	C	0	-1.1820	-1.5220	-0.0980
8	H	0	-1.2240	-2.5950	0.0550
9	O	0	0.0570	1.0620	0.7170
10	O	0	0.0360	-1.1110	-0.6160
11	P	0	1.0430	-0.0640	0.0970
12	O	0	2.0100	-0.5680	1.0890
13	O	0	1.6950	0.5900	-1.2250
14	H	0	2.6560	0.6850	-1.1160

13. Optimization of the concentration, drying agents, solvents, and substrates in the reaction of 2 with 1.

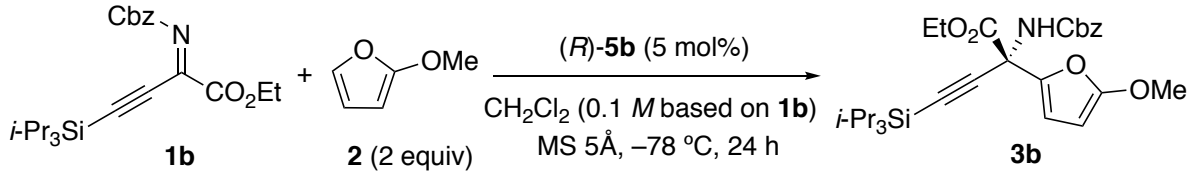
The effects of the concentration of substrate **1b** and drying agents were examined (Table S3). As a result, 0.1 *M* (based on **1b**) conditions showed better enantioselectivity than 0.05 *M* and 0.2 *M* (entries 1–3). The drying agent used did not significantly affect the enantioselectivity, but did affect the reactivity (i.e., the reaction time for full conversion) and chemoselectivity for unknown byproducts, which might be triggered by the reaction of water with **1b** and/or **2** (entries 4–7). As a result, MS 5Å was better than MS 3Å, MS 4Å, and $MgSO_4$. Next, the general solvent effect was examined (Table S4). As a result, polar solvents were not suitable at all, and dichloromethane was much better than the other solvents tested. The reaction temperature was also examined (entries 7–9), and a lower temperature gave higher enantioselectivity (92–94% ee), although the yields were decreased (46–52%).

Table S3 Effect of molecular sieves and concentration of substrate **1b**.



Entry	Drying agent	Concentration (*M*) based on **1b**	Reaction time (h)	Yield (%)	ee (%)
1	–	0.05	12	87	84
2	–	**0.1**	17	**72**	**90**
3	–	0.2	12	68	88
4	MS 3Å	0.1	48	85	89
5	MS 4Å	0.1	24	74	89
6	**MS 5Å**	**0.1**	24	**83**	**91**
7	$MgSO_4$	0.1	24	59	89

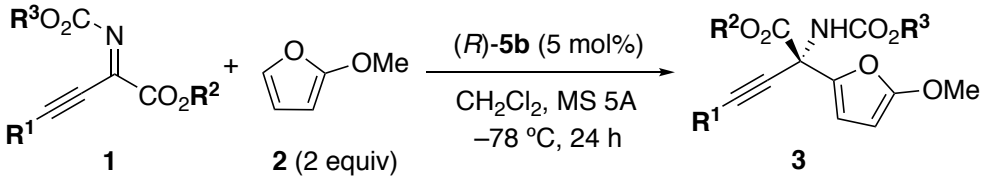
Table S4 Effect of solvents and temperature.



Entry	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)	ee (%)
1	Et_2O	–78	24	0	–
2	EtOAc	–78	24	0	–
3	$EtNO_2$	–78	24	0	–
4	EtCN	–78	24	0	–
5	toluene	–78	24	35	9
6	**CH_2Cl_2**	**–78**	24	**83**	**91**
7	CH_2Cl_2	–60	14	78	76
8	CH_2Cl_2	–90	48	52	92
9	CH_2Cl_2	–95	48	46	94

Next, β,γ-alkynyl-α-imino esters **1** were optimized with the use of (*R*)-**5b** (Table S5). To avoid the effect of adventitious water, which might react with **1** and **2** to give undesired products, powdered MS 5Å was used as a drying agent. As a result, the reaction of **2** with **1a** (R^1 = Ph CO_2R^2 = CO_2Et, CO_2R^3 = Cbz) proceeded smoothly, and a slightly better result (88% yield and 76% ee) was observed (entry 1). Next, we changed the terminal R^1 group of the acetylene from a Ph group to sterically hindered silyl groups (entries 2–6). As a result, the enantioselectivity of the corresponding product **3** was improved according to the bulkiness of the silyl group (also see a possible transition state on page S72). Ultimately, when we used **1b** (R^1 = *i*-Pr_3Si, CO_2R^2 = CO_2Et, CO_2R^3 = Cbz) with a bulky *i*-Pr_3Si group, **3b** was obtained in 83% yield with 91% ee (entry 6). The ester groups CO_2R^2 and C=NCO_2R^3 in **1** were also optimized. However, we did not find better ester groups to replace CO_2Et for CO_2R^2 and Cbz for CO_2R^3 (entries 7–10). Based on these results, we selected **1b** (R^1 = *i*-Pr_3Si, CO_2R^2 = CO_2Et, CO_2R^3 = Cbz) as an optimized catalyst for this reaction.

Table S5 Screening of substrates.[a]

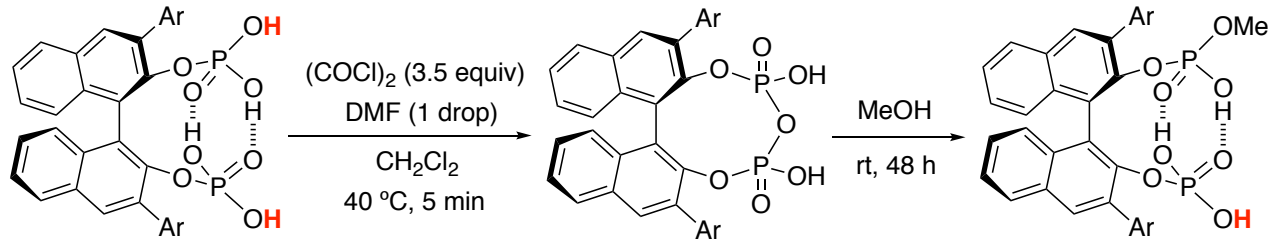


1 **2** (2 equiv) **3**

Entry	R^1	CO_2R^2	CO_2R^3	Yield (%)	ee (%)
1[b]	Ph	CO_2Et	CO_2Bn (Cbz)	88	76
2	Et_3Si	CO_2Et	Cbz	82	85
3	Ph_3Si	CO_2Et	Cbz	89	79
4	*t*-BuMe_2Si	CO_2Et	Cbz	88	82
5	*t*-BuPh_2Si	CO_2Et	Cbz	76	88
6[c]	***i*-Pr_3Si**	**CO_2Et**	**Cbz**	**83**	**91**
7	*i*-Pr_3Si	CO_2Et	CO_2Me	39	88
8	*i*-Pr_3Si	CO_2Et	CO_2*t*-Bu (Boc)	33	57
9	*i*-Pr_3Si	CO_2Me	Cbz	80	83
10	*i*-Pr_3Si	Cbz	Cbz	91	86

[a] The reaction was carried out with (*R*)-**5b** (5 mol%), **1** (1 equiv), and **2** (2 equiv) in dichloromethane (0.1 *M* based on **1**) at –78 °C for 24 h. [b] **1a**/**3a** system. Reaction time was 6 h. [c] **1b**/**3b** system. Reaction time was 6 h

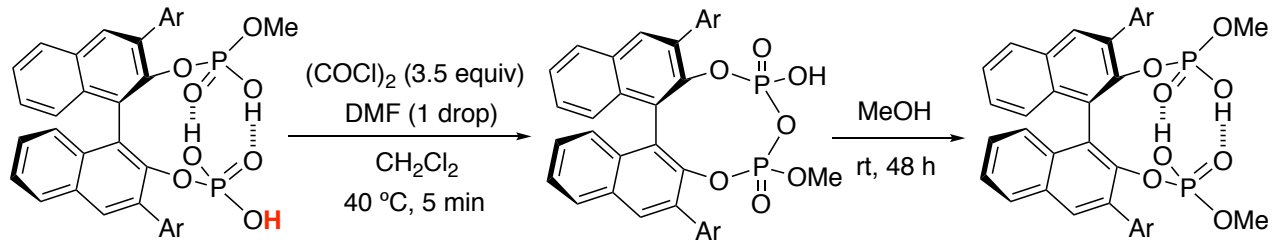
14. Preparation of (*R*)-6 (Scheme 1).



(*R*)-**5b** (Ar = 3,5-(*o*-Tol)$_2$C$_6$H$_3$) (*R*)-**S27** (*R*)-**6a**

To a solution of (*R*)-**5b** (9.6 mg, 0.010 mmol) in dichloromethane (0.2 mL), one drop of *N*,*N*-dimethylformamide was added at room temperature. Then oxalyl chloride (3.0 μL, 0.035 mmol) was added at room temperature, and the mixture was warmed to 40 °C. The mixture was stirred at 40 °C for 5 min. Volatiles were removed *in vacuo* under heat conditions (ca. 40–50 °C). The obtained product (*R*)-**S27** would be used in the next step without further purification. (*R*)-**S27** was dissolved in methanol (2 mL) and the solution was stirred at room temperature for 4 h. Excess mthanol was then removed *in vacuo*. The obtained product was dissolved in toluene (2 mL), and the volatiles were thoroughly removed under reduced pressure to give pure (*R*)-**6a** as white-yellow solid (>99%, 9.7 mg). A trace amount of DMF remained.

Methyl ester (*R*)-6a: ^{1}H NMR (400 MHz, THF-d_8) 2.38 (s, 6H), 2.39 (s, 6H), 3.15 (d_{H-P}, J = 11.5 Hz, 3H), 4.84 (br, 3H), 7.16-7.40 (m, 20H), 7.43-7.49 (m, 2H), 7.54 (t, J = 8.7 Hz, 2H), 7.60 (t, J = 2.3 Hz, 4H), 7.98 (d, J = 8.2 Hz, 2H), 8.13 (s, 1H), 8.15 (s, 1H). ^{13}C NMR (100 MHz, THF-d_8) Many peaks were overlapped. δ 20.8 (2C), 20.9 (2C), 54.2 (d, J_{C-P} = 5.7 Hz), 125.4, 125.9, 126.5-126.8 (m, 8C), 127.6 (2C), 127.9 (2C), 128.1 (2C), 129.0 (2C), 129.8, 129.9, 130.6 (8C), 131.0 (2C), 131.1 (2C), 132.3, 132.4, 132.7 (2C), 133.4, 133.6, 136.2 (2C), 136.4 (3C), 136.5, 139.3 (2C), 142.2 (2C), 142.4 (2C), 142.6 (2C), 143.0 (2C), 146.7 (d, J_{C-P} = 7.6 Hz), 147.2 (d, J_{C-P} = 5.7 Hz) [Contamination of a trace amount of acetone (δ 30.2) through the ^{13}C NMR analysis.]. ^{31}P NMR (160 MHz, THF-d_8) δ –0.27, 0.75. IR (KBr) 3448, 2924, 2854, 1593, 1492, 1450, 1398, 1239, 1188, 1058 cm^{-1}. M.p. 142 °C (decomposition). $[\alpha]_D^{23}$ = +189.6 (*c* 1.00, $CHCl_3$). HRMS (ESI–) calcd for $C_{61}H_{49}O_8P_2$ $[M-H]^-$ 971.2908, found 971.2911.



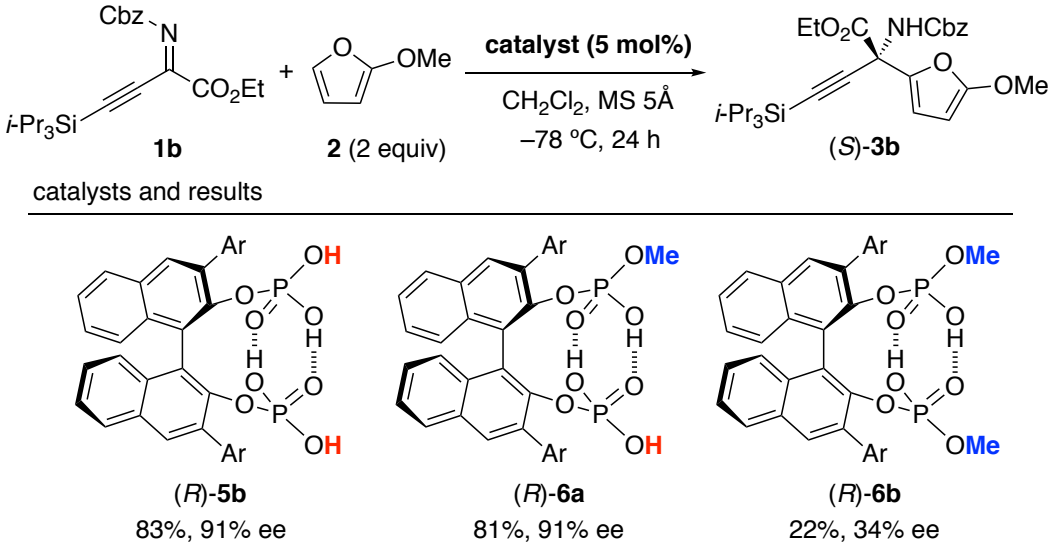
(*R*)-**6a** (Ar = 3,5-(*o*-Tol)$_2$C$_6$H$_3$) (*R*)-**S28** (*R*)-**6b**

To a solution of (*R*)-**6a** (97.3 mg, 0.10 mmol) in dichloromethane (2 mL), three drops of *N*,*N*-dimethylformamide was added at room temperature. Then oxalyl chloride (15 μL, 0.175 mmol) was added at room temperature, and the mixture was warmed to 40 °C. The mixture was

stirred at 40 °C for 5 min. Then oxalyl chloride (15 μL, 0.175 mmol) was added at room temperature, and the mixture was warmed to 40 °C. The mixture was stirred at 40 °C for 5 min. Volatiles were removed *in vacuo* under heat conditions (ca. 40–50 °C). The obtained product (*R*)-**S28** would be used in the next step without further purification. (*R*)-**S28** was dissolved in mixed solvent of dichloromethane (2 mL) and methanol (4 ml) the solution was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: $CHCl_3$:MeOH = 8:1 to 1:1) to give (*R*)-**6b**, which would be contaminated with alkali and alkali earth metal ions. The obtained (*R*)-**6b** was dissolved in dichloromethane, and throughly washed with 1 *M* HCl aqueous solution, and the organic phase was separated. After the removal of volatiles under reduced pressure, the residue was dissolved in toluene, and the volatiles were thoroughly removed under reduced pressure to give pure (*R*)-**6b** as white-yellow solid (87%, 86.1 mg).

Dimethyl ester (*R*)-6b: ^{1}H NMR (400 MHz, THF-d_8) δ 2.40 (s, 12H), 3.10 ($d_{H–P}$, J = 11.5 Hz, 6H), 4.19 (br, 2H), 7.19-7.30 (m, 12H), 7.32-7.43 (m, 8H), 7.47 (t, J = 7.8 Hz, 2H). 7.57 (d, J = 8.7 Hz, 2H), 7.61 (s, 4H), 7.98 (d, J = 7.8 Hz, 2H), 8.15 (s, 2H). ^{13}C NMR (100 MHz, THF-d_8) δ 20.9 (4C), 54.3 (d, $J_{C–P}$ = 4.8 Hz, 2C), 125.6 (2C), 126.6 (4C), 126.7 (2C), 126.9 (2C), 127.7 (2C), 128.1 (4C), 129.0 (2C), 130.0 (2C), 130.5 (4C), 130.6 (4C), 131.1 (4C), 132.6 (2C), 132.7 (2C), 133.5 (2C), 136.2 (6C), 139.3 (2C), 142.4 (4C), 142.7 (4C), 146.5 (d, $J_{C–P}$ = 6.7 Hz, 2C) [Contamination of a trace amount of acetone (δ 30.2) through the ^{13}C NMR analysis.]. ^{31}P NMR (160 MHz, THF-d_8) δ –1.4. IR (KBr) 3433, 2953, 2927, 2853, 1593, 1492, 1450, 1400, 1241, 1187, 1151, 1060 cm^{-1}. M.p. 140 °C (decomposition). $[\alpha]_D^{22}$ = +212.4 (*c* 1.00, $CHCl_3$). HRMS (ESI–) calcd for $C_{62}H_{51}O_8P_2$ $[M–H]^-$ 985.3065, found 985.3065.

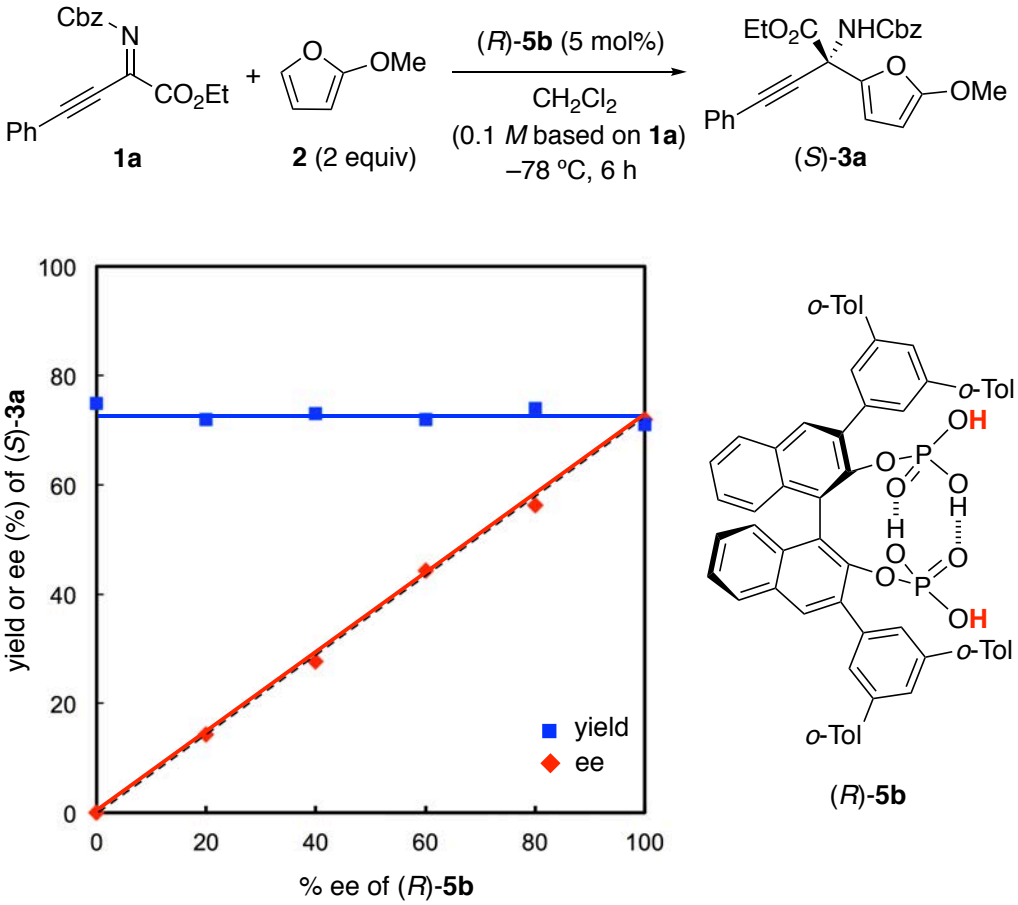
Summary of the reaction with the use of (*R*)-**5b**, (*R*)-**6a**, and (*R*)-**6b** is shown in Scheme S3.



Scheme S3 Role of Brønsted acid in the catalysts.

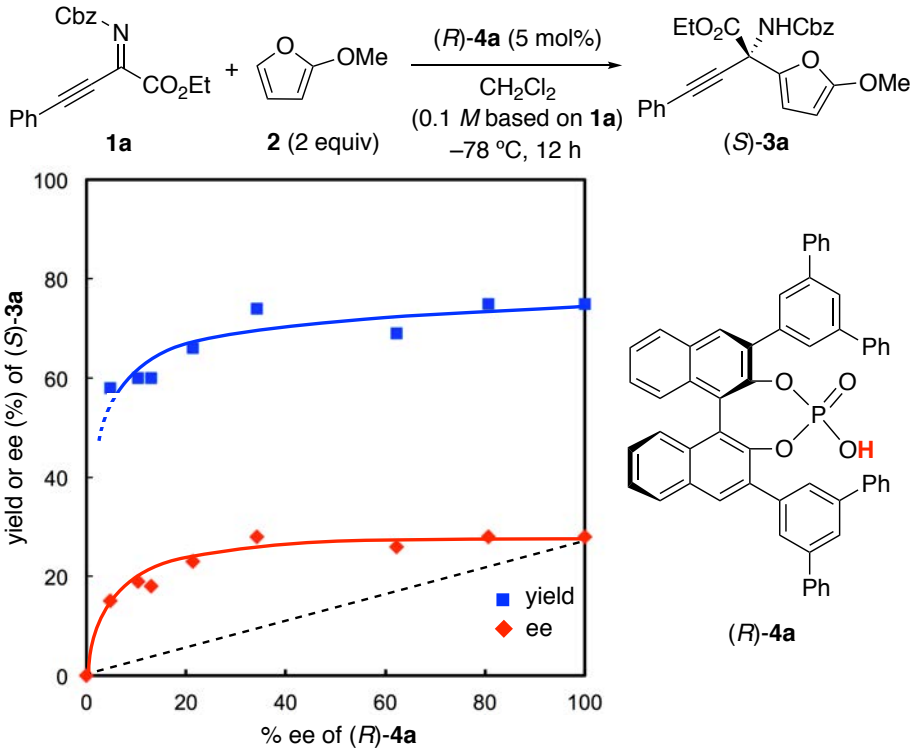
15. Non-linear effect in the reaction of 2 with 1a (Fig. 3).

The presence of a non-linear effect was examined in the reaction of 2-methoxyfuran **2** (0.80 mmol) with α-ketimino ester **1a** (0.40 mmol) in the presence of (*R*)-**5b** (5 mol%, 0% ee to 100% ee) in dichloromethane (0.1 *M* based on **1a**) at –78 °C for 6 h. As shown in Scheme S4, a non-linear effect was not observed. Moreover, the yields of (*S*)-**3a** were independent of the enantiopurity of (*R*)-**5b**, and (*S*)-**3a** was obtained in a consistent yield of 71–75%. Therefore, a possible active species might be the monomeric structure of (*R*)-**5b**.

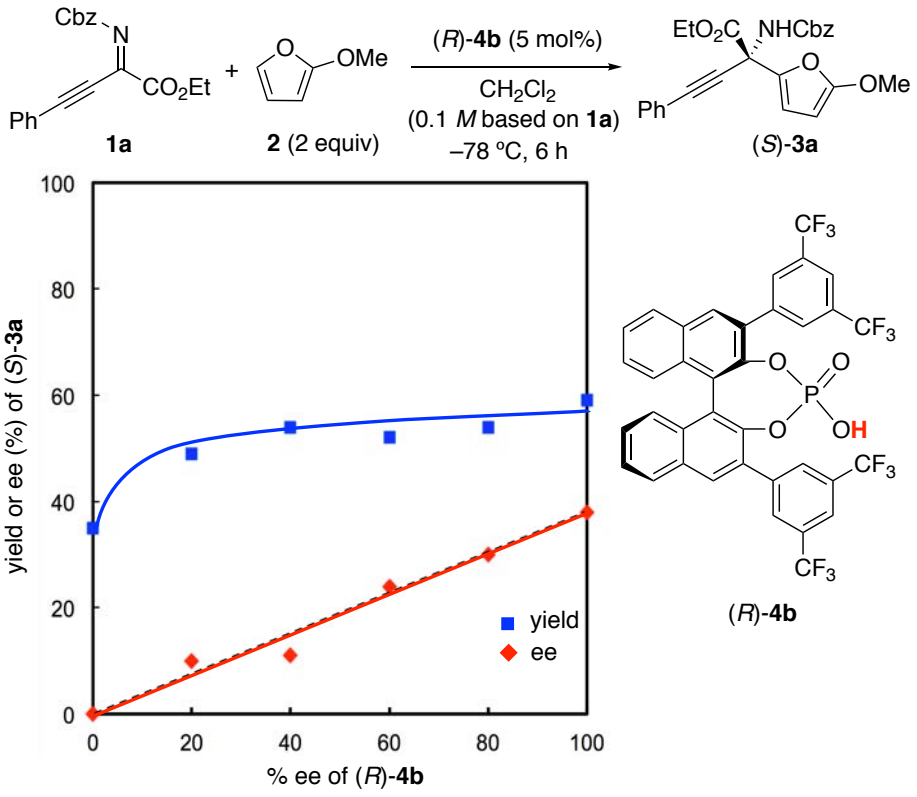


Scheme S4 Plot of the yield (%) and ee of (*S*)-**3a** vs. ee of (*R*)-**5b**.

We also examined the reaction of **2** with **1a** in the presence of (*R*)-**4a** or (*R*)-**4b** (5 mol%, 0% ee to 100% ee) in dichloromethane (0.1 *M* based on **1a**) at –78 °C (Schemes S5 and S6). The reaction time was 12 h for (*R*)-**4a** catalysis, and 6 h for (*R*)-**4b** catalysis. As shown in Scheme S5, a positive non-linear effect was observed for (*R*)-**4a**-catalysis. This result strongly suggests that (*R*)-**4a**-catalysis might involve the dimeric structure of (*R*)-**4a**. In contrast, as shown in Scheme S6, a non-linear effect was not observed for (*R*)-**4b**-catalysis. This result strongly suggests again that a possible active species might be the monomeric structure of (*R*)-**4b**. The P=O moiety of (*R*)-**4b** is much less basic than (*R*)-**4a**, and therefore, the dimeric structure might not be involved in (*R*)-**4b** catalysis.



Scheme S5 Plot of the yield (%) and ee of (*S*)-**3a** vs. ee of (*R*)-**4a**.



Scheme S6 Plot of the yield (%) and ee of (*S*)-**3a** vs. ee of (*R*)-**4b**.

16. ESI-MS analysis of catalysts.

[Preparation of the samples for S20 (Fig. S7a), (*R*)-S15 (Fig. S7b), and (*R*)-S3 (Fig. S7c)] Acid (0.01 mmol) was dissolved in dichloromethane (200 μL) in a test tube at room temperature. After 30 min, 20 μL of the resulting solution was diluted with mixed solvent of dichloromethane (80 μL), methanol (50 μL) and acetonitrile (50 μL) in a test tube (final concentration: 5.0 m*M*), and passed through a membrane filter (200 mm mesh) just before injection. The spectra are shown in Figs. S5a–c.

[Preparation of the samples for (*R*)-S3 (Fig. S7d), (*R*)-5b (Fig. S7e), (*R*)-10c (Fig. S7f)] Acid (0.01 mmol) was dissolved in dichloromethane (200 μL) in a test tube at room temperature. After 30 min, 20 μL of the resulting solution was diluted with dichloromethane (180 μL) in a test tube (final concentration: 5.0 m*M*), and passed through a membrane filter (200 mm mesh) just before injection. The spectra are shown in Figs. S5d–f.

Since **S20** and (*R*)-**S15** could not be detected in less polar solvents such as dichloromethane probably due to the inherent ionization problem with **S20** and (*R*)-**S15**, we first used polar solvents. As a result, the ESI-MS (negative) analysis of **S20** in CH_2Cl_2/MeOH/CH_3CN = 2/1/1, as shown in Fig. S7a, clearly suggests that **S20** would not be a monomer. Instead, a dimer, trimer, tetramer, 5-mer, and 6-mer were observed under polar solvent conditions. (*R*)-**S15** as shown in Figs. S5b would be a monomer, but a dimer, trimer, and tetramer were also observed as major species. In sharp contrast, the population of dimer, trimer, and tetramer of (*R*)-**S3** in CH_2Cl_2/MeOH/CH_3CN = 2/1/1 was reduced, as shown in Fig. S7c. Next, we used CH_2Cl_2 alone for highly soluble (*R*)-**S3**, as shown in Fig. S7d. As a result, a trimer and tetramer were not observed and the population of dimer was greatly decreased. Less polar solvents might be favored for hydrogen bonding, and the intramolecular double hydrogen bond network might be maintained under CH_2Cl_2 solvent conditions. Moreover, much more sterically hindered (*R*)-**5b** and (*R*)-**10c** in CH_2Cl_2 gave spectra (Figs.S5e and S5f) that were quite similar to that in Fig. S7d. Overall, this ESI-MS analysis suggests that bis(phosphoric acid)s, such as (*R*)-**S3**, (*R*)-**5b**, (*R*)-**10c**, would remain mostly as a monomer, whereas phosphoric acids, such as **S20** and (*R*)-**S15**, would easily exhibit dimer, trimer, and tetramer forms. Overall, Fig. S8 summarizes the possible aggregation of the catalysts **S20**, (*R*)-**S15**, (*R*)-**5b**, and (*R*)-**10c**.

The correlation between the possible acidity (see Table S1, and Figs. S5 and S6), aggregation (see Figs. S7 and S8), and catalytic activity (see Table S1 and Scheme S1) of the catalysts is shown in Fig. S9. Catalyst (*R*)-**5b** might have much better Brønsted acidity than the others, and might avoid aggregation due to neutralization of the highly Brønsted basic P=O moiety through the conjugated double hydrogen bond network. As a result, catalyst (*R*)-**5b** would show better results than the others.

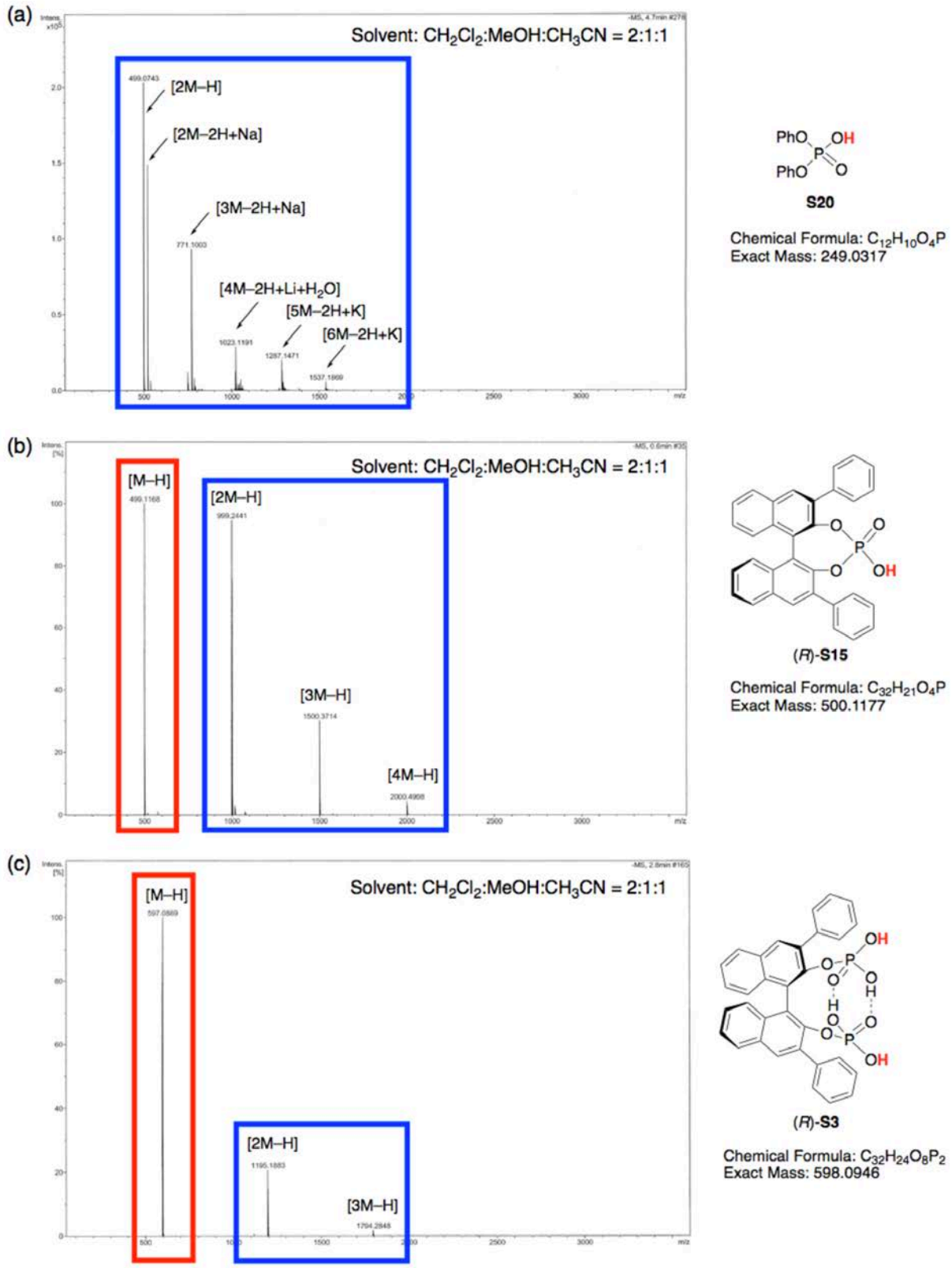


Fig. S7 ESI-MS (negative) spectrum of catalysts. (a) **S20** in CH_2Cl_2/MeOH/CH_3CN. (b) (*R*)-**S15** in CH_2Cl_2/MeOH/CH_3CN. (c) (*R*)-**S3** in CH_2Cl_2/MeOH/CH_3CN. (d) (*R*)-**S3** in CH_2Cl_2. (e) (*R*)-**5b** in CH_2Cl_2. (f) (*R*)-**10c** in CH_2Cl_2

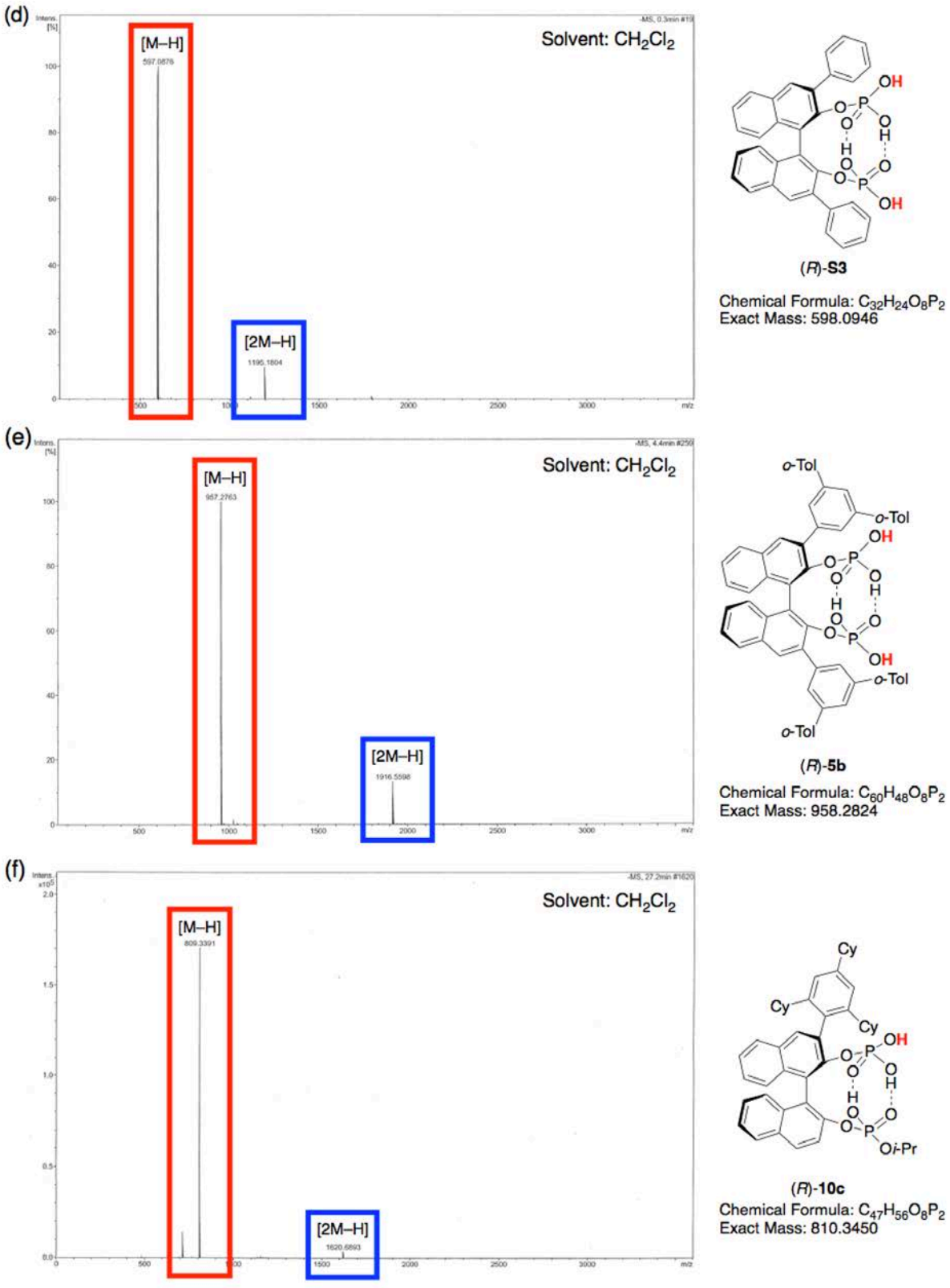


Fig. S7 *(continued)*

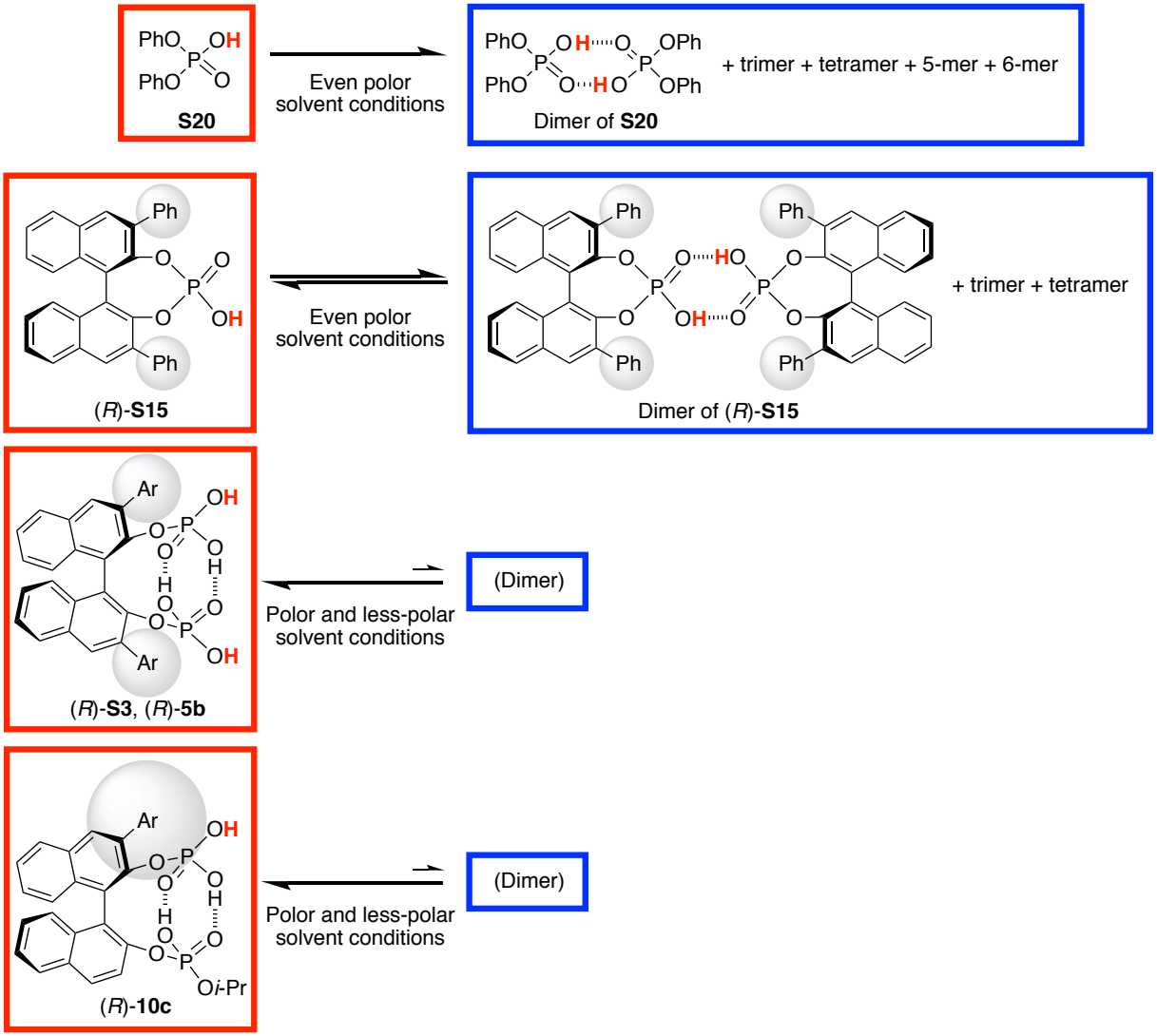


Fig. S8 Possible equilibriums among monomer, dimer, and trimer of catalysts.

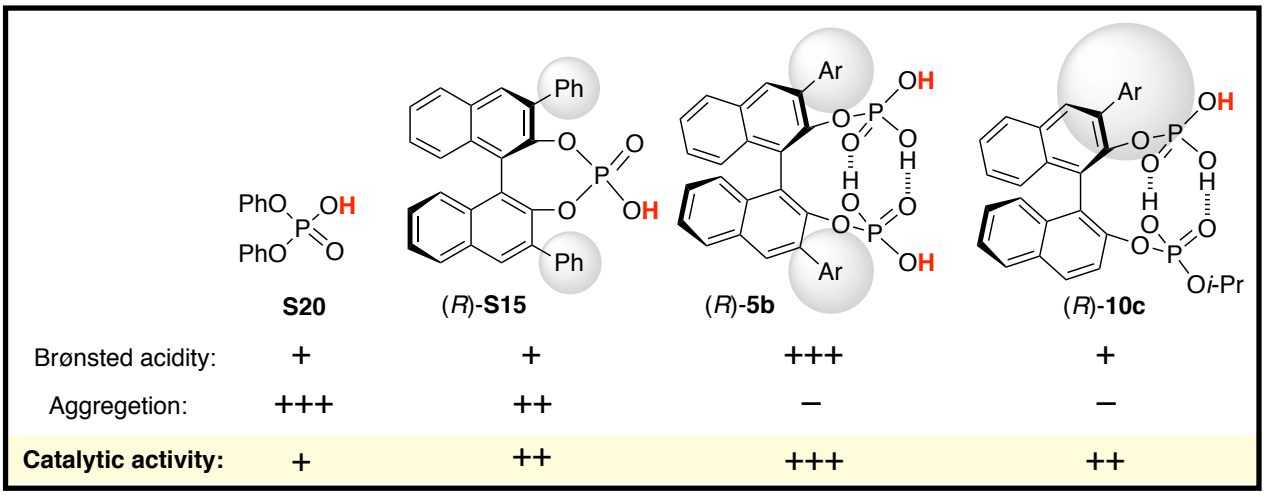
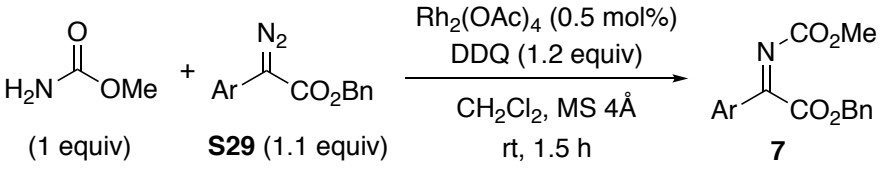


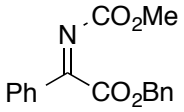
Fig. S9 Correlations among the possible acidity, aggregation, and catalytic activity of the catalysts.

17. Preparation of α-ketimino esters 7.

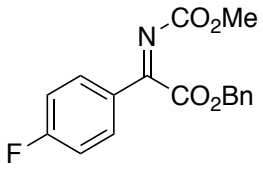


(1 equiv) **S29** (1.1 equiv) **7**

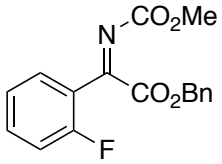
α-Ketimino esters **7** were prepared based on the literature procedure.[18] A suspension of rhodium(II) acetate dimer ($Rh_2(OAc)_4$, 6.6 mg, 0.5 mol%), methyl carbamate (225 mg, 3.0 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 817 mg, 3.6 mmol), and well-dried MS 4Å (2 g) in dichloromethane (15 mL) was stirred at room temperature. Then the diazo compound **S29**[19] (3.3 mmol) in dichloromethane (10 mL) was added to the suspension over 1 h *via* a syringe pump. After completion of the addition, the reaction mixture was stirred for another 0.5 h. The resulting mixture was filtered through a pad of Celite, and the filtrate was condensed under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane) to give the desired product **7**.



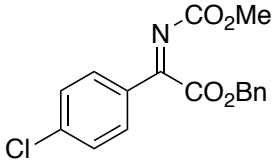
Benzyl 2-((methoxycarbonyl)imino)-2-phenylacetate (7a): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 5.37 (s, 2H), 7.36-7.46 (m, 7H), 7.56 (t, J = 7.3 Hz, 1H), 7.86 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.7, 68.4, 128.7 (2C), 128.8 (2C), 128.9, 129.0 (2C), 129.4 (2C), 132.0, 133.3, 134.2, 162.1, 162.4, 162.9. IR (neat) 2953, 1739, 1635, 1450, 1316, 1232, 1004 cm^{-1}. HRMS (FAB+) calcd for $C_{17}H_{16}NO_4$ $[M+H]^+$ 298.1079, found 298.1069.



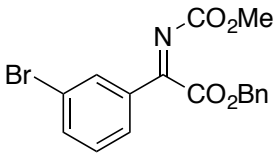
Benzyl 2-(4-fluorophenyl)-2-((methoxycarbonyl)imino)acetate (7b): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 5.36 (s, 2H), 7.08-7.15 (m, 2H), 7.35-7.45 (m, 5H), 7.86-7.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.7, 68.5, 116.1 (d, J_{C-F} = 21.9 Hz, 2C), 128.2 (d, J_{C-F} = 2.9 Hz), 128.8 (2C), 129.0 (3C), 131.9 (d, J_{C-F} = 8.6 Hz, 2C), 134.0, 161.4, 161.9, 162.1, 165.8 (d, J_{C-F} = 254.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –104.2. IR (neat) 2954, 2846, 1739, 1636, 1593, 1509, 1437, 1415, 1324, 1229, 1158, 1037, 1002 cm^{-1}. HRMS (FAB+) calcd for $C_{17}H_{15}FNO_4$ $[M+H]^+$ 316,0985, found 316.0994.



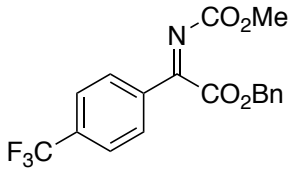
Benzyl 2-(2-fluorophenyl)-2-((methoxycarbonyl)imino)acetate (7c): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 3.70 (s, 3H), 5.31 (s, 2H), 7.08 (t, J = 8.7 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.30-7.40 (m, 5H), 7.49 (q, J = 6.9 Hz, 1H), 7.75 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 53.7, 68.6, 116.2 (d, J_{C-F} = 21.0 Hz,), 121.9 (d, J_{C-F} = 10.5 Hz), 124.7 (d, J_{C-F} = 2.9 Hz), 128.7 (2C), 128.8 (3C), 130.5, 134.4, 134.5 (d, J_{C-F} = 8.6 Hz,), 158.9, 161.5, 161.6, 161.7 (d, J_{C-F} = 253.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$,) δ –111.5. IR (neat) 3035, 2955, 1745, 1639, 1613, 1486, 1457, 1266, 1229, 1000 cm^{-1}. HRMS (ESI+) calcd for $C_{17}H_{15}FNO_4$ $[M+H]^+$ 316,0980, found 316.0986.



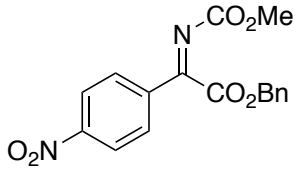
Benzyl 2-(4-chlorophenyl)-2-((methoxycarbonyl)imino)acetate (7d): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 5.36 (s, 2H), 7.35-7.44 (m, 7H), 7.82 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 68.6, 128.8 (2C), 129.1 (5C), 130.5, 130.7 (2C), 134.0, 139.8, 161.4, 161.9 (2C). IR (neat) 2953, 1739, 1633, 1592, 1568, 1492, 1436, 1405, 1377, 1321, 1284, 1232, 1176, 1092, 1037, 1002 cm^{-1}. HRMS (FAB+) calcd for $C_{17}H_{15}ClNO_4$ $[M+H]^+$ 332.0690, found 332.0681.



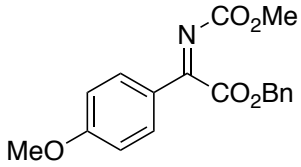
Benzyl 2-(3-bromophenyl)-2-((methoxycarbonyl)imino)acetate (7e): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 5.36 (s, 2H), 7.30 (t, J = 7.8 Hz, 1H), 7.35-7.45 (m, 5H), 7.67 (dm, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 68.7, 122.9, 128.0, 128.9 (2C), 129.1 (3C), 130.2, 132.2, 134.0 (2C), 136.1, 160.9, 161.6, 161.7. IR (neat) 2953, 1739, 1638, 1231, 1198 cm^{-1}. HRMS (FAB+) calcd for $C_{17}H_{15}BrNO_4$ $[M+H]^+$ 376.0184, found 376.0174.



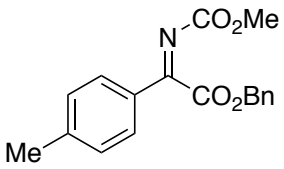
Benzyl 2-((methoxycarbonyl)imino)-2-(4-(trifluoromethyl)phenyl)acetate (7f): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 5.37 (s, 2H), 7.37-7.45 (m, 5H), 7.69 (d, J = 8.7 Hz, 2H), 7.98 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.9, 68.8, 123.6 (q, J_{C-F} = 271.3 Hz), 125.7 (q, J_{C-F} = 3.8 Hz, 2C), 128.9 (2C), 129.2 (3C), 129.8 (2C), 133.9, 134.4 (q, J_{C-F} = 32.4 Hz), 135.4, 160.6, 161.3, 161.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.1. IR (neat) 2956, 1740, 1643, 1438, 1413, 1328, 1233, 1129, 1068, 1001 cm^{-1}. HRMS (FAB+) calcd for $C_{18}H_{15}F_3NO_4$ $[M+H]^+$ 366.0953, found 366.0957.



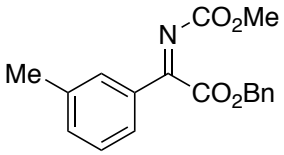
Benzyl 2-((methoxycarbonyl)imino)-2-(4-nitrophenyl)acetate (7g): Yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 5.38 (s, 2H), 7.39-7.44 (m, 5H), 8.05 (d, J = 8.3 Hz, 2H), 8.27 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.9, 69.1, 123.7 (2C), 128.9 (2C), 129.2 (2C), 129.3, 130.5 (2C), 133.7, 137.7, 150.2, 159.4, 160.7, 161.3. IR (KBr) 3115, 2962, 1742, 1724, 1644, 1522, 1350, 1318, 1246, 1199, 1004 cm^{-1}. M.p. 72-74 °C (decomposition). HRMS (FAB+) calcd for $C_{17}H_{15}N_2O_6$ $[M+H]^+$ 343.0930, found 343.0932.



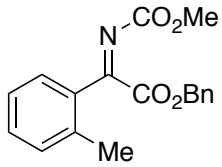
Benzyl 2-((methoxycarbonyl)imino)-2-(4-methoxyphenyl)acetate (7h): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.87 (s, 3H), 5.36 (s, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.34-7.47 (m, 5H), 7.85 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.7, 55.6, 68.2, 114.3 (2C), 124.5, 128.8 (2C), 128.9, 129.0 (2C), 131.7 (2C), 134.4, 162.4, 163.1, 163.2, 164.0. IR (neat) 2953, 1739, 1598, 1571, 1514, 1310, 1228, 1168 cm^{-1}. HRMS (FAB+) calcd for $C_{18}H_{17}NNaO_5$ $[M+Na]^+$ 350.1004, found 350.1016.



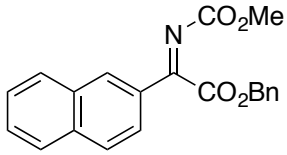
Benzyl 2-((methoxycarbonyl)imino)-2-(*p*-tolyl)acetate (7i): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.65 (s, 3H), 5.36 (s, 2H), 7.23 (d, J = 8.2 Hz, 2H), 7.33-7.49 (m, 5H), 7.76 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 53.7, 68.3, 128.8 (2C), 128.9, 129.0 (2C), 129.3, 129.5 (2C), 129.6 (2C), 134.3, 144.5, 162.3, 162.8, 163.2. IR (neat) 3033, 2953, 1740, 1633, 1605, 1436, 1323, 1228, 1177, 1038, 1003 cm^{-1}. HRMS (FAB+) calcd for $C_{18}H_{17}NNaO_4$ $[M+Na]^+$ 334.1055, found 334.1047.



Benzyl 2-((methoxycarbonyl)imino)-2-(*m*-tolyl)acetate (7j): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.66 (s, 3H), 5.37 (s, 2H), 7.30-7.44 (m, 7H), 7.65 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 53.8, 68.3, 126.7, 128.7, 128.8 (2C), 129.0, 129.1 (2C), 129.8, 132.0, 134.30, 134.34, 138.7, 162.2, 162.7, 163.5. IR (neat) 3034, 2953, 1739, 1634, 1436, 1323, 1229, 1163, 1025 cm^{-1}. HRMS (ESI+) calcd for $C_{18}H_{18}NO_4$ $[M+H]^+$ 312.1230, found 312.1237.

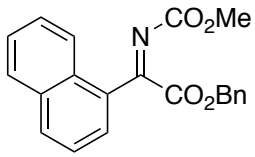


Benzyl 2-((methoxycarbonyl)imino)-2-(*m*-tolyl)acetate (7k): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (br, 3H), 3.68 (s, 3H), 5.31 (s, 2H), 7.23 (t, J = 7.8 Hz, 3H), 7.34-7.42 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.8, 53.6, 68.4, 126.1, 128.6 (3C), 128.8 (2C), 129.9, 131.3, 131.6, 132.4, 134.4, 137.4, 161.0, 161.4, 162.4. IR (neat) 3065, 3033, 2954, 1740, 1643, 1456, 1436, 1379, 1320, 1213, 1029, 1000 cm^{-1}. HRMS (FAB+) calcd for $C_{18}H_{17}NNaO_4$ $[M+Na]^+$ 334.1055, found 334.1062.

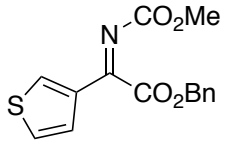


Benzyl 2-((methoxycarbonyl)imino)-2-(naphthalen-2-yl)acetate (7l): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 5.43 (s, 2H), 7.38-7.50 (m, 5H), 7.52 (d, J = 6.9 Hz, 1H),

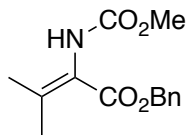
7.60 (d, J = 6.9 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 68.4, 124.1, 127.0, 127.9, 128.8 (3C), 128.9, 129.0, 129.2 (2C), 129.4, 129.5, 132.3, 132.5, 134.3, 135.7, 162.2, 162.7, 163.3. IR (neat) 3065, 3031, 2957, 2894, 2838, 1739, 1638, 1562, 1435, 1231, 1010 cm^{-1}. HRMS (FAB+) calcd for $C_{21}H_{18}NO_4$ $[M+H]^+$ 348.1236, found 348.1243.



Benzyl 2-((methoxycarbonyl)imino)-2-(naphthalen-1-yl)acetate (7m): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 3.68 (s, 3H), 5.28 (s, 2H), 7.20-7.32 (m, 5H), 7.40-7.41 (m, 3H), 7.61 (d, J = 6.4 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 8.11 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 53.6, 68.5, 124.7, 124.9, 126.6, 127.6, 128.66 (6C), 128.71, 128.76, 130.7, 132.1, 133.7, 134.5, 161.6, 162.5, 163.1. IR (neat) 3035, 2953, 1738, 1642, 1436, 1313, 1227, 1177, 1101, 1026 cm^{-1}. HRMS (ESI+) calcd for $C_{21}H_{18}NO_4$ $[M+H]^+$ 348.1230, found 348.1230.

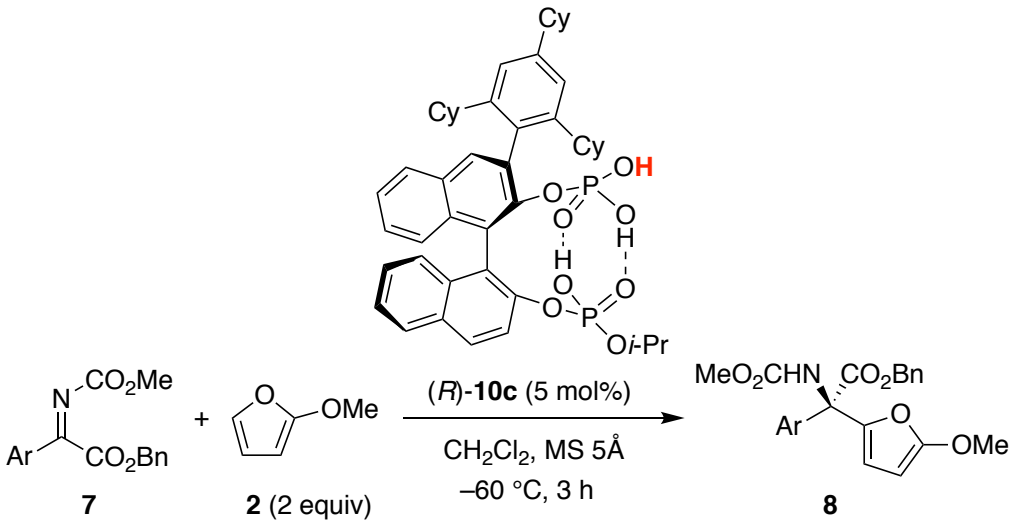


Benzyl 2-((methoxycarbonyl)imino)-2-(thiophen-3-yl)acetate (7n): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 5.35 (s, 2H), 7.34 (dd, J = 5.3, 3.0 Hz, 1H), 7.35-7.46 (m, 5H), 7.60 (d, J = 4.6 Hz, 1H), 8.12 (d, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.6, 68.6, 126.7, 127.3, 128.8 (2C), 129.0 (3C), 134.1, 134.3, 135.4, 155.8, 161.5, 162.1. IR (neat) 3112, 2952, 1739, 1628, 1517, 1434, 1303, 1227, 1171, 1080, 1018 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{13}NNaO_4S$ $[M+H]^+$ 326.0463, found 326.0470.

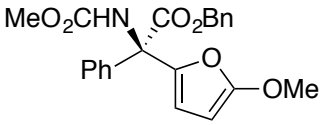


Benzyl 2-((methoxycarbonyl)amino)-3-methylbut-2-enoate (7o): Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.17 (s, 3H), 3.48-3.85 (br, 3H), 5.19 (s, 2H), 5.62-6.00 (br, 1H), 7.29-7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.6, 52.6, 66.7, 121.1, 128.2 (3C), 128.6 (2C), 135.9, 147.0, 155.4, 164.8. IR (KBr) 3297, 3035, 2954, 1719, 1697, 1517, 1380, 1304, 1271, 1225, 1094, 1068 cm^{-1}. M.p. 54 °C. HRMS (FAB+) calcd for $C_{14}H_{17}NNaO_4$ $[M+Na]^+$ 286.1055, found 286.1053.

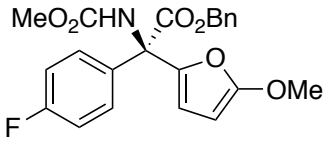
18. Representative procedures for the enantioselective aza-Friedel–Crafts reaction of 2 with 7 (Table 2 and Scheme 2).



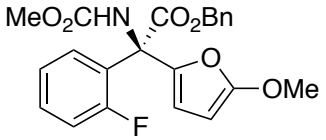
To a well-dried pyrex Schlenk tube charged with activated MS 5Å (50 mg) under a nitrogen atmosphere were added (*R*)-**10c** (8.1 mg, 0.010 mmol) in dichloromethane (1 mL) at –78 °C. After 5 min, α-ketimino ester **7** (0.20 mmol) in dichloromethane (1 mL), and 2-methoxyfuran **2** (37 μL, 0.40 mmol) were added at –78 °C. The reaction mixture was allowed to warm to –60 °C and was then stirred at that temperature for 3 h. To quench the reaction, triethylamine (0.1 mL) was added to the mixture at –60 °C, and the mixture was concentrated under reduced pressure at room temperature. The residue was purified by the silica gel column chromatography (eluent: *n*-hexane/EtOAc = 3/1 to 1/1) to give the desired product **8**. The enantiomeric purity was determined by chiral HPLC analysis.



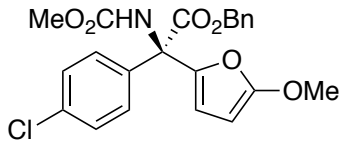
Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-phenylacetate (8a): –60 °C, 3 h, 93% yield, 95% ee. Coloreless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.78 (s, 3H), 5.12 (d, *J* = 3.2 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 6.22 (s, 1H), 6.38 (s, 1H), 7.12-7.18 (m, 2H), 7.24-7.29 (3H), 7.29-7.35 (m, 3H), 7.44-7.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 57.6, 65.3, 68.0, 80.2, 112.4, 127.3 (2C), 127.8 (2C), 128.2, 128.3 (2C), 128.41 (2C), 128.43, 135.1, 137.2, 140.6, 154.8, 161.1, 169.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –113.8. IR (neat) 3399, 2952, 1731, 1574, 1495, 1450. 1367, 1262, 1024 cm^{-1}. $[\alpha]_D^{27}$ = –2.4 (*c* 1.00, $CHCl_3$, 95% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 13.6 min (minor, *S*), 17.5 min (major, *R*). HRMS (FAB+) calcd for $C_{22}H_{21}NNaO_6$ $[M+Na]^+$ 418.1267, found 418.1252.



Benzyl (*R*)-2-(4-fluorophenyl)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)acetate (8b): –60 °C, 3 h, 96% yield, 96% ee. Coloreless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.80 (s, 3H), 5.12 (d, J = 3.2 Hz, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.21 (d, J = 12.4 Hz, 1H), 6.24 (s, 1H), 6.32 (d, J = 3.2 Hz, 1H), 6.96-7.03 (m, 2H), 7.13-7.19 (m, 2H), 7.26-7.31 (m, 3H), 7.43-7.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 57.7, 64.8, 68.2, 80.2, 112.5, 115.1 (d, $J_{C–F}$ = 21.9 Hz, 2C), 127.9 (2C), 128.3, 128.5 (2C), 129.3 (d, $J_{C–F}$ = 7.6 Hz, 2C), 132.9, 134.9, 140.4, 154.8, 161.2, 162.6 (d, $J_{C–F}$ = 246.9 Hz), 169.2. ^{19}F NMR (367 MHz, $CDCl_3$) δ –113.8. IR (neat) 3409, 2952, 1734, 1615, 1576, 1507, 1456, 1367, 1262, 1024 cm^{-1}. $[\alpha]_D^{26}$ = –8.4 (*c* 1.00, $CHCl_3$, 96% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 240 nm, 0.6 mL/min, t_R = 12.6 min (minor, *S*), 15.5 min (major, *R*). HRMS (FAB+) calcd for $C_{22}H_{21}FNO_6$ $[M+H]^+$ 414.1353, found 414.1364.

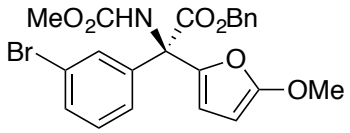


Benzyl (*R*)-2-(2-fluorophenyl)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)acetate (8c): –60 °C, 3 h, 90%, 97% ee. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (br, 3H), 3.80 (s, 3H), 5.17 (d, J = 3.2 Hz, 1H), 5.18 (d, J = 12.4 Hz, 1H), 5.28 (d, J = 12.4 Hz, 1H), 6.32 (d, J = 3.2 Hz, 1H), 6.53 (br, 1H), 7.00 (dd, J = 11.4, 8.3 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.16-7.21 (m, 2H), 7.25-7.34 (m, 4H), 7.44 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 57.9, 62.6, 68.5, 81.1, 112.3, 115.5 (d, $J_{C–F}$ = 21.9 Hz), 123.5 (d, $J_{C–F}$ = 3.8 Hz), 128.0 (2C), 128.4, 128.5 (3C), 130.4 (d, $J_{C–F}$ = 8.6 Hz), 131.7, 135.1, 138.1, 154.6, 160.2 (d, $J_{C–F}$ = 246.0 Hz), 161.7, 169.3. ^{19}F NMR (367 MHz, $CDCl_3$) δ –114.1. IR (neat) 3410, 2953, 1734, 1614, 1573, 1489, 1456, 1369, 1262, 1038 cm^{-1}. $[\alpha]_D^{26}$ = –30.0 (*c* 1.00, $CHCl_3$, 97% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 1.0 mL/min, t_R = 10.0 min (major, *R*), 16.2 min (minor, *S*). HRMS (FAB+) calcd for $C_{22}H_{20}NNaO_6$ $[M+Na]^+$ 436.1172, found 436.1185.

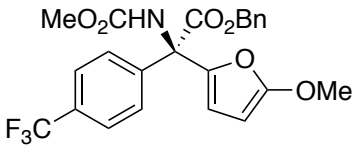


Benzyl (*R*)-2-(4-chlorophenyl)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)acetate (8d): –60 °C, 3 h, 96% yield, 96% ee. Coloreless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.80 (s, 3H), 5.12 (d, J = 3.7 Hz, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.21 (d, J = 12.4 Hz, 1H), 6.25 (s, 1H), 6.30 (d, J = 3.2 Hz, 1H), 7.13-7.19 (m, 2H), 7.26-7.32 (m, 5H), 7.40-7.45 (m, 2H).

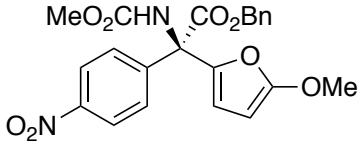
^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 57.7, 64.9, 68.3, 80.3, 112.5, 127.9 (2C), 128.4 (3C), 128.5 (2C), 128.9 (2C), 134.4, 134.9, 135.7, 140.2, 154.8, 161.3, 169.0. IR (neat) 3407, 2952, 1733, 1615, 1577, 1492, 1367, 1262, 1024 cm^{-1}. $[\alpha]_D^{27}$ = –8.8 (*c* 1.00, $CHCl_3$ 96% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 13.2 min (minor, *S*), 18.9 min (major, *R*). HRMS (FAB+) calcd for $C_{22}H_{21}ClNO_6$ $[M+H]^+$ 430.1057, found 430.1063.



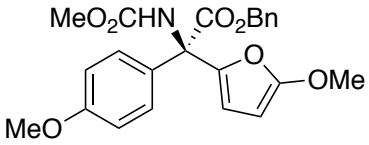
Benzyl (*R*)-2-(3-bromophenyl)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)acetate (8e): –60 °C, 3 h, 98% yield, 97% ee. Coloreless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.79 (s, 3H), 5.12 (d, *J* = 3.2 Hz, 1H), 5.19 (s, 2H), 6.26 (br, 1H), 6.33 (br, 1H), 7.13-7.22 (m, 3H), 7.25-7.33 (m, 3H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 57.7, 64.9, 68.4, 80.3, 112.7, 122.4, 126.1, 127.9 (2C), 128.4, 128.5 (2C), 129.8, 130.6, 131.6, 134.8, 139.4, 140.0, 154.7, 161.3, 168.8. IR (neat) 3400, 2952, 2842, 1732, 1615, 1576, 1496, 1261, 1058, 1024 cm^{-1}. $[\alpha]_D^{29}$ = –8.4 (*c* 1.00, $CHCl_3$, 97% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 10.6 min (minor, *S*), 12.5 min (major, *R*). HRMS (FAB+) calcd for $C_{22}H_{20}BrNNaO_6$ $[M+Na]^+$ 496.0372, found 496.0382.



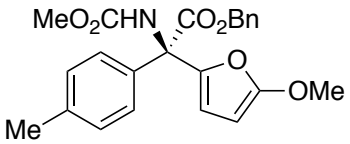
Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(4-(trifluoromethyl) phenyl)acetate (8f): –60 °C, 3 h, 92% yield, 97% ee. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.81 (s, 3H), 5.13 (d, *J* = 3.2 Hz, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 6.29 (d, *J* = 3.2 Hz, 1H), 6.33 (s, 1H), 7.10-7.16 (m, 2H), 7.24-7.31 (m, 3H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 57.8, 65.2, 68.5, 80.4, 112.6, 124.0 (q, J_{C-F} = 270.8 Hz), 125.2 (q, J_{C-F} = 2.9 Hz, 2C), 127.9 (2C), 128.0 (2C), 128.5 (3C), 130.5 (q, J_{C-F} = 32.1 Hz), 134.8, 140.0, 141.1 154.8, 161.4, 168.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6. IR (neat) 3410, 2953, 1734, 1615, 1575, 1497, 1328, 1263, 1168, 1125, 1070, 1020 cm^{-1}. $[\alpha]_D^{27}$ = –16.4 (*c* 1.00, $CHCl_3$, 97% ee). HPLC analysis; IC-3, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 1.0 mL/min, t_R = 18.1 min (major, *R*), 29.5 min (minor, *S*). HRMS (FAB+) calcd for $C_{23}H_{21}F_3NO_6$ $[M+H]^+$ 464.1321, found 464.1319.



Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(4-nitrophenyl)acetate (8g): –60 °C, 3 h, 95% yield, 96% ee. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (br, 3H), 3.81 (s, 3H), 5.14 (d, *J* = 3.7 Hz, 1H), 5.19 (d, *J* = 12.4 Hz, 1H), 5.23 (d, *J* = 12.4 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 6.37 (s, 1H), 7.13-7.21 (m, 2H), 7.27-7.32 (m, 3H), 7.69 (dt, *J* = 9.6, 2.3 Hz, 2H), 8.16 (dt, *J* = 9.6, 2.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 57.8, 65.1, 68.8, 80.5, 112.6, 123.2 (2C), 128.1 (2C), 128.5 (2C), 128.6, 128.8 (2C), 134.5, 139.4, 144.3, 147.6, 154.8, 161.5, 168.3. IR (neat) 3400, 3031, 2953, 2841, 1732, 1615, 1574, 1521, 1496, 1350, 1262, 1112, 1024 cm^{-1}. $[\alpha]_D^{27}$ = –22.0 (*c* 1.00, $CHCl_3$, 96% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 16.7 min (minor, *S*), 17.8 min (major, *R*). HRMS (FAB+) calcd for $C_{22}H_{20}N_2NaO_8$ $[M+Na]^+$ 463.1117, found 463.1120.

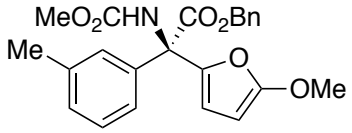


Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(4-methoxyphenyl) acetate (8h): –60 °C, 6 h, 83% yield, 82% ee. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (br, 3H), 3.79 (s, 6H), 5.12 (d, *J* = 3.2 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 6.18 (br, 1H), 6.37 (d, *J* = 3.2 Hz, 1H), 6.83 (d, *J* = 10.1 Hz, 2H), 7.14-7.20 (m, 2H), 7.25-7.32 (m, 3H), 7.38 (d, *J* = 10.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 55.3, 57.6, 64.8, 68.0, 80.1, 112.3, 113.7 (2C), 127.8 (2C), 128.2, 128.4 (2C), 128.6 (2C), 129.2, 135.2, 140.8, 154.9, 159.6, 161.1, 169.5. IR (neat) 3398, 2953, 1733, 1614, 1576, 1509, 1457, 1367, 1258, 1181, 1026 cm^{-1}. $[\alpha]_D^{28}$ = –0.4 (*c* 1.00, $CHCl_3$, 82% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 22.0 min (minor, *S*), 34.1 min (major, *R*). HRMS (FAB+) calcd for $C_{23}H_{23}NNaO_7$ $[M+Na]^+$ 448.1372, found 448.1367.

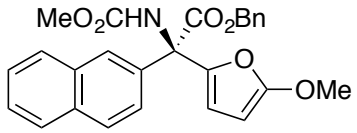


Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(*p*-tolyl)acetate (8i): –60 °C, 6 h, 91% yield, 94% ee. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.60 (br, 3H), 3.79 (s, 3H), 5.11 (d, *J* = 3.2 Hz, 1H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 6.20 (br, 1H), 6.38 (d, *J* = 2.8 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.14-7.19 (m, 2H), 7.25-7.31 (m,

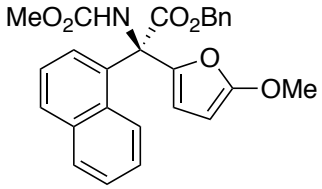
3H), 7.35 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 52.1, 57.6, 65.1, 68.0, 80.1, 112.3, 127.1 (2C), 127.8 (2C), 128.2, 128.4 (2C), 129.1 (2C), 134.3, 135.2, 138.3, 140.8, 154.8, 161.1, 169.5. IR (neat) 3412, 2952, 2840, 1733, 1615, 1576, 1496, 1456, 1367, 1262, 1060, 1024 cm^{-1}. $[\alpha]_D^{26}$ = –1.6 (*c* 1.00, $CHCl_3$, 94% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 16.4 min (minor, *S*), 22.8 min (major, *R*). HRMS (FAB+) calcd for $C_{23}H_{23}NNaO_6$ $[M+Na]^+$ 432.1423, found 432.1421.



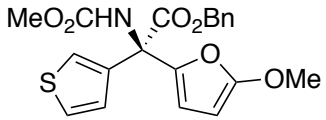
Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(*m*-tolyl)acetate (8j): –60 °C, 3 h, 94% yield, 95% ee. Coloreless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.61 (br, 3H), 3.80 (s, 3H), 5.12 (d, J = 3.2 Hz, 1H), 5.20 (s, 2H), 6.16 (br, 1H), 6.40 (d, J = 2.8 Hz, 1H), 7.11 (d, J = 7.3 Hz, 1H), 7.14-7.29 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 52.2, 57.7, 65.2, 68.0, 80.1, 112.4, 124.4, 127.8, 129.9 (2C), 128.2, 128.3, 128.4 (2C), 129.3, 135.3, 137.2, 138.1, 140.7, 154,9, 161.1, 169.4. IR (neat) 3402, 2951, 1731, 1615, 1575, 1495, 1367, 1262, 1213, 1024 cm^{-1}. $[\alpha]_D^{26}$ = –2.0 (*c* 1.00, $CHCl_3$, 95% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 11.5 min (minor, *S*), 15.5 min (major, *R*). HRMS (FAB+) calcd for $C_{23}H_{23}NNaO_6$ $[M+Na]^+$ 432.1423, found 432.1422.



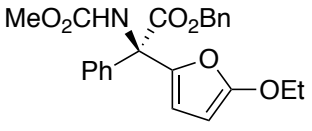
Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(naphthalen-2-yl)acetate (8l): –60 °C, 12 h, 96% yield, 95% ee. Coloreless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.79 (s, 3H), 5.15 (d, J = 3.2 Hz, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.22 (d, J = 12.4 Hz, 1H), 6.33 (s, 1H), 6.42 (s, 1H), 7.12-7,17 (m, 2H), 7.19-7.27 (m, 3H), 7.43-7.51 (m, 2H), 7.58 (dd, J = 8.7, 2.3 Hz, 1H), 7.73-7.83 (m, 3H), 7.92 (d, J = 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 57.7, 65.5, 68.2, 80.3, 112.6, 124.9, 126.3, 126.6, 126.8, 127.5, 127.9 (2C), 128.1, 128.3, 128.4 (2C), 128.6, 132.9, 133.1, 134.7, 135.1, 140.6, 155.0, 161.2, 169.3. IR (neat) 3406, 2952, 1731, 1614, 1575, 1496, 1368, 1262, 1024 cm^{-1}. $[\alpha]_D^{25}$ = –1.6 (*c* 1.00, $CHCl_3$, 95% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 18.4 min (minor, *S*), 28.3 min (major, *R*). HRMS (FAB+) calcd for $C_{26}H_{23}NNaO_6$ $[M+Na]^+$ 468.1423, found 468.1429.



Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(naphthalen-1-yl)acetate (8m): –60 °C, 12 h, 85% yield, 90% ee. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (br, 3H), 3.81 (s, 3H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.19 (d, *J* = 12.4 Hz, 1H), 5.20 (d, *J* = 3.2 Hz, 1H), 6.36 (d, *J* = 3.2 Hz, 1H), 6.42 (s, 1H), 6.96 (d, *J* = 7.4 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.30 (td, *J* = 7.8, 1.4 Hz, 1H), 7.35-7.43 (m, 3H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 57.8, 66.3, 68.4, 80.9, 112.2, 123.6, 124.9, 125.4, 126.5, 128.0 (2C), 128.2, 128.3 (2C), 128.4, 129.4, 129.7, 130.5, 133.8, 134.3, 134.7, 139.9, 154.7, 161.6, 170.5. IR (KBr) 3400, 2942, 1728, 1614, 1570, 1496, 1367, 1262, 1037 cm^{-1}. M.p. 38-50 °C (decomposition). $[\alpha]_D^{25}$ = –50.0 (*c* 1.00, $CHCl_3$, 90% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 1.0 mL/min, t_R = 9.0 min (major, *R*), 22.9 min (minor, *S*). HRMS (FAB+) calcd for $C_{26}H_{23}NNaO_6$ $[M+Na]^+$ 468.1423, found 468.1429.



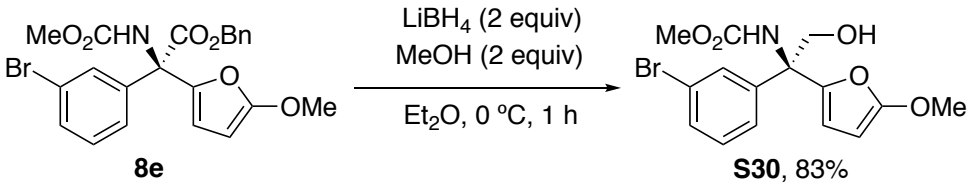
Benzyl (*R*)-2-((methoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(thiophen-3-yl)acetate (8n): –60 °C, 3 h, 96% yield, 87% ee. Coloreless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.80 (s, 3H), 5.11 (d, *J* = 3.2 Hz, 1H), 5.20 (d, *J* = 12.8 Hz, 1H), 5.24 (d, *J* = 12.4 Hz, 1H), 6.26 (s, 1H), 6.29 (d, *J* = 3.2 Hz, 1H), 7.14 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.17-7.21 (m, 2H), 7.25 (dd, *J* = 5.0, 3.2 Hz, 1H), 7.27-7.32 (m, 3H), 7.36 (dd, *J* = 3.2, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 57.7, 62.7, 68.1, 80.3, 111.9, 124.3, 125.5, 127.3, 127.8 (2C), 128.3, 128.5 (2C), 135.1, 137.9, 140.6, 154.8, 161.1, 169.0. IR (neat) 3400, 2952, 2839, 1732, 1615, 1577, 1497, 1365, 1262, 1059, 1024 cm^{-1}. $[\alpha]_D^{27}$ = –7.6 (*c* 1.00, $CHCl_3$, 87% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 254 nm, 0.6 mL/min, t_R = 14.3 min (minor, *S*), 16.2 min (major, *R*). HRMS (FAB+) calcd for $C_{20}H_{19}NNaO_6S$ $[M+Na]^+$ 424.0831, found 424.0828.



Benzyl (*R*)-2-(5-ethoxyfuran-2-yl)-2-((methoxycarbonyl)amino)-2-phenylacetate (8p): –60 °C, 12 h, 94% yield, 94% ee. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.1 Hz, 3H), 3.60 (br, 3H), 4.02 (q, *J* = 7.2 Hz, 2H), 5.12 (d, *J* = 3.2 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 6.22 (s, 1H), 6.37 (d, *J* = 2.8 Hz, 1H), 7.12-7.18 (m, 2H), 7.25-7.36 (m, 6H), 7.45-7.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 52.2, 65.3, 66.8, 68.0, 81.1, 112.4, 127.3

(2C), 127.8 (2C), 128.2, 128.3 (2C), 128.4 (3C), 135.1, 137.2, 140.4, 154.8, 160.2, 169.4. IR (neat) 3410, 2982, 2953, 1734, 1612, 1572, 1496, 1450, 1261, 1026 cm^{-1}. $[\alpha]_D^{26} = -7.6$ (*c* 1.00, $CHCl_3$, 94% ee). HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 1/1, 230 nm, 0.6 mL/min, t_R = 11.7 min (minor, *S*), 12.8 min (major, *R*). HRMS (FAB+) calcd for $C_{23}H_{23}NNaO_6$ $[M+Na]^+$ 432.1423, found 432.1422.

Determination of absolute stereochemistry of 8e:



8e **S30**, 83%

To a solution of **8e** (76.0 mg, 0.16 mmol, 97% ee) in diethyl ether (1.6 mL) was added methanol (13 μL, 0.32 mmol) followed by lithium borohydride (6.9 mg, 0.32 mmol) under nitrogen atmosphere at –78 °C. The mixture was stirred at 0 °C for 1 h. Saturated NH_4Cl aqueous solution (2 mL) was then added to the mixture. The mixture was extracted with diethyl ether (5 mL × 2), and the combined organic layer was dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 2:1 to 1:1), to give the desired product **S30** in 83% yield (49.1 mg). White soild. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 4H), 3.83 (s, 3H), 4.14 (m, 1H), 4.25 (dd, *J* = 12.1, 6.6 Hz, 1H) 5.12 (d, *J* = 3.2 Hz, 1H), 5.72 (s, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 7.18-7.28 (m, 2H), 7.41-7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 57.8, 63.3, 68.3, 80.0, 110.8, 122.6, 125.4, 129.8, 130.0, 131.1, 142.8 (2C), 156.5, 161.4. IR (KBr) 3232, 3073, 2953, 1690, 1615, 1567, 1439, 1370, 1283, 1261, 1098, 1047, 1021 cm^{-1}. M.p. was not available due to decomposition. $[\alpha]_D^{27}$ = +4.0 (*c* 1.00, $CHCl_3$, 97% ee). HRMS (FAB+) calcd for $C_{15}H_{16}BrNNaO_5$ $[M+Na]^+$ 392.0110, found 392.0101.

Crystal data of S30 (Fig. S10): Compound **S30** was recrystallized in diethyl ether for X-ray analysis. Formula $C_{15}H_{16}BrNO_5$, colorless, crystal dimensions 0.35 × 0.30 × 0.25 mm^3, monoclinic, space group *P2₁* (#4), *a* = 5.8577(16) Å, *b* = 14.389(4) Å, *c* = 9.621(3) Å, α = 90.00 °, β = 94.654(6) °, γ = 90.00 °, *V* = 808.2(4) $Å^3$, *Z* = 2, ρ_{calc} = 1.521 g cm^{-3}, F(000) = 376, μ(MoKα)= 2.565 mm^{-1}, *T* = 103 K. 6877 reflections collected, 3178 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.492 °), and 217 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Flack x = 0.002(5). R_1 = 0.0248 and wR_2 = 0.0504. GOF = 0.826. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1834631. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Web page: http://www.ccdc.cam.ac.uk/].

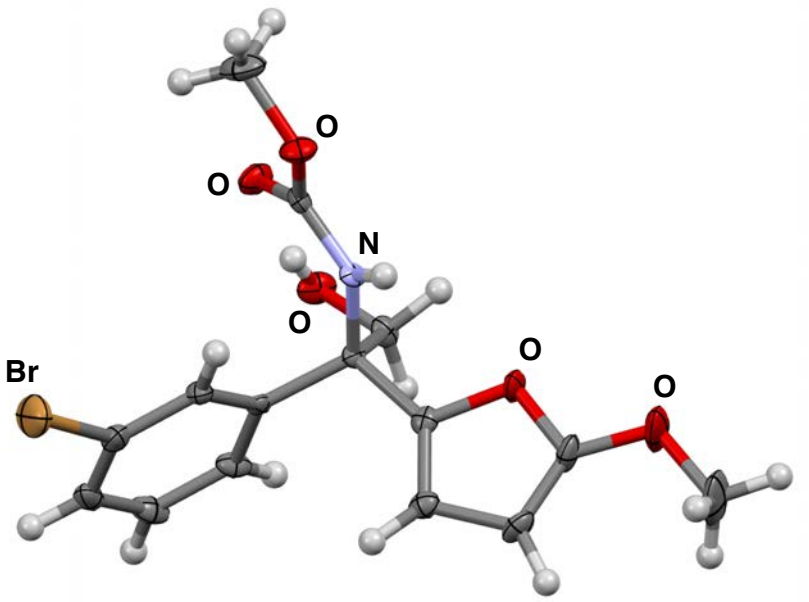
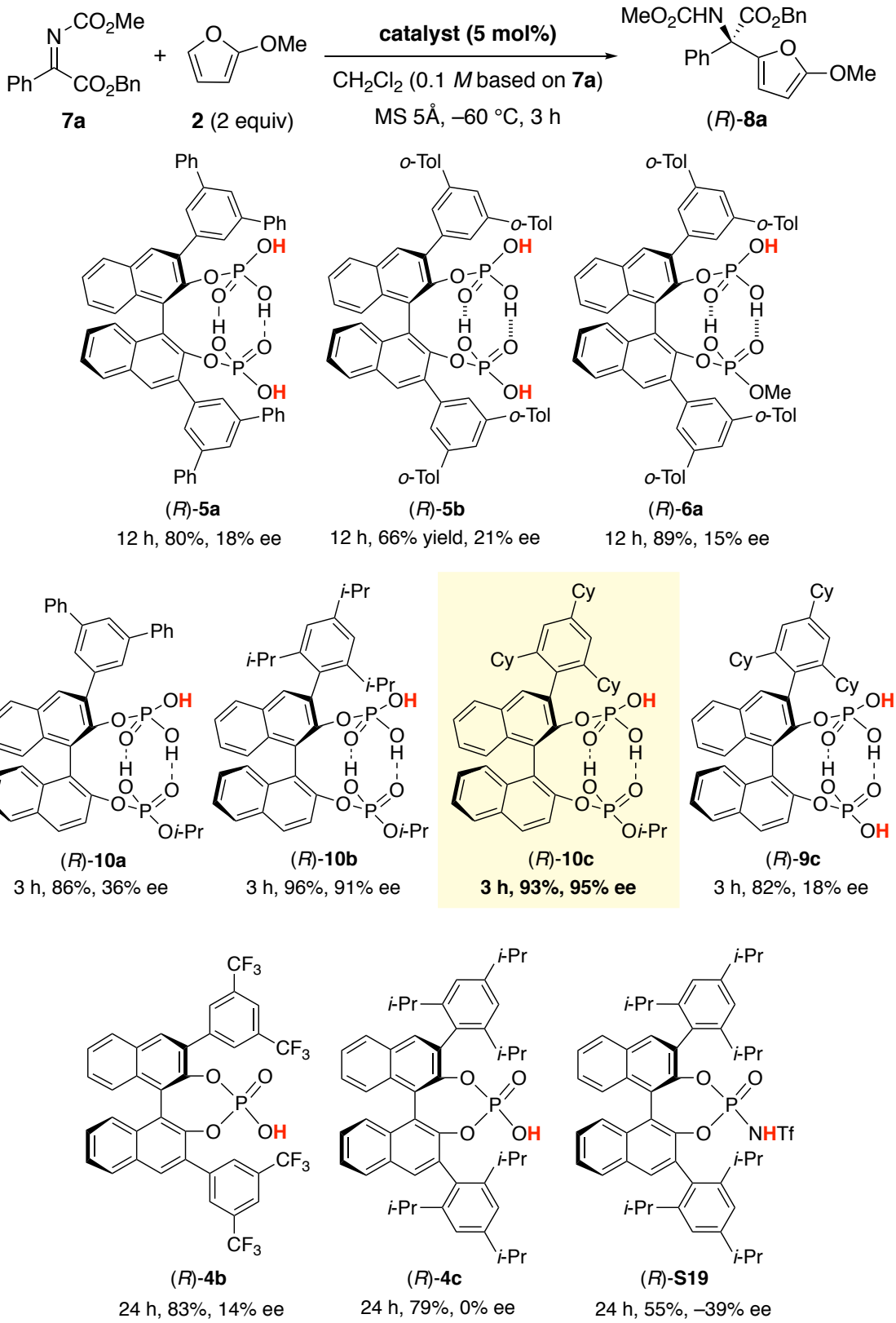


Fig. S10 ORTEP drawing of (*R*)-**S30**.

19. Optimization of catalysts, protecting groups on substrates, and reaction temperature in the reaction of 2 with 7a.

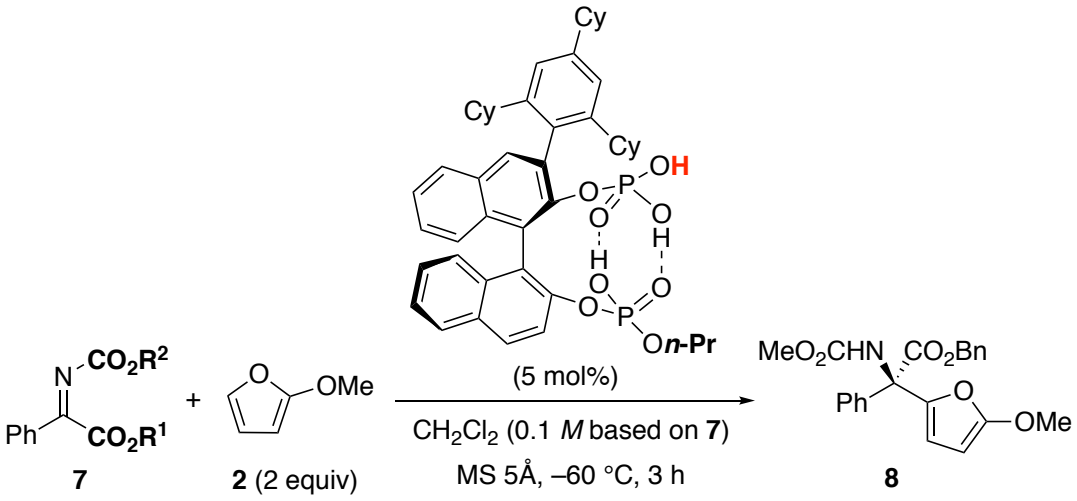
Screening of the chiral catalysts in the probe reaction of **2** with **7a** is summarized in Scheme S7. The catalytic activities of chiral BINOL-derived phosphoric acids, such as (*R*)-**4b** and (*R*)-**4c** (i.e., TRIP), had no effect on either the yield or the enantioselectivity, and a prolonged reaction time (24 h) was needed. Chiral phosphoramide (*R*)-**S19** was also ineffective. Our chiral C_2-symmetric bis(phosphoric acid)s (*R*)-**5a** and (*R*)-**5b** showed better catalytic activities (12 h) than (*R*)-**4b**, (*R*)-**4c**, and (*R*)-**S19**, although the enantioselectivity was still low. Mono-methyl ester catalyst (*R*)-**6a** showed a similar result to (*R*)-**5a** and (*R*)-**5b**. In contrast, chiral C_1-symmetric bis(phosphoric acid)s (*R*)-**10b** and (*R*)-**10c** showed much better catalytic activity, and the reactions were finished within 3 h. In particular, **8a** was obtained in 93% yield with 95% ee within 3h when we used (*R*)-**10c**. Based on these results, we selected (*R*)-**10c** as an optimized catalyst for this reaction.



Scheme S7 Screening of the catalysts in the probe reaction of **2** with **7a**.

Next, the protecting groups of the substrates **7** were optimized (Table S6). Here, we used unoptimized chiral bis(phosphoric acid) catalyst with *n*-Pr protection. As a result, for *N*-CO_2Me-substrates, CO_2Bn (Cbz) (entry 4) was much better than CO_2Et (entry 1), CO_2*i*-Pr (entry 2), and CO_2*t*-Bu (Boc) (entry 3). Moreover, for Cbz-substrates, *N*-CO_2Me (entry 4) was much better than *N*-Cbz (entry 5) and *N*-Boc (entry 6).

Table S6 Optimization of the protecting groups of the substrates **7**.

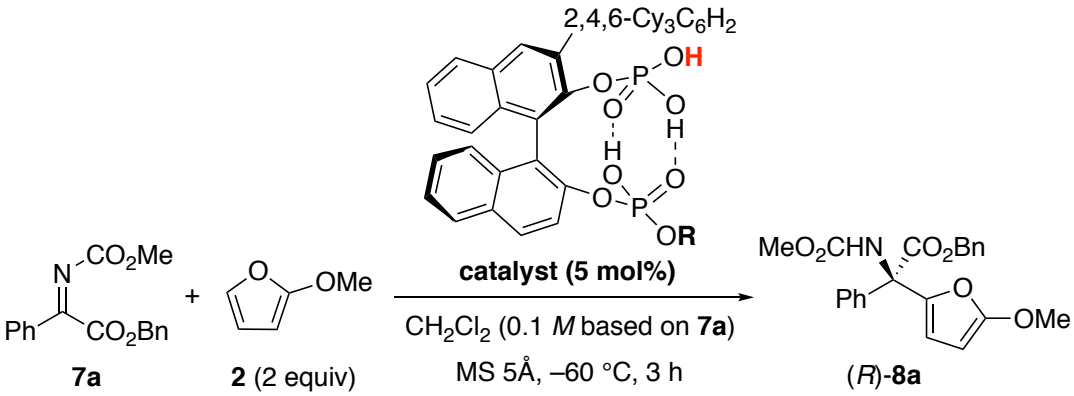


7 **2** (2 equiv) **8**

Entry	CO_2R^1	*N*-CO_2R^2	Yield (%)	ee (%)
1	CO_2Et	*N*-CO_2Me	83	67
2	CO_2*i*-Pr	*N*-CO_2Me	89	69
3	CO_2*t*-Bu (Boc)	*N*-CO_2Me	78	72
4	**CO_2Bn (Cbz)**	***N*-CO_2Me**	**89**	**92**
5	Cbz	*N*-Cbz	76	19
6	Cbz	*N*-Boc	83	0

Next, the ester moiety of the catalysts was optimized in a probe reaction of **2** with **7a** (Table S7). Without protection, the enantioselectivity of **8a** was low (entry 1). In contrast, either catalyst with Me (entry 2), *n*-Pr (entry 3), or *i*-Pr (entry 4) protection was effective, and **8a** was obtained in high yields with high enantioselectivities (92–95% ee). In particular, the catalyst with the *i*-Pr moiety (i.e., (*R*)-**10c**, entry 4) slightly more effective (95% ee) than the others.

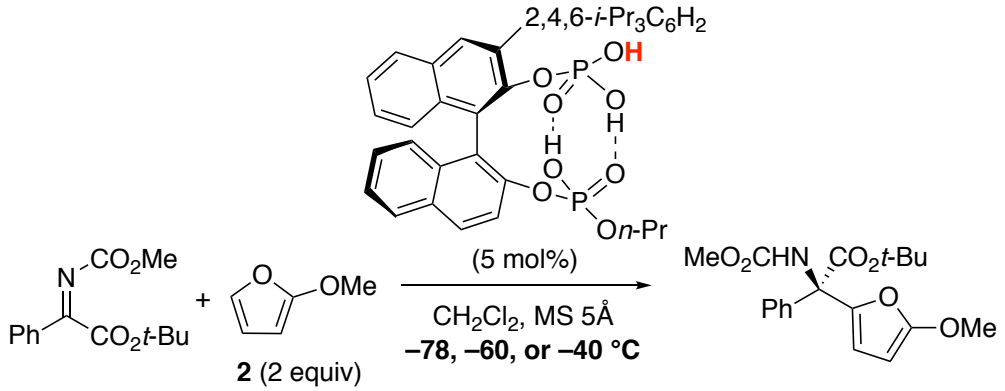
Table S7 Optimization of the ester moiety of the catalysts.



Entry	R	Yield (%)	ee (%)
1	H [(*R*)-**9c**]	82	18
2	Me	92	92
3	*n*-Pr	89	92
4	***i*-Pr** [(*R*)-**10c**]	**93**	**95**

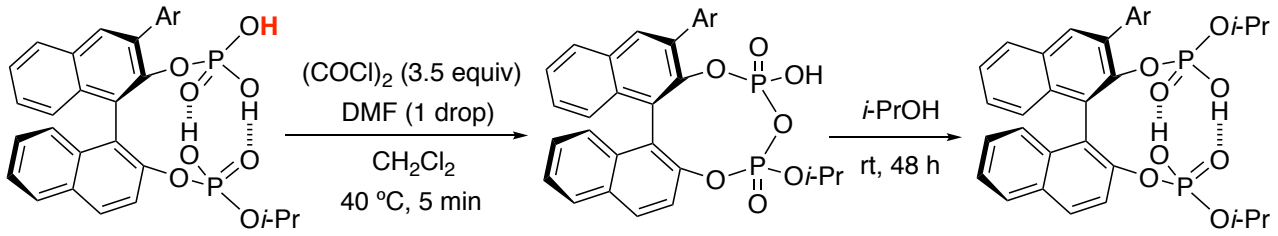
Next, the reaction temperature was examined in an unoptimized probe reaction (Table S8). At –78 °C, the reaction proceeded sluggishly, and the product was obtained in 79% yield with 70% ee (entry 1). At –40 °C, the reaction proceeded very smoothly, although the enantioselectivity was slightly reduced (64% ee) (entry 3). In contrast, at –60 °C, the reaction proceeded smoothly, and the product was obtained in 78% yield with 72% ee (entry 2). Based on these results, we set the temperature at –60 °C.

Table S8 Optimization of the reaction temperature.



Entry	Temperature (°C)	Reaction time [h]	Yield (%)	ee (%)
1	–78	24	79	70
2	**–60**	**12**	**78**	**72**
3	–40	1	87	64

20. Preparation of (*R*)-S32 and the control experiments.

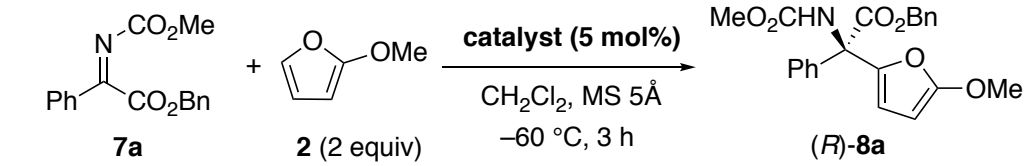


(*R*)-**10c** (Ar = 2,4,6-$Cy_3C_6H_2$) (*R*)-**S31** (*R*)-**S32**

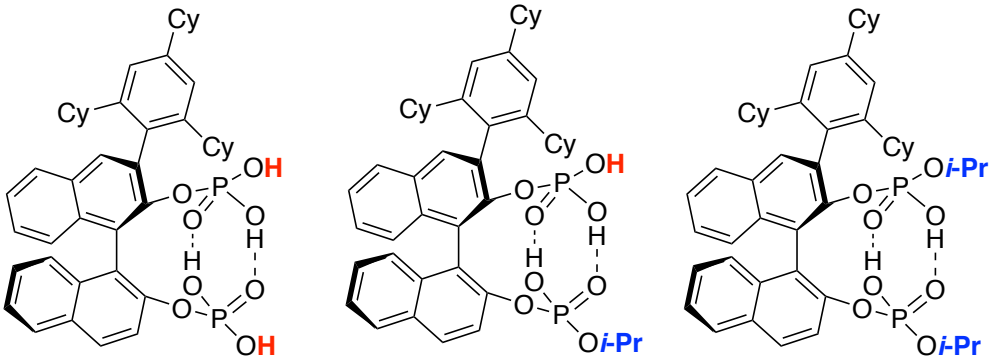
To a solution of (*R*)-**10c** (8.1 mg, 0.010 mmol) in dichloromethane (0.2 mL), one drop of *N*,*N*-dimethylformamide was added at room temperature. Then oxalyl chloride (3.0 μL, 0.035 mmol) was added at room temperature, and the mixture was warmed to 40 °C. The mixture was stirred at 40 °C for 5 min. Volatiles were removed *in vacuo* under heat conditions (ca. 40–50 °C). The obtained (*R*)-**S31** was used in the next step without further purification. (*R*)-**S31** was dissolved in methanol (2 mL) and the solution was stirred at room temperature for 4 h. Excess mthanol was then removed *in vacuo*. The obtained product was dissolved in toluene (2 mL), and the volatiles were thoroughly removed under reduced pressure to give (*R*)-**S32** as light brown solid. (80% yield (ca. 90% purity, (*R*)-**10c** was involved), 6.8 mg).

Diisopropyl ((*R*)-3-(2,4,6-tricyclohexylphenyl)-[1,1'-binaphthalene]-2,2'-diyl) bis(hydrogen phosphate) ((*R*)-S32): ca. 90% purity (Impurity is inseparable (*R*)-**10c**, which might be generated by the reaction of (*R*)-**S31** with adventitious water.). Light brown solid. ^{1}H NMR (400 MHz, THF-d_8) δ 0.69 (d, J = 6.4 Hz, 3H), 0.73 (d, J = 6.4 Hz, 3H), 0.85-1.80 (m, 23H), 0.96 (d, J = 6.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 1.81-1.98 (m, 5H), 2.05-2.08 (m, 2H), 2.43-2.61 (m, 3H), 3.27 (m, 1H), 4.31 (m, 1H), 6.52 (br, 2H), 7.05 (s, 1H), 7.12 (s, 1H), 7.23-7.45 (m, 6H), 7.83 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.90-7.94 (m, 1H), 7.93 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, THF-d_8) Many peaks overlapped and are splited. δ 23.2, 23.3, 23.4, 23.5, 23.7, 23.8, 26.9, 27.0, 27.1, 27.6, 27.7, 27.8, 27.9, 30.5, 33.6, 33.7, 35.4, 35.5, 36.0, 37.8, 42.4, 42.6, 45.8, 72.3, 73.0, 73.1, 121.3, 122.3, 123.3, 125.1, 125.2, 125.5, 126.2, 126.3, 126.7, 127.1, 127.2, 128.5, 128.8, 130.6, 131.8, 132.0, 132.7, 133.6, 133.7, 134.3, 146.7, 147.0, 147.1, 147.9, 148.0, 149.1, 149.2. ^{31}P NMR (160 MHz, THF-d_8) δ –7.01, –4.83. IR (KBr) 3644, 3313, 2926, 2851, 1729, 1602, 1509, 1468, 1448, 1235, 1031, 997 cm^{-1}. M.p. 229-253 °C (decomposition). $[\alpha]_D^{23}$ = +186.0 (*c* 1.00, $CHCl_3$). HRMS (FAB+) calcd for $C_{50}H_{63}O_8P_2$ $[M+H]^+$ 853.3998, found 853.4006.

Summary of the reaction with the use of (*R*)-**9c**, (*R*)-**10c**, and (*R*)-**S32** is shown in Scheme S8.

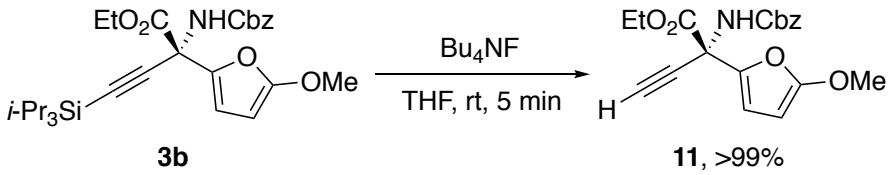


catalysts and results



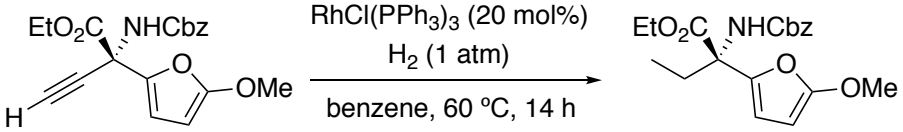
Scheme S8 Role of Brønsted acid in the catalysts.

21. Transformation of 3b to 12–14 by selective reduction (Scheme 3a).



3b **11**, >99%

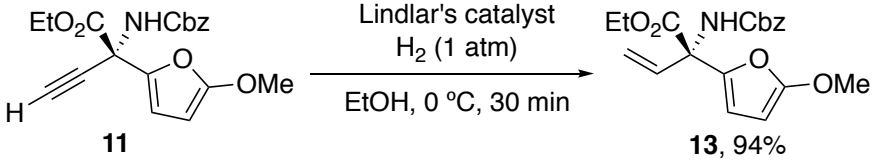
Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(5-methoxyfuran-2-yl)but-3-ynoate (11): THF (24 mL) was added to a two-necked round bottom flask with (*S*)-**3b** (1.04 g, 2.02 mmol, 91% ee), and the solution was stirred at room temperature. Tetrabuthylammonium fluoride (1.0 *M* in THF, 2.4 mL, 2.4 mmol) was added to the solution, and the mixture was stirred at room temperature for 5 min. The reaction mixture was passed through short silica gel with *n*-hexane and ethyl acetate (2:1). The filtrate was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 2:1) to give the desired product **11** as yellow oil (724 mg, >99% yield). A trace amount of EtOAc and Et_2O remained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.3 Hz, 3H), 2.62 (s, 1H), 3.82 (s, 3H), 4.29 (br, 2H), 5.09 (d, *J* = 12.4 Hz, 1H), 5.14 (d, *J* = 4.1 Hz, 1H), 5.15 (d, *J* = 12.4 Hz, 1H), 6.13 (br, 1H), 6.56 (br, 1H) 7.29-7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 55.8, 57.6, 63.5, 66.8, 73.1, 77.9, 80.7, 111.7, 128.0 (3C), 128.3 (2C), 135.9, 137.6, 153.8, 161.5, 166.3. IR (neat) 3413, 3292, 2979, 2898, 2124, 1758, 1614, 1574, 1504, 1369, 1020 cm^{-1}. $[\alpha]_D^{23}$ = +14.4 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{19}H_{19}NNaO_6$ $[M+Na]^+$ 380.1110, found 380.1103.



11 **12**, 99%

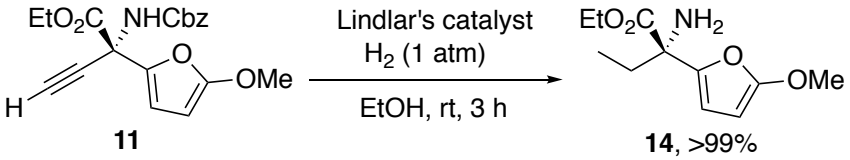
Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(5-methoxyfuran-2-yl)butanoate (12): To a round bottom flask with **11** (129.7 mg, 0.363 mmol) and chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's catalyst) (37.0 mg, 0.040 mmol) was added benzene (10 mL) under a nitrogen atmosphere. The flask was purged with hydrogen with a balloon (1 atm). The mixture was stirred at 60 °C for 14 h. The reaction mixture was passed through short silica gel with *n*-hexane and ethyl acetate (3:1). The solution was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 9:1 to 3:1) to give the desired product **12** as colorless oil (131.1 mg, >99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.3 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H), 2.28 (m, 1H), 2.65 (br, 1H), 3.79 (s, 3H), 4.11-4.30 (m, 2H), 5.01 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 5.09 (d, *J* = 2.7 Hz, 1H), 6.18 (br, 1H), 6.25 (br, 1H), 7.27-7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 14.0, 25.5, 57.6, 62.3, 62.4, 66.4, 80.3, 108.9, 127.9 (2C), 128.0, 128.5 (2C), 136.5, 141.7, 153.9, 160.9, 170.6. IR (neat) 3420, 2978, 1726, 1616, 1578, 1496, 1369, 1304, 1251, 1069, 1022 cm^{-1}. $[\alpha]_D^{24}$ =

+46.4 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{19}H_{23}NNaO_6$ $[M+Na]^+$ 384.1423, found 384.1423.



11 **13**, 94%

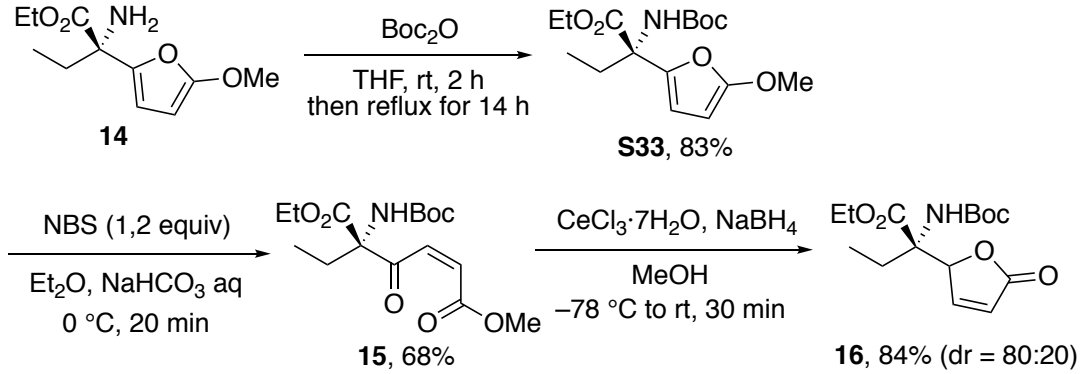
Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(5-methoxyfuran-2-yl)but-3-enoate (13): To a round bottom flask with **11** (79.8 mg, 0.223 mmol) and Lindlar's catalyst (120 mg, 150 w/w%) was added ethanol (2 mL). The flask was purged with hydrogen with a balloon (1 atm). The mixture was stirred at 0 °C for 30 min. The reaction mixture was passed through a pad of Celite with diethyl ether (20 mL). The solution was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 6:1 to 2:1) to give the desired product **13** as colorless oil (75.3 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 6.9 Hz, 3H), 3.81 (s, 3H), 4.22 (br, 2H), 5.03 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 2.7 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.38 (d, *J* = 10.5 Hz, 1H), 5.39 (d, *J* = 17.4 Hz, 1H), 6.14 (br, 1H), 6.26 (br, 1H), 6.40 (dd, *J* = 17.2, 10.5 Hz, 1H), 7.30-7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 57.7, 62.7, 62.9, 66.7, 80.4, 110.6, 117.1, 128.1 (3C), 128.5 (2C), 133.2, 136.4, 140.2, 154.0, 161.3, 169.2. IR (neat) 3414, 2940, 1731, 1614, 1576, 1496, 1386, 1259, 1023 cm^{-1}. $[\alpha]_D^{26}$ = +12.8 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{19}H_{21}NNaO_6$ $[M+Na]^+$ 382.1267, found 382.1283.



11 **14**, >99%

Ethyl (*S*)-2-amino-2-(5-methoxyfuran-2-yl)butanoate (14): To a round bottom flask with **11** (198.9 mg, 0.557 mmol) and Lindlar's catalyst (300 mg, 150 w/w%) was added ethanol (5.6 mL). The flask was purged with hydrogen with a balloon (1 atm). The mixture was stirred at room tempurature for 2 h. The reaction mixture was passed through a pad of Celite with diethyl ether (80 mL). The solution was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 7:3 to 1:1) to give the desired product **14** as colorless oil (126.5 mg, >99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.25 (t, *J* = 7.3 Hz, 3H), 1.89 (br, 2H), 1.96 (m, 1H), 2.11 (m, 1H), 3.81 (s, 3H), 4.12-4.26 (m, 2H), 5.07 (d, *J* = 3.2 Hz, 1H), 6.14 (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 14.1, 30.3, 57.6, 60.7, 61.5, 79.9, 106.9, 145.7, 160.9, 173.6. IR (neat) 3391, 2977, 2941, 1733, 1615, 1578, 1458, 1367, 1261, 1230, 1056, 1021 cm^{-1}. $[\alpha]_D^{27}$ = +29.2 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{11}H_{17}NNaO_4$ $[M+Na]^+$ 250.1055, found 250.1061.

22. Transformation of 14 to γ-butenolide 16 (Scheme 3a).



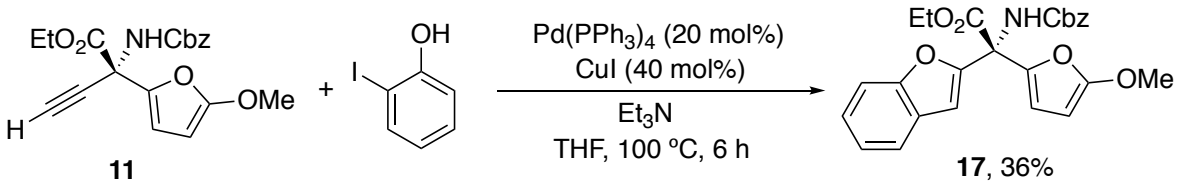
Ethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-(5-methoxyfuran-2-yl)butanoate (S33): S33 was synthesized based on the literature procedure.[20] THF (0.14 mL) was added to a pyrex Schlenk tube with **14** (61.1 mg, 0.268 mmol, 91% ee), and the solution was stirred at room temperature. Di-*tert*-butyl dicarbonate (61 μL, 0.282 mmol) was added to the solution, and the mixture was stirred at reflux temperature for 14 h. Volatiles were removed at room temperature under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 9:1 to 7:3) to give the desired product **S33** as colorless oil (72.8 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.3 Hz, 3H), 1.23 (t, *J* = 7.3 Hz, 3H), 1.40 (s, 9H), 2.27 (m, 1H), 2.55 (br, 1H), 3.81 (s, 3H), 4.13-4.27 (m, 2H), 5.10 (d, *J* = 3.2 Hz, 1H), 5.82 (br, 1H) 6.21 (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 14.1, 25.8, 28.3 (3C), 57.7, 62.1 (2C), 79.4, 80.4, 108.6, 142.1, 153.6, 160.8, 170.9. IR (neat) 3429, 3134, 2978, 1724, 1615, 1578, 1487, 1367, 1307, 1261, 1168, 1135, 1068, 1022 cm^{-1}. $[\alpha]_D^{22}$ = +42.0 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{16}H_{25}NNaO_6$ $[M+Na]^+$ 350.1580, found 350.1581.

6-Ethyl 1-methyl (*S,Z*)-5-((*tert*-butoxycarbonyl)amino)-5-ethyl-4-oxohex-2-enedioate (15): 15 was synthesized based on the literature procedure.[21] Diethyl ether (3 mL) and saturated aqueous $NaHCO_3$ (3 mL) were added to a round bottom flask with **S33** (106.3 mg, 0.325 mmol, 91% ee), and the solution was stirred at 0 °C. *N*-bromosuccinimide (69.0 mg, 0.387 mmol) was added to the solution, and the mixture was stirred at 0 °C for 20 min. The resulting mixture was extracted with diethyl ether (10 mL × 3), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 4:1 to 3:2) to give the desired product **15** as colorless oil (75.6 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.44 (s, 9H), 2.33 (m, 1H), 2.49 (m, 1H), 3.77 (s, 3H), 4.16-4.30 (m, 2H), 6.06 (s, 1H), 6.23 (d, *J* = 12.4 Hz, 1H) 6.63 (d, *J* = 11.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5, 14.0, 25.5, 28.3 (3C), 52.3, 62.7, 72.3, 80.3, 131.3, 131.8, 154.1, 166.1, 168.3, 193.0. IR (neat) 3423, 2979, 1717, 1486, 1368, 1247, 1168, 1054 cm^{-1}. $[\alpha]_D^{23}$ = –20.8 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{16}H_{25}NNaO_7$ $[M+Na]^+$

366.1529, found 366.1526.

Ethyl (2*S*)-2-((*tert*-butoxycarbonyl)amino)-2-(5-oxo-2,5-dihydrofuran-2-yl)butanoate (16): 16 was synthesized based on the literature procedure.[22] Methanol (4 mL) was added to a round bottom flask with **15** (75.6 mg, 0.220 mmol, 91% ee), and the solution was stirred at room temperature. Cerium(III) chloride heptahydrate (82.0 mg, 0.220 mmol) was added to the solution, and the mixture was stirred at room temperature for 10 min. The mixture was cooled to –78 °C, and sodium borohydride (8.3 mg, 0.219 mmol) was added. Then the mixture was warmed to room temperature and stirred at that temperature for 30 min. The resulting mixture was quenched with saturated aqueous NH_4Cl (5 mL), extracted with diethyl ether (10 mL × 3), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 4:1 to 3:2) to give the desired product **16** as colorless oil (57.9 mg, 84% yield, dr = 80:20). The absolute configuration has not been determined. Two diastereomers could not be separated from each other. IR (neat, mixture of **isomer I** and **isomer II**) 3422, 2979, 1762, 1497, 1369, 1315, 1252, 1164, 1092 cm^{-1}. HRMS (FAB+, mixture of **I** and **II**) calcd for $C_{15}H_{23}NNaO_6$ $[M+Na]^+$ 336.1423, found 336.1425. **Major isomer I:** ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.3 Hz, 3H), 1.31 (t, *J* = 7.3 Hz, 3H), 1.40 (s, 9H), 1.95 (m, 1H), 2.64 (m, 1H), 4.28 (q, *J* = 7.3 Hz, 2H), 5.53 (m, 2H), 6.09 (dd, *J* = 5.5, 1.8 Hz, 1H), 7.71 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 14.1, 23.8, 28.2 (3C), 62.8, 65.6, 80.0, 85.3, 121.6, 153.7, 156.0, 170.4, 172.6. **Minor isomer II:** ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.28 (t, *J* = 7.3 Hz, 3H), 1.36 (s, 9H), 1.89-2.10 (m, 2H), 4.23 (q, *J* = 7.3 Hz, 2H), 4.84 (br, 1H), 5.57 (br, 1H), 5.99 (dd, *J* = 5.5, 1.8 Hz, 1H), 7.77 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 14.2, 28.1 (3C), 29.0, 61.7, 63.9, 80.4, 82.9, 120.1, 154.1, 154.3, 169.8, 173.3.

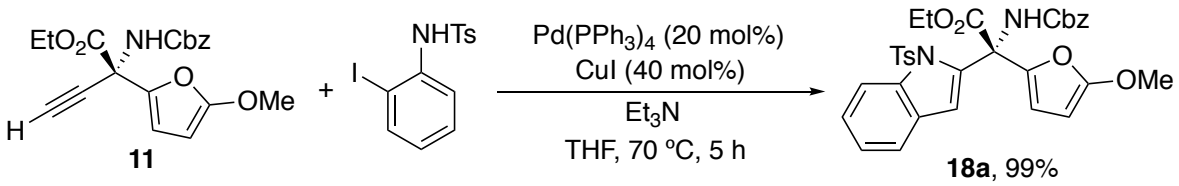
23. Transformation of 11 to 17 (Scheme 3b).



Ethyl (*S*)-2-(benzofuran-2-yl)-2-(((benzyloxy)carbonyl)amino)-2-(5-methoxyfuran-2-yl) acetate (17): 17 was synthesized based on the literature procedure.[22] To a two-necked round bottom flask with **11** (233 mg, 0.651 mmol, 91% ee), 2-iodophenol (404 mg, 1.83 mmol), tetrakis(triphenylphosphine) palladium(0) (80 mg, 0.069 mmol), and copper(I) iodide (27 mg, 0.14 mmol) were added THF (3 mL) under a nitrogen atmosphere. Triethylamine (7 mL) was added to the solution at 0 °C, and the mixture was stirred at 70 °C for 6 h. The resulting mixture was then

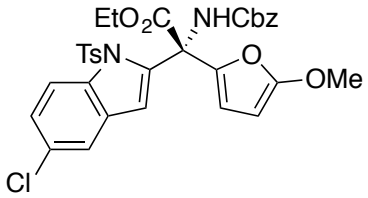
cooled in ice bath, and diluted with diethyl ether (20 mL) and 1 *M* HCl aqueous solution (10 mL). The mixture was extracted with diethyl ether (20 mL × 2) and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:2) to give the product **17** as orange oil (104 mg, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 6.9 Hz, 3H), 3.83 (s, 3H), 4.26 (q, *J* = 6.9 Hz, 2H), 5.05 (s, 2H), 5.17 (d, *J* = 3.2 Hz, 1H), 6.44 (br, 1H), 6.49 (br, 1H), 6.94 (br, 1H), 7.20-7.40 (m, 7H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 57.8, 61.5, 63.4, 66.9, 80.8, 107.0, 111.4, 111.9, 121.5, 123.0, 124.6, 128.0 (4C), 128.4 (2C), 136.2, 138.3, 152.0, 154.0, 154.7, 161.4, 167.5. IR (neat) 3412, 2975, 2938, 1734, 1615, 1574, 1496, 1454, 1369, 1256, 1121, 1024 cm^{-1}. $[\alpha]_D^{29}$ = +4.4 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{25}H_{23}NNaO_7$ $[M+Na]^+$ 472.1372, found 472.1382.

24. Transformation of 11 to 18 (Scheme 3c).

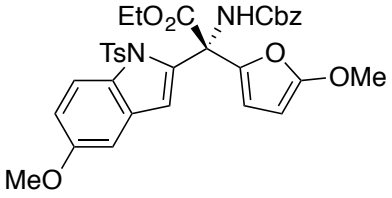


Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(5-methoxyfuran-2-yl)-2-(1-tosyl-1*H*-indol-2-yl) acetate (18a): 18a was synthesized based on the literature procedure.[22] To a two-necked round bottom flask with **11** (154 mg, 0.432 mmol, 91% ee), *N*-(2-iodophenyl)-4-toluenesulfonamide (323 mg, 0.865 mmol), tetrakis(triphenylphosphine) palladium(0) (104 mg, 0.090 mmol), and copper(I) iodide (34 mg, 0.18 mmol) was added THF (1 mL) under a nitrogen atmosphere. Triethylamine (1 mL, 7.2 mmol) was added to the solution at 0 °C, and the mixture was stirred at 70 °C for 5 h. The resulting mixture was then cooled in ice bath, and diluted with diethyl ether (5 mL) and 1 *M* HCl aqueous solution (10 mL). The mixture was extracted with diethyl ether (20 mL × 2) and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give the product **18a** as orange oil (257 mg, 99% yield). A trace amount of Et_2O and EtOAc remained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.3 Hz, 3H), 2.25 (s, 3H), 3.82 (s, 3H), 4.32 (q, *J* = 7.3 Hz, 2H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.99 (d, *J* = 12.4 Hz, 1H), 5.19 (d, *J* = 3.2 Hz, 1H), 6.32 (br, 1H), 6.62 (br, 1H), 6.82 (br, 1H), 7.02 (d, *J* = 7.8 Hz, 2H), 7.17-7.37 (m, 7H), 7.48 (d, *J* = 6.4 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.88 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.2, 57.5, 62.2, 63.1, 66.1, 80.9, 111.7, 114.3, 116.7, 121.5, 123.2, 124.9, 126.3 (2C), 127.5 (2C), 127.8, 127.9, 128.3 (2C), 129.4 (2C), 136.1, 136.2, 136.8, 137.2, 138.8, 144.3, 153.5, 161.1, 167.6. IR (neat) 3415, 2978,

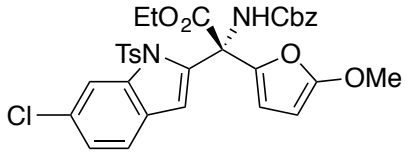
1736, 1613, 1572, 1495, 1452, 1366, 1250, 1175, 1036 cm^{-1}. $[\alpha]_D^{26} = -79.2$ (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{32}H_{30}N_2NaO_8S$ $[M+Na]^+$ 625.1621, found 625.1635.



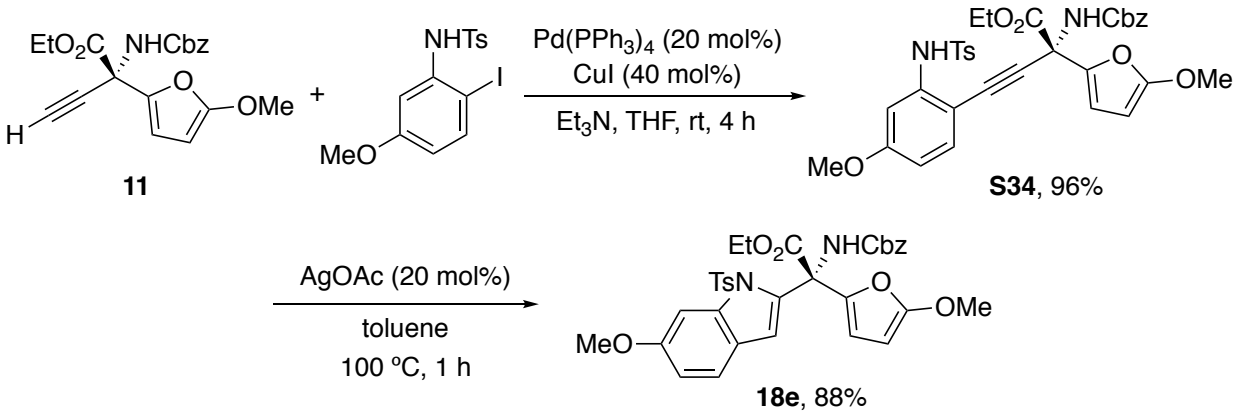
Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(5-chloro-1-tosyl-1*H*-indol-2-yl)-2-(5-methoxy furan-2-yl)acetate (18b): A trace amount of Et_2O remained. Orange oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.3 Hz, 3H) 2.27 (s, 3H), 3.82 (s, 3H), 4.32 (q, *J* = 7.3 Hz, 2H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.99 (d, *J* = 12.4 Hz, 1H), 5.19 (d, *J* = 3.7 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 6.60 (br, 1H), 6.74 (br, 1H), 7.04 (d, *J* = 7.3 Hz, 2H), 7.20 (d, *J* = 9.2 Hz, 1H), 7.26-7.37 (m, 5H), 7.45 (s, 1H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.5, 57.8, 62.3, 63.5, 66.4, 81.3, 112.0, 115.7, 116.1, 121.2, 125.3, 126.6 (2C), 127.9 (2C), 128.1, 128.6 (2C), 129.1, 129.4, 129.7 (2C), 135.8, 136.3 (2C), 138.6, 138.8, 144.7, 153.7, 161.3, 167.6. IR (neat) 3411, 2926, 1738, 1613, 1496, 1448, 1368, 1248, 1172, 1036 cm^{-1}. $[\alpha]_D^{25} = -111.6$ (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{32}H_{29}ClN_2NaO_8S$ $[M+Na]^+$ 659.1231, found 659.1231.



Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(5-methoxy-1-tosyl-1*H*-indol-2-yl)-2-(5-methoxy furan-2-yl)acetate (18c): Orange oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.3 Hz, 3H), 2.24 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.32 (q, *J* = 7.3 Hz, 2H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.99 (d, *J* = 12.8 Hz, 1H), 5.18 (d, *J* = 3.2 Hz, 1H), 6.30 (d, *J* = 2.8 Hz, 1H), 6.62 (s, 1H), 6.76 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.92 (s, 1H), 7.01 (d, *J* = 7.8 Hz, 2H), 7.25-7.39 (m, 5H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.3, 55.4, 57.6, 62.2, 63.1, 66.1, 81.0, 103.5, 111.7, 114.2, 115.3, 117.0, 126.3 (2C), 127.6 (2C), 127.9, 128.3 (2C), 128.9, 129.4 (2C), 131.9, 136.2, 136.3, 137.4, 138.9, 144.2, 153.5, 156.2, 161.1, 167.7. IR (neat) 3414, 2983, 1737, 1613, 1495, 1472, 1365, 1258, 1213, 1174, 1035 cm^{-1}. $[\alpha]_D^{26} = -124.8$ (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{33}H_{32}N_2NaO_9S$ $[M+Na]^+$ 655.1726, found 655.1730.



Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(6-chloro-1-tosyl-1*H*-indol-2-yl)-2-(5-methoxy furan-2-yl)acetate (18d): A trace amount of Et_2O remained. Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.3 Hz, 3H), 2.27 (s, 3H), 3.82 (s, 3H), 4.32 (q, *J* = 7.3 Hz, 2H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.98 (d, *J* = 11.9 Hz, 1H), 5.18 (d, *J* = 3.2 Hz, 1H), 6.29 (d, *J* = 3.2 Hz, 1H), 6.58 (br, 1H), 6.76 (br, 1H), 7.06 (d, *J* = 7.8 Hz, 2H), 7.18 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.25-7.42 (m, 6H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.5, 57.7, 62.3, 63.4, 66.3, 81.2, 111.9, 114.7, 116.3, 122.4, 124.1, 126.5 (2C), 126.6, 127.7 (2C), 128.1, 128.5 (2C), 129.7 (2C), 131.0, 136.2 (2C), 137.8 (2C), 138.9, 144.7, 153.7, 161.3, 167.6. IR (neat) 3411, 2936, 1737, 1613, 1495, 1448, 1368, 1250, 1174, 1035 cm^{-1}. $[\alpha]_D^{26}$ = –173.2 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{32}H_{29}ClMN_2NaO_8S$ $[M+Na]^+$ 659.1231, found 659.1209.

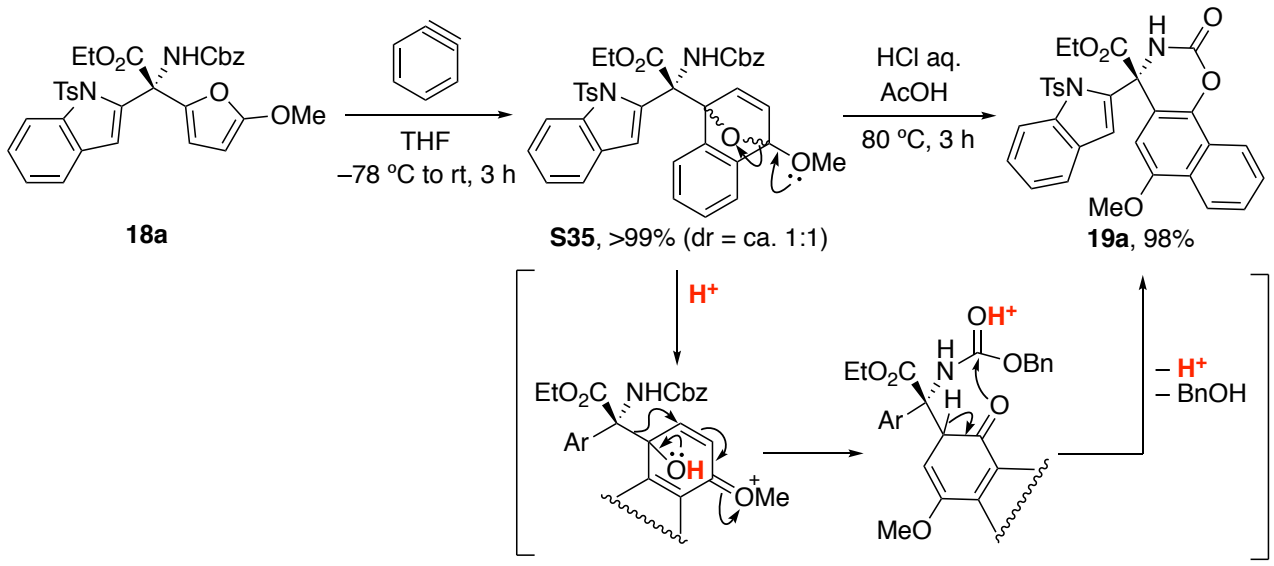


Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-4-(4-methoxy-2-((4-methylphenyl)sulfonamido) phenyl)-2-(5-methoxyfuran-2-yl)but-3-ynoate (S34): S34 was synthesized based on the literature procedure.[23] To a two-necked roundbottom flask with **11** (261 mg, 0.730 mmol, 91% ee), *N*-(2-iodophenyl)-4-toluenesulfonamide (590 mg, 1.46 mmol), tetrakis(triphenylphosphine) palladium(0) (42 mg, 0.0363 mmol), and copper(I) iodide (14 mg, 0.0735 mmol) was added THF (6 mL) under a nitrogen atmosphere. Triethylamine (2 mL, 14.3 mmol) was added to the solution at 0 °C, and the mixture was stirred at room temperature for 4 h. The resulting mixture was then cooled in ice bath, and diluted with diethyl ether (5 mL) and 1 *M* HCl aqueous solution (10 mL). The mixture was extracted with diethyl ether (20 mL × 2) and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 4:1 to 3:2) to give the product **S34** as orange oil (442.9 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.3 Hz, 3H), 2.35 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 4.35 (q, *J* = 7.3 Hz, 2H), 5.15 (d, *J* = 3.2 Hz, 1H), 5.20 (d, *J* = 11.9 Hz, 1H), 5.29 (d, *J* = 11.9 Hz, 1H), 6.25

(br, 1H), 6.45 (d, J = 3.2 Hz, 1H), 6.52 (dd, J = 8.7, 2.8 Hz, 1H), 7.13-7.43 (m, 9H), 7.77 (d, J = 8.2 Hz, 2H), 8.19 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.6, 55.5, 56.7, 57.9, 64.0, 67.5, 80.7, 80.8, 88.6, 104.3, 104.5, 110.1, 111.7, 127.4 (2C), 128.2, 128.4 (2C), 128.5 (2C), 129.6 (2C), 132.6, 136.0, 136.6, 138.0, 141.2, 143.6, 154.4, 161.0, 161.8, 166.7. IR (neat) 3405, 1717, 1613, 1574, 1507, 1407, 1340, 1261, 1159, 1091 cm^{-1}. $[\alpha]_D^{26}$ = –11.6 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{33}H_{32}N_2NaO_9S$ $[M+Na]^+$ 655.1726, found 655.1717.

Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-2-(6-methoxy-1-tosyl-1*H*-indol-2-yl)-2-(5-methoxy furan-2-yl)acetate (18e): 18e was synthesized based on the literature procedure.[24] Toluene (7 mL) was added to a round bottom flask with **S34** (443 mg, 0.70 mmol), and the solution was stirred at room tempurature. Silver(I) acetate (23.0 mg, 0.138 mmol) was added to the solution, and the mixture was stirred at 100 °C for 1 h. The reaction mixture was passed through short silica gel (eluent: *n*-hexane:EtOAc = 2:1). The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 4:1 to 3:2) to give the desired product **18e** as orange oil (390 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ .28 (t, J = 7.3 Hz, 3H), 2.26 (s, 3H), 3.79 (br, 3H), 3.82 (s, 3H), 4.31 (q, J = 7.3 Hz, 2H), 4.70 (d, J = 12.4 Hz, 1H), 5.00 (d, J = 12.4 Hz, 1H), 5.18 (d, J = 3.7 Hz, 1H), 6.30 (br, 1H), 6.60 (br, 1H), 6.75 (br, 1H), 6.83 (dd, J = 8.7, 2.3 Hz, 1H), 7.03 (d, J = 8.2 Hz, 2H), 7.26-7.42 (m, 7H), 7.56 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.5, 55.7, 57.8, 62.5, 63.3, 66.3, 81.2, 99.0, 111.8, 112.7, 117.0, 122.0, 122.3, 126.5 (2C), 127.8 (2C), 128.0, 128.5 (2C), 129.6 (2C), 135.7, 136.5 (2C), 138.6, 139.2, 144.4, 153.7, 158.2, 161.2, 168.0. IR (neat) 3416, 2975, 1737, 1613, 1492, 1364, 1260, 1172, 1028 cm^{-1}. $[\alpha]_D^{25}$ = –204.0 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{33}H_{32}N_2NaO_9S$ $[M+Na]^+$ 655.1726, found 655.1701.

25. Transformation of 18a to 19 (Scheme 3d).



Ethyl (2*S*)-2-(((Benzyloxy)carbonyl)amino)-2-(4-methoxy-1,4-epoxynaphthalen-1(4*H*)-yl)-2-(1-tosyl-1*H*-indol-2-yl)acetate (S35): S35 was synthesized based on the literature procedure.[25] To a well-dried pyrex Schlenk tube with cesium fluoride (261 mg, 1.72 mmol) in THF (4 mL) was added 18-crown-6 (680 mg, 2.58 mmol) in THF (4 mL). 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (210 μL, 0.86 mmol) was added, and the mixture was stirred at room temperature for 30 min. The mixture was cooled to –78 °C, and **18a** (257 mg, 0.426 mmol) in THF (2 mL) was added. Then the mixture was warmed to room temperature and stirred at that temperature for 2 h. The resulting mixture was diluted with water (5 mL), extracted with diethyl ether (20 mL × 2), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was roughly purified by short silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give the product **S35** as light blue oil (294 mg, >99% yield, dr = ca. 1:1), which was used in the next step as soon as possible. ^{1}H NMR (400 MHz, $CDCl_3$) Many peaks of the diastereomers (dr = ca. 1:1) overlapped. δ 1.27 (t, *J* = 7.3 Hz, 6H), 2.29 (s, 6H), 3.65 (s, 6H), 4.19-4.43 (m, 4H), 4.79 (d, *J* = 11.9 Hz, 2H), 5.12 (d, *J* = 10.5 Hz, 2H), 6.66-8.87 (m, 38H), 8.15 (d, *J* = 7.4 Hz, 2H), 8.28 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) Many peaks of the diastereomers (dr = ca. 1:1) overlapped. δ 13.8, 14.0, 15.1, 21.6, 29.8, 55.4, 59.1, 63.1, 64.2, 65.6, 66.5, 66.8, 83.5, 102.5, 114.5, 114.7, 119.5, 121.4, 121.9, 122.2, 123.2, 123.5, 123.6, 125.0, 125.6, 126.1, 126.4, 126.7, 126.9, 127.4, 127.8, 127.9, 128.1, 128.3, 128.5, 129.7, 136.3, 137.7, 144.4, 144.7, 149.3, 153.8, 166.9, 169.7. HRMS (FAB+) calcd for $C_{38}H_{34}N_2NaO_8S$ $[M+Na]^+$ 701.1934, found 701.1909.

Ethyl (*R*)-6-methoxy-2-oxo-4-(1-tosyl-1*H*-indol-2-yl)-3,4-dihydro-2*H*-naphtho[2,1-e][1,3]oxazine-4-carboxylate (19a): To a two-necked round bottom flask with **S35** (294 mg, 0.43 mmol) were added acetic acid (9 mL) and 12 *M* HCl aqueous solution (1 mL). The solution was stirred at 80 °C for 3 h. Then the resulting mixture was diluted with diethyl ether (20 mL) and $NaHCO_3$ aqueous solution (200 mL). The mixture was extracted with diethyl ether (20 mL × 2) and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give the product **19a** as colorless solid (241 mg, 98% yield). The enantiomeric purity of **19a** was determined by chiral HPLC analysis (91% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 6.9 Hz, 3H), 2.37 (s, 3H), 3.69 (s, 3H), 4.31 (m, 1H), 4.44 (m, 1H), 6.09 (s, 1H), 6.81 (s, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.2 Hz, 1H), 7.24-7.34 (m, 4H), 7.61-7.70 (m, 3H), 7.80 (d, *J* = 8.2 Hz, 2H), 8.31 (d, *J* = 9.1 Hz, 1H), 8.37 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.7, 56.0, 63.5, 64.5, 99.4, 111.5, 114.2, 114.7, 121.7, 121.9, 122.1, 123.8, 124.3, 125.8, 126.4, 127.2 (2C), 127.6 (2C), 127.9, 130.2 (2C), 135.3, 136.8, 139.8, 140.9, 145.5, 149.0, 152.3, 168.9. IR (KBr) 3359, 2925, 1731, 1593, 1460, 1354, 1243, 1170, 1106, 1089, 1057 cm^{-1}. M.p. 142 °C (decomposition). $[\alpha]_D^{30}$ = –204.3 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{31}H_{26}N_2NaO_7S$ $[M+Na]^+$ 593.1358, found

593.1340. HPLC analysis; OD-3 × 2, *n*-hexane/*i*-PrOH = 4/1, 254 nm, 0.6 mL/min, t_R = 25.2 min (major, *R*), 29.9 min (minor, *S*).

Crystal data of 19a (Fig. S11): Compound **19a** was recrystallized in benzene for X-ray analysis. Formula $C_{32}H_{27}Cl_3N_2O_7S$, colorless, crystal dimensions 0.75 × 0.12 × 0.10 mm^3, monoclinic, space group $P2_1$ (#4), a = 10.664(3) Å, b = 10.372(2) Å, c = 14.789(4) Å, α = 90.00 °, β = 104.778(6) °, γ = 90.00 °, V = 1581.7(7) Å^3, Z = 2, ρ_{calc} = 1.449 g cm^{-3}, F(000) = 712, μ(MoKα) = 0.407 mm^{-1}, T = 123 K. 13598 reflections collected, 6894 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.48 °), and 469 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Flack x = 0.009(16). R_1 = 0.0318 and wR_2 = 0.0794. GOF = 1.041. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1520624. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Web page: http://www.ccdc.cam.ac.uk/].

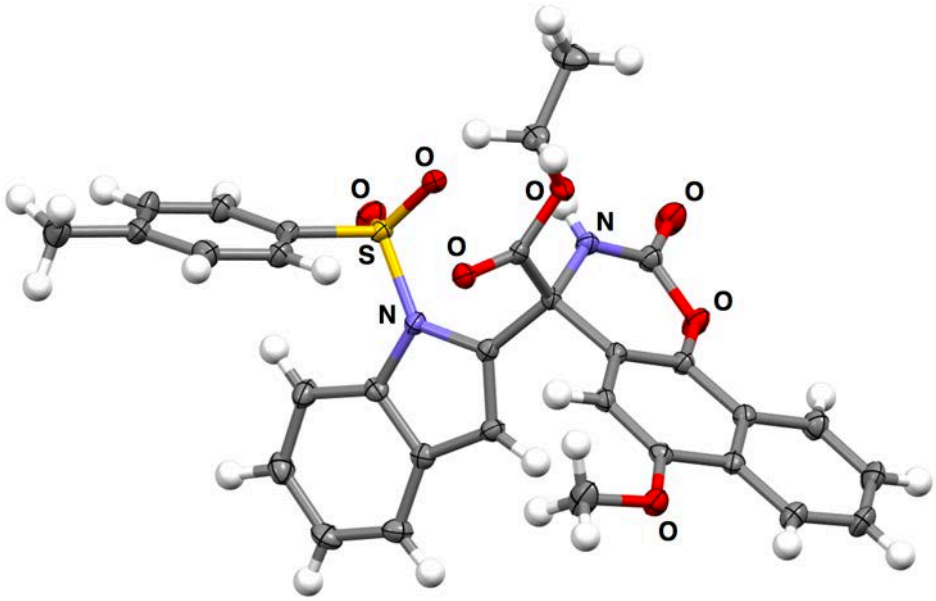
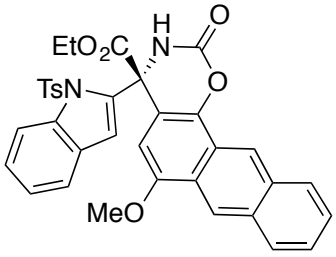


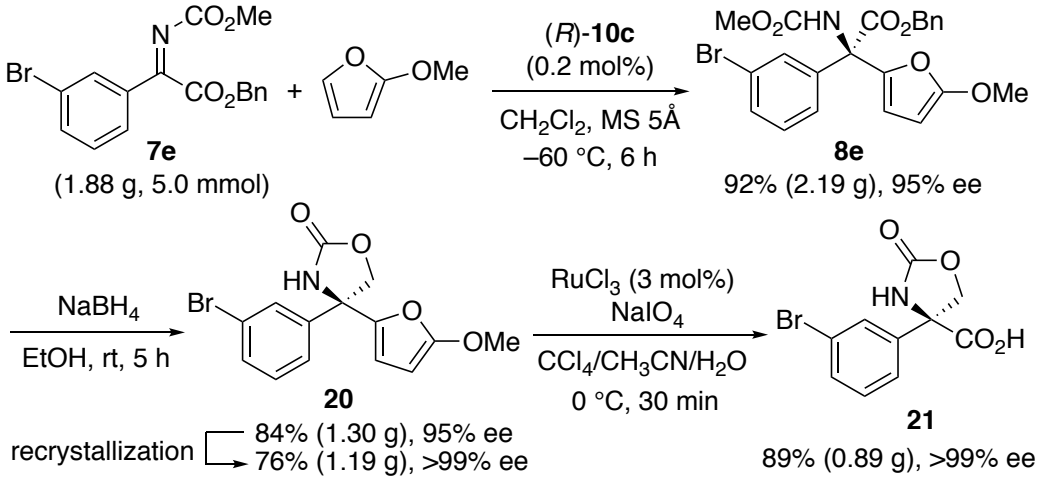
Fig. S11 ORTEP drawing of **19a**.



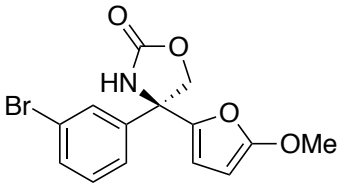
Ethyl (*R*)-6-methoxy-2-oxo-4-(1-tosyl-1*H*-indol-2-yl)-3,4-dihydro-2*H*-anthra[2,1-e][1,3] oxazine-4-carboxylate (19b): 3-(Trimethylsilyl)-2-naphthyl trifluoromethanesulfonate was used

in place of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate in the procedure above. A trace amount of Et_2O remained. Yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 6.9 Hz, 3H), 2.38 (s, 3H), 4.03 (s, 3H), 4.33 (m, 1H), 4.45 (m, 1H), 6.19 (s, 1H), 6.69 (s, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.29-7.31 (m, 3H), 7.36 (s, 1H), 7.56-7.59 (m, 2H), 7.64 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 2H), 8.06-8.13 (m, 2H), 8.87 (s, 1H), 8.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.7, 56.0, 63.5, 64.6, 97.1, 109.7, 114.3, 114.7, 121.5, 121.6, 121.7, 122.7, 123.8, 125.1, 125.8, 126.8 (2C), 127.3 (2C), 127.7, 128.7, 128.8, 130.2 (2C), 132.4, 132.5, 135.4, 136.9, 139.9, 140.8, 145.5, 149.0, 152.5, 169.0. IR (neat) 3416, 2975, 2927, 1741, 1459, 1358, 1308, 1239, 1173, 1089, 1041 cm^{-1}. $[\alpha]_D^{31}$ = –92.0 (*c* 1.00, $CHCl_3$, 91% ee). HRMS (FAB+) calcd for $C_{35}H_{28}N_2NaO_7S$ $[M+Na]^+$ 643.1515, found 643.1504.

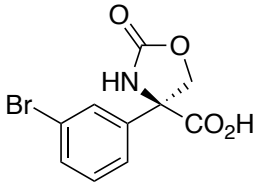
26. Gram-scale reaction and transformation to amino acid 21 (Scheme 4).



5 mmol scale reaction of 7e: To a well-dried two-necked flask charged with activated MS 5Å (1.25 g) under a nitrogen atmosphere were added (*R*)-**10c** (8.1 mg, 0.010 mmol) in dichloromethane (40 mL) at –78 °C. After 5 min, α-ketimino ester **7e** (1.881 g, 5.00 mmol) in dichloromethane (10 mL), and 2-methoxyfuran (930 μL, 10.0 mmol) were added at –78 °C. The reaction mixture was allowed to warm to –60 °C and was then stirred at that temperature for 6 h. The resulting mixture was quenched with triethylamine (0.1 mL) at –60 °C, and concentrated under reduced pressure at room temperature. The residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 3:1 to 1:1) to give the product **8e** (2.187 g, 92% yield). The enantiomeric purity was determined by chiral HPLC analysis (95% ee).



(*S*)-4-(3-Bromophenyl)-4-(5-methoxyfuran-2-yl)oxazolidin-2-one (20): To a solution of **8e** (2.187 g, 4.61 mmol, 95% ee) in ethanol (15 mL) was added sodium borohydride (0.698 g, 18.4 mmol). The mixture was stirred at room temperature for 5 h, and concentrated under reduced pressure. The resultant residue was dissolved in dichloromethane (30 mL). Saturated NH_4Cl aqueous solution (30 mL) was added, and the mixture was extracted with dichloromethane (10 mL × 3), and the combined organic layer was dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 2:1 to 1:1) to give the desired product **20** (1.302 g, 84% yield, 95% ee). Compound **20** was recrystallized from dichloromethane/diethyl ether/*n*-hexane (1:10:5) at room temperature (1.190 g, 76% yield, >99% ee). Coloreless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 4.41 (d, J = 8.7 Hz, 1H), 4.91 (d, J = 8.7 Hz, 1H), 5.11 (d, J = 3.2 Hz, 1H), 6.09 (d, J = 3.7 Hz, 1H), 6.34 (s, 1H), 7.24-7.32 (m, 2H), 7.46-7.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.9, 62.5, 75.1, 80.2, 110.4, 122.9, 124.4, 128.9, 130.4, 131.6, 142.6, 142.7, 158.8, 162.1. IR (KBr) 3317, 3071, 1761, 1736, 1615, 1575, 1372, 1262, 1038 cm^{-1}. M.p. 122 °C. $[\alpha]_D^{26}$ = +119.6 (*c* 1.00, $CHCl_3$, >99% ee). HPLC analysis; IA-3, CH_2Cl_2, 254 nm, 0.9 mL/min, t_R = 14.0 min (major, *S*), 33.7 min (minor, *R*). HRMS (FAB+) calcd for $C_{14}H_{12}BrNO_4$ $[M]^+$ 336.9950, found 336.9940.



(*S*)-4-(3-Bromophenyl)-2-oxooxazolidine-4-carboxylic acid (21): **21** was synthesized based on the literature procedure.[26] To a solution of **20** (1.190 g, 3.52 mmol) in acetonitrile (18 mL) and carbon tetrachloride (18 mL), water (35 mL) and sodium periodate (11.29 g, 52.8 mmol) were added at 0 °C. After stirred for 5 min, ruthenium(III) chloride (21.9 mg, 0.11 mmol) was added, and the mixture was stirred at 0 °C for 30 min. The mixture was filtered and the filtrate was extracted with ethyl acetate (15 mL × 3). Diethyl ether (10 mL) was added to the combined organic layer, and the solution was stirred at room temperature for 2 h. Ruthenium(IV) oxide was gradually precipitated. The suspension was dried over Na_2SO_4, and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform (20 mL), and extracted with $NaHCO_3$ aqueous solution (20 mL × 2). The combined aqueous layer was acidified with 3 *M* HCl aqueous solution (20 mL), and extracted with chloroform (15 mL × 3). The combined organic layer was dried over Na_2SO_4, and concentrated

under reduced pressure to give the desired product **21** (0.893 g, 89% yield). Light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (d, J = 9.2 Hz, 1H), 5.22 (d, J = 9.2 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 1.8 Hz, 1H), 7.78 (s, 1H), 8.87 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.7, 74.2, 123.4, 123.5, 128.0, 130.9, 132.4, 139.6, 160.2, 172.9. IR (neat) 3291, 1739, 1475, 1421, 1261, 1052 cm^{-1}. $[\alpha]_D^{27}$ = +106.0 (*c* 1.00, $CHCl_3$, >99% ee). HRMS (FAB+) calcd for $C_{10}H_9BrNO_4$ $[M+H]^+$ 285.9715, found 285.9709.

27. Theoretical study on the *E*/*Z*-geometry of substrates 1b and 7a.

With regard to Eqs. 2 and 3 in the main text, we considered the *E*/*Z*-geometry of the substrates. According to the literature, **1b** would have an *E*-geometry,[6] whereas **7a** would have a Z-geometry.[27] Indeed, a preliminary theoretical study was preliminary performed by a molecular mechanics method (MM2, Chem3D for Windows) (Fig. S12). As a result, (*E*)-**1b** was more stable than (*Z*)-**1b** by 8.12 kcal/mol (Fig. S12a). On the other hand, (*Z*)-**7a** was more stable than (*E*)-**7a** by 2.97 kcal/mol (Fig. S12b). Moreover, ^{1}H and ^{13}C NMR analyses of either **1b** or **7a** showed a single geometric isomer in $CDCl_3$ at room temperature, and thus the observed geometry (i.e., (*E*)-**1b** and (*Z*)-**7a**) should be quite stable.

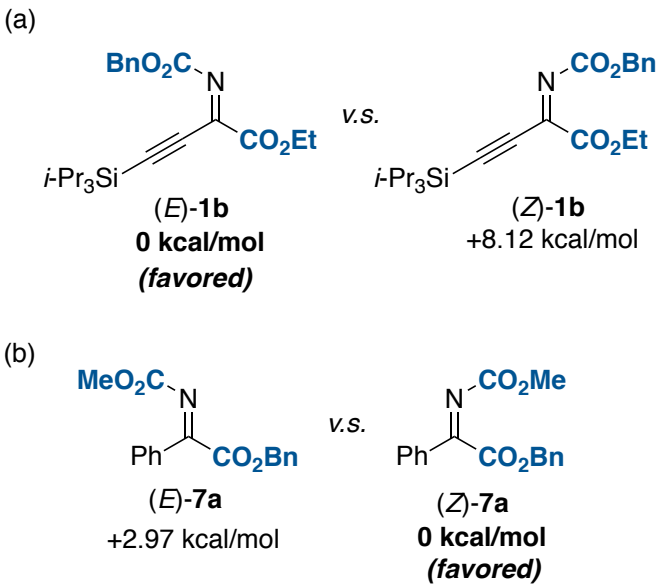


Fig. S12 Theoretical study for the *E*/*Z*-geometry of substrates **1b** and **7a**.

28. Possible transition states for the reactions.

Fig. S13a shows a possible transition state with the use of (*R*)-**5b**/**1b**/**2**. The imino nitrogen atom of **1b** might coordinate to the C_2-symmetric chiral Brønsted acid center of (*R*)-**5b**. Under these conditions, the sterically hindered *i*-Pr_3Si moiety of **1b** might be far from the 3,5-(*o*-Tol)C_6H_3 moiety and turned outward to avoid steric constraints. Nucleophile **2** would then selectively attack the activated **1b** from the *si*-face. As a result, enantioenriched (*S*)-**3b** might be provided (up to 91% ee). The steric effect of the silyl moiety might play an important role in the orientation of the substrates, and the sterically more hindered silyl moiety could induce high enantioselectivity: Ph (76% ee) < Ph_3Si (79% ee) < *t*-$BuMe_2Si$ (82% ee) < *t*-$BuPh_2Si$ (88% ee) < *i*-Pr_3Si (91% ee) (see Table S5).

Fig. S13b shows a possible transition state with the use of (*R*)-**10c**/**7a**/**2**. The imino nitrogen atom of **7a** might coordinate to the C_1-symmetric chiral Brønsted acid center of (*R*)-**10c**. Under these conditions, the sterically hindered phenyl moiety of **7a** might avoid steric constraints from the outstandingly bulky 2,4,6-$Cy_3C_6H_2$ moiety of catalyst (*R*)-**10c**. Nucleophile **2** would then selectively attack the activated **7a** from the *re*-face. As a result, enantioenriched (*R*)-**8a** might be provided (up to 95% ee).

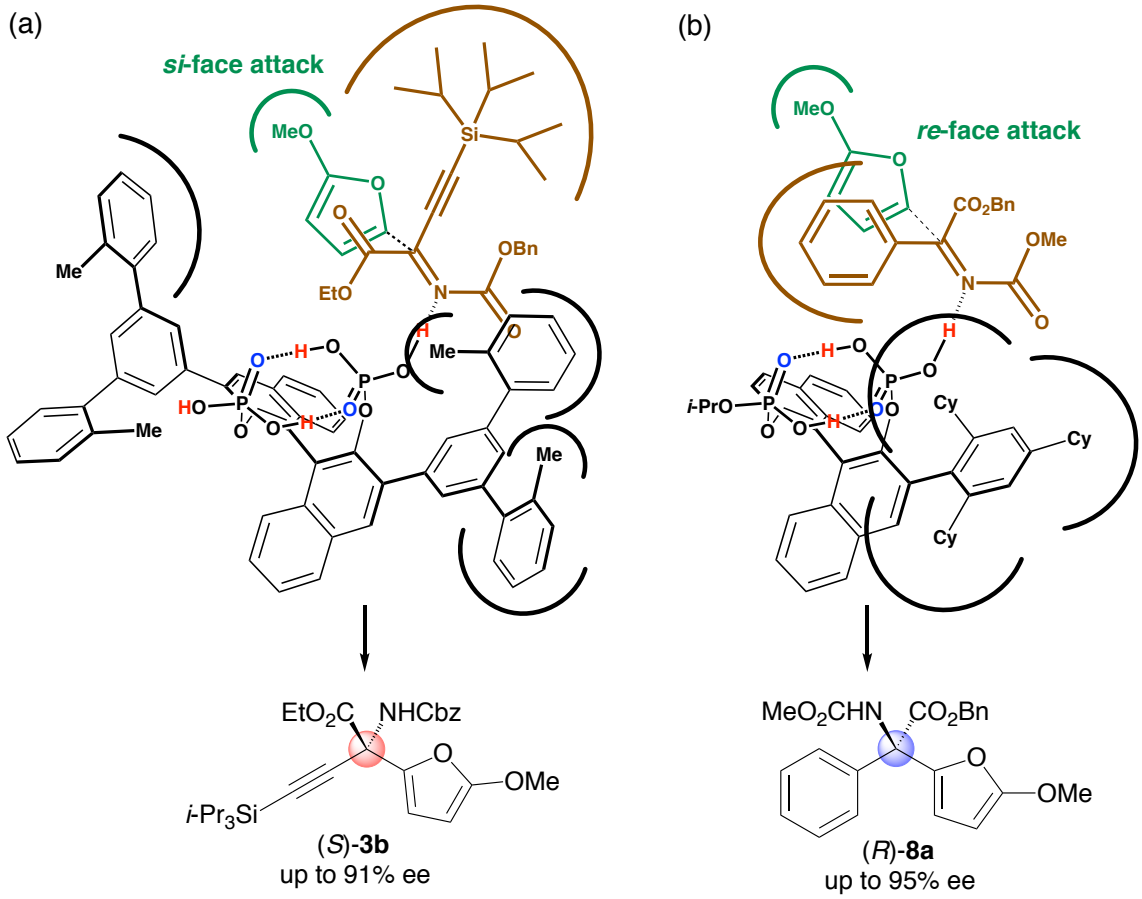


Fig. S13 Possible transition states for the reactions with the use of (*R*)-**5b** and (*R*)-**10c**.

29. References.

1 D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, 1956, **21**, 516.

2 B. Wang, C. M. Yu, Z. W. Chen and W. K. Su, *Chinese Chem. Lett.*, 2008, **19**, 904.

3 T. Harada and K. Kanda, *Org. Lett.*, 2006, **8**, 3817.

4 I. Mizota, Y. Matsuda, S. Kamimura, H. Tanaka and M. Shimizu, *Org. Lett.*, 2013, **15**, 4206.

5 M. Guo, D. Li and Z. Zhang, *J. Org. Chem.*, 2003, **68**, 10172.

6 M. Hatano, K. Yamashita, M. Mizuno, O. Ito and K. Ishihara, *Angew. Chem., Int. Ed.*, 2015, **54**, 2707.

7 W. Yan, D. Wang, J. Feng, P. Li, D. Zhao and R. Wang, *Org. Lett.*, 2012, **14**, 2512.

8 P. Calí and M. Begtrup, *Synthesis*, 2002, **2002**, 2515.

9 D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356.

10 M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem., Int. Ed.*, 2009, **48**, 2553.

11 T. Akiyama, H. Morita, J. Itoh and K. Fuchibe, *Org. Lett.*, 2005, **7**, 2583.

12 (*a*) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem., Int. Ed.* 2005, **44**, 7424; (*b*) M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett*, 2010, **2010**, 2189.

13 M. Hatano, T. Ozaki, K. Nishikawa and K. Ishihara, *J. Org. Chem.*, 2013, **78**, 10405.

14 S. Liu and L. G. Pedersen, *J. Phys. Chem. A*, 2009, **113**, 3648.

15 F. Krasovec and J. Jan, *Croat. Chem. Acta*, 1963, **35**, 183.

16 D. Shamir, I. Zilbermann, E. Maimon, A. I. Shames, H. Cohen and D. Meyerstein, *Inorg. Chim. Acta,* 2010, **363**, 2819.

17 P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Neudröfl, A. Berkessel and A. M. C. O'Donoghue, *Chem. Eur. J.*, 2011, **17**, 8524.

18 Y. Qian, C. Jing, C. Zhai and W.-h. Hua, *Adv. Synth. Catal.*, 2012, **354**, 301.

19 H. M. L. Davies, T. Hansen and M. R. Churchill, *J. Am. Chem. Soc.*, 2000, **122**, 3063.

20 K. Dolbeare, G. F. Pontoriero, S. K. Gupta, R. K. Mishra and R. L. Johnson, *J. Med. Chem.*, 2003, **46**, 727.

21 D. Uraguchi, K. Sorimachi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 11804.

22 B. Prasad, R. Adepu, S. Sandra, D. Rambabu, G. R. Krishna, C. M. Reddy, G. S. Deora, P. Misra and M. Pal, *Chem. Commun.*, 2012, **48**, 10434.

23 E. Chong and S. A. Blum, *J. Am. Chem. Soc.*, 2015, **137**, 10144.

24 (*a*) T. Kurisaki, T. Naniwa, H. Yamamoto, H. Imagawa and M. Nishizawa, *Tetrahedron Lett.*, 2007, **48**, 1871; (*b*) B. C. J. van Esseveldt, F. L. van Delft, J. M. M. Smits, R. de Gelder, H. E. Schoemaker and F. P. J. T. Rutjes, *Adv. Synth. Catal.*, 2004, **346**, 823.

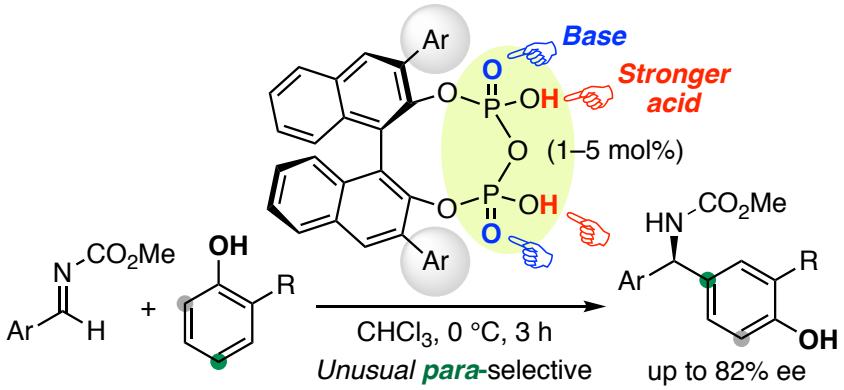
25 G. E. Collis and A. K. Burrell, *Tetrahedron Lett.*, 2005, **46**, 3653.

26 (*a*) F. Köhler, H.-J. Gais and G. Raabe, *Org. Lett.*, 2007, **9**, 1231; (*b*) H. Liu, J. Xu and D.-M. Du, *Org. Lett.*, 2007, **9**, 4725.

27 T. Hashimoto, K. Yamamoto and K. Maruoka, *Chem. Lett.*, 2011, **40**, 326.

Chapter 3

Chiral Pyrophosphoric Acid Catalysts for the *para*-Selective and Enantioselective Aza-Friedel–Crafts Reaction of Phenols

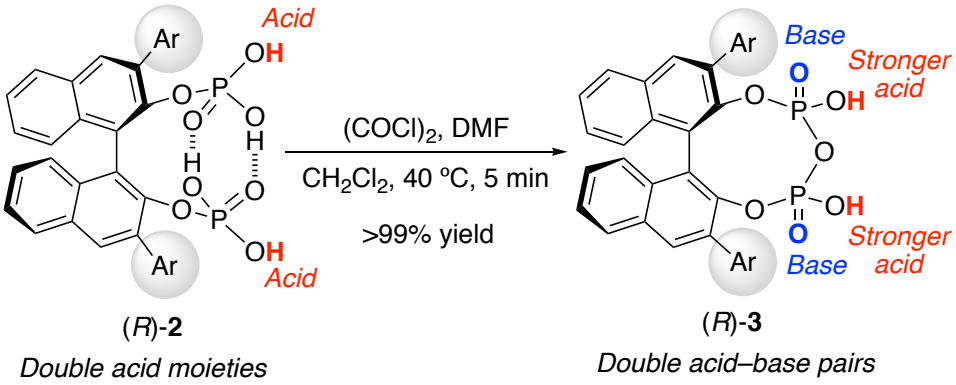


Abstract: Chiral BINOL-derived pyrophosphoric acid catalysts were developed and used for the regio- and enantioselective aza-Friedel–Crafts reaction of phenols with aldimines. *ortho/para*-Directing phenols could react at the *para*-position selectively with moderate to good enantioselectivities. Moreover, the gram-scale transformation of a product into the key intermediate for the antifungal agent (*R*)-bifonazole was demonstrated.

3-1 Introduction

Pyrophosphoric acid ($H_4P_2O_7$) is a dehydrative condensate of phosphoric acid (H_3PO_4) and is frequently provided *in vivo* as magnesium(II), calcium(II), and alkali metal(I) pyrophosphates from adenosine triphosphate (ATP).[1] Remarkably, pyrophosphoric acid ($pK_{a1}(H_2O) = 0.91$, $pK_{a2}(H_2O) = 2.10$) is a stronger acid than phosphoric acid ($pK_{a1}(H_2O) = 2.16$, $pK_{a2}(H_2O) = 7.21$).[2] Indeed, even pK_{a2} of pyrophosphoric acid is lower than pK_{a1} of phosphoric acid. Despite its potential as a strong diprotic acid motif for new chiral organocatalysts, to the best of our knowledge, a chiral pyrophosphoric acid has not yet been developed for asymmetric catalysis. In this regard, chiral BINOL (1,1'-bi-2-naphthol)-derived phosphoric acids **1** have been shown to be highly practical and powerful catalysts for a variety of asymmetric reactions.[3,4] Moreover, several BINOL-derived bis(phosphoric acid)s have recently been developed by Gong,[5] Momiyama/Terada,[6] and our group.[7] In particular, our recent chiral bis(phosphoric acid)s (*R*)-**2**[7] were highly effective for the enantioselective aza-Friedel–Crafts (aza-FC) reaction of 2-methoxyfuran[8] with α-ketimino esters. During the course of our previous study, we found that dehydrative condensation of (*R*)-**2** successfully provided the corresponding chiral pyrophosphoric acids (*R*)-**3** (Scheme 1).[7] Fortunately, since (*R*)-**3** are not very sensitive to moisture, we envisioned that a suitable catalytic system could make the best use of the possible double acid–base cooperative function of novel (*R*)-**3**.

Scheme 1. Preparation of chiral pyrophosphoric acid (*R*)-**3**.



(*R*)-**2**
Double acid moieties

(*R*)-**3**
Double acid–base pairs

In this study, we developed a regio- and enantioselective aza-FC reaction[9] of phenols **5**[10,11] with aldimines **4** through the use of chiral BINOL-derived pyrophosphoric acids (*R*)-**3** (Figure 1a). In this reaction, the catalyst should control both the regioselectivity of **5** (i.e.,

para- and *ortho*-control of **5** leading to **6** and **7**, respectively) and the enantioface-selectivity of **4**. Although simple phenols have an *ortho/para*-orientation,[12] *ortho*-addition is often preferred, particularly for basic carbonyl compounds due to the inherent directing properties of acidic phenols,[10] as seen in the traditional Betti reaction[13] between phenols, aldehydes, and amines (Figure 1b). Therefore, the *para*-selective catalytic asymmetric FC reaction of phenols has been very limited.[11] Moreover, in spite of the interesting remote regio-control by the asymmetric catalytic system, there has been no previous report on the reason or strategy for the prioritization of *para*-selectivity.[11] In this context, we were interested in the remote control of *para*-selectivity of **5** with aldimines **4** in the presence of the novel catalysts (*R*)-**3**. We cannot completely deny that two P(=O)OH sites in (*R*)-**3** might act independently and activate **4** and **5**. However, unlike a reaction using (*R*)-**1**, which can promote the *ortho*-addition of **5** to **4** (Figure 1c),[14] a reaction through the single P(=O)OH

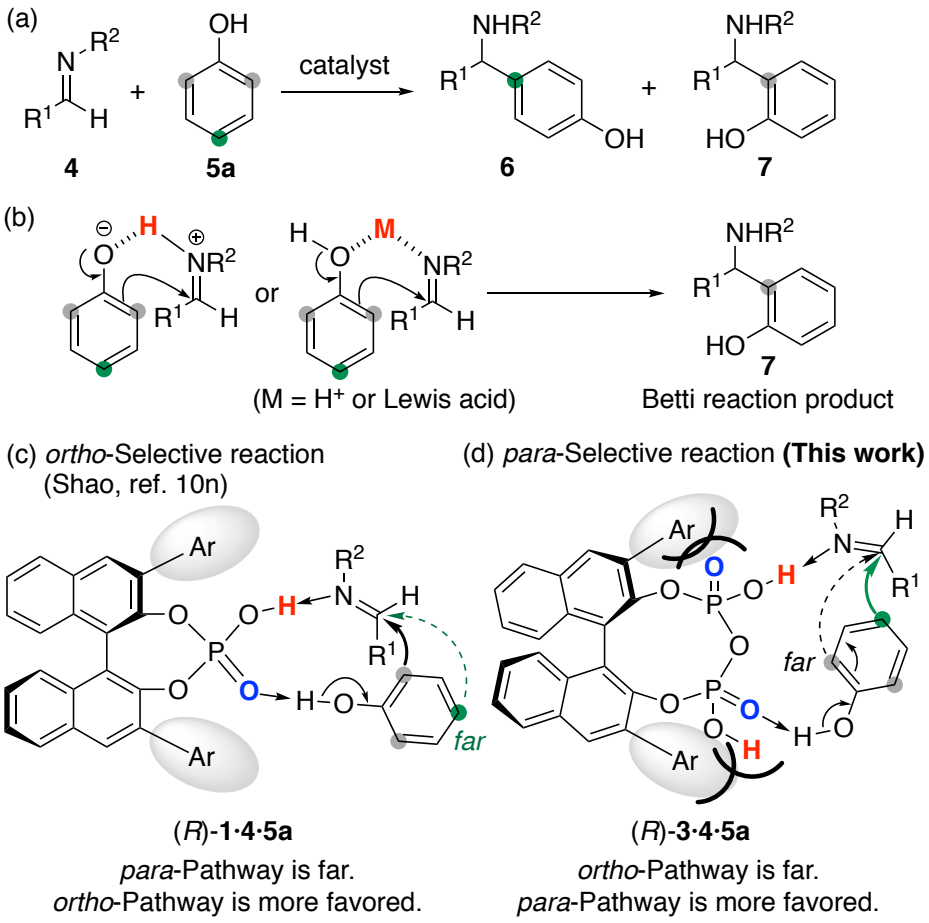


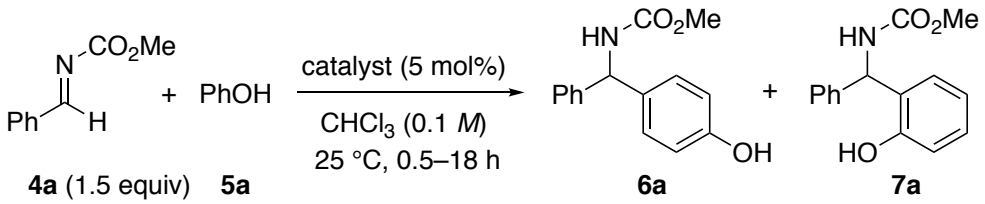
Fig. 1. Strategy for the regio- and enantioselective aza-Friedel–Crafts reaction of phenols with aldimines

site of (*R*)-**3** might be geometrically disfavored due to the steric hindrance of the 3,3'-moieties of (*R*)-**3**, and we strongly envisioned that **4** and **5** would be activated respectively on either site of the P(=O)OH moieties (Figure 1d). Overall, with the use of (*R*)-**3**, normally difficult *para*-addition of **5** to **4** might be exclusive, since the *ortho*-positions of **5** would be far from the imino-carbon of **4**.

3-2 Results and Discussion

We initially examined the reaction of phenol **5a** with aldimine **4a** through the use of achiral Brønsted acid catalysts (5 mol%) in chloroform (0.1 *M* based on **5a**) at 25 °C (Table 1). As a result, carboxylic acid catalysts, which are more or less acidic than phosphoric acids, gave **6a** and **7a** in low yields under such mild conditions (entries 1, 2, 4, 5, and 7). Although much more acidic sulfonic acids greatly promoted the conversion of **5a**, many unknown polar byproducts were obtained due to overreaction/decomposition *via* **4a** and/or **5a** (entries 8 and 9).[15] In contrast, phosphoric acids, which have not only an acid function

Table 1. Screening of Achiral Brønsted Acid Catalysts[a]



4a (1.5 equiv) **5a** **6a** **7a**

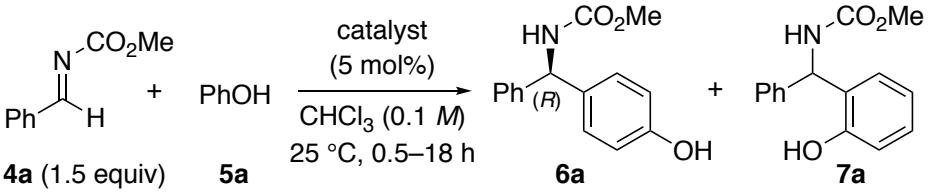
Entry	Catalyst	pK_a in H_2O	Reaction time (h)	Conversion (%) of **5a**	Yield (%) of **6a**	Yield (%) of **7a**
1	CH_3CO_2H	4.76	18	0	0	0
2	CH_2BrCO_2H	2.86	18	0	0	0
3	**$PhOP(=O)(OH)_2$**	1.42	18	**40**	**25**	**15**
4	CHF_2CO_2H	1.24	18	0	0	0
5	CCl_3CO_2H	0.65	18	16	2	14
6	**$(PhO)_2P(=O)OH$**	0.26	18	**24**	**15**	**9**
7	CF_3CO_2H	0.26	18	8	6	2
8	*p*-$CH_3C_6H_4SO_3H$	–1.34	0.5	>99	45	11
9	CF_3SO_3H	–13.0	0.5	>99	53	7

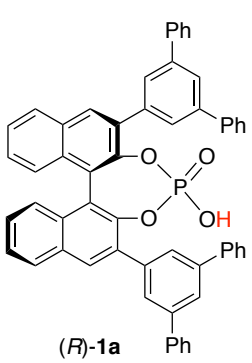
[a] The reaction was carried out with catalyst (5 mol%), **4a** (1.5 equiv), and **5a** (1 equiv) in chloroform (0.1 *M* based on **5a**) at 25 °C.

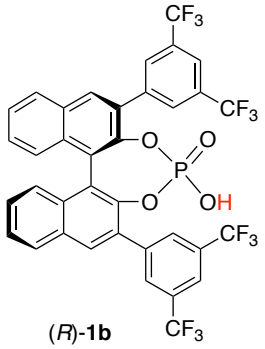
(POH) but also a conjugate base function (P=O), did not give any byproducts, although the catalytic activity was moderate, and meaningful regioselectivity (i.e., **6a** vs. **7a**) was not observed (entries 3 and 6). Overall, we found that phosphoric acids with the bifunctional acid–base moieties would be suitable for promoting the present reaction efficiently without side reactions.

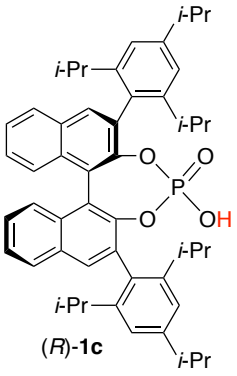
Next, we examined the use of chiral phosphoric acids (*R*)-**1a**–**c**, chiral bis(phosphoric acid) (*R*)-**2a**, and chiral pyrophosphoric acids (*R*)-**3a**–**c** (Table 2). As a result, although catalysts (*R*)-**1a** and (*R*)-**1b** promoted the reaction, the desired **6a** was obtained in low yields with low enantioselectivities, along with undesired **7a** (entries 1 and 2). The reaction did not proceed with the use of highly regarded chiral phosphoric acid (*R*)-**1c** (TRIP)[16], which would be less acidic and sterically more hindered than (*R*)-**1a** and (*R*)-**1b** (entry 3). Moreover, catalyst (*R*)-**2a**,[7] which has stronger acidity and much weaker basicity than (*R*)-**1a**, showed lower catalytic activity than (*R*)-**1a** (entry 4). In sharp contrast, as a novel stronger acid catalyst with a conjugate base function, chiral pyrophosphoric acid (*R*)-**3a** dramatically facilitated the reaction, and **6a** was obtained in 82% yield with 52% ee within 30 min (entry 5). At that time, **7a** was provided in only 1% yield. The substituent effect at the 3,3'-positions of the binaphthyl backbone was important, and sterically less hindered (*R*)-**3b** and (*R*)-**3c** showed much lower catalytic activity than (*R*)-**3a** (entries 6 and 7). Moreover, much stronger Brønsted acids, such as chiral phosphoramide (*R*)-**8**[17] and chiral disulfonic acid (*R*)-**9**[18] also facilitated the reaction and the substrates were consumed within 30 min (entries 8 and 9). However, the enantio-control was hardly achieved and many unknown polar byproducts were generated. The tendency of the results in Table 2 was mostly similar to that with achiral catalysts in Table 1; the sterically-optimized chiral catalysts should have both appropriate acid and base functions to promote the desired reaction.[19]

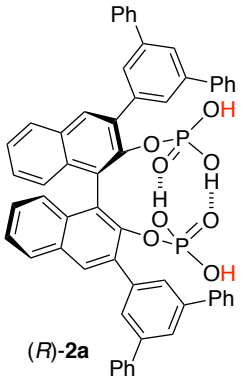
Table 2. Screening of Brønsted acid catalysts[a]

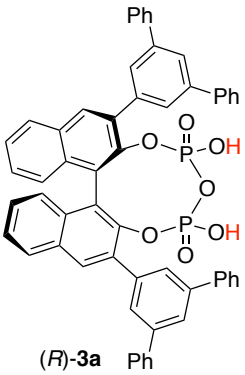


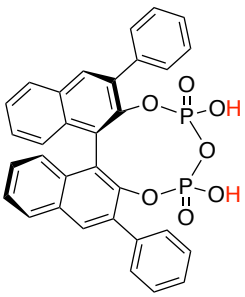


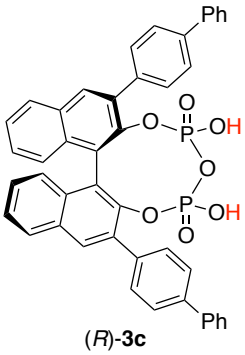


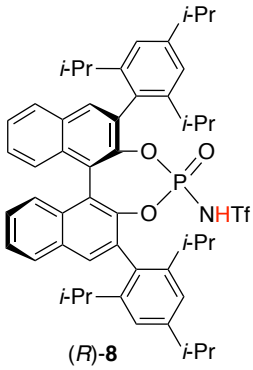


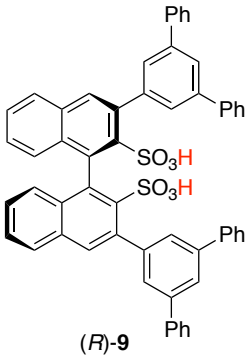










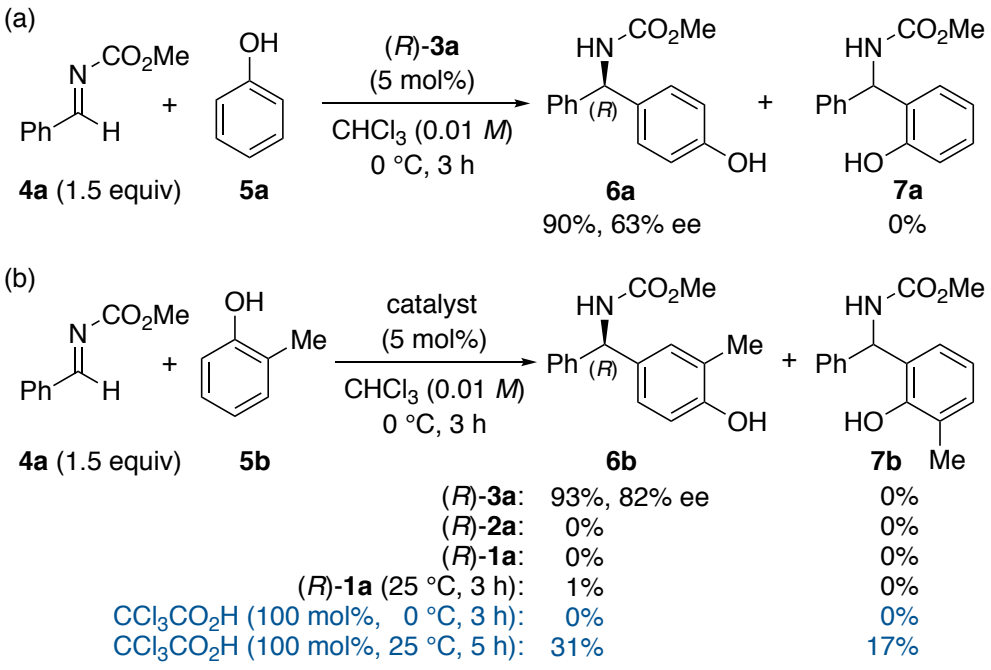


Entry	Catalyst	Reaction time (h)	Yield (%) of **6a**	ee (%) of **6a**	Yield (%) of **7a**	ee (%) of **7a**
1	(*R*)-**1a**	3	40	0	12	0
2	(*R*)-**1b**	3	16	4	7	7
3	(*R*)-**1c**	18	0	–	0	–
4	(*R*)-**2a**	3	15	23	10	0
5	(*R*)-**3a**	**0.5**	**82**	**52**	**1**	–
6	(*R*)-**3b**	0.5	41	4	0	–
7[b]	(*R*)-**3c**	0.5	4	–3	0	–
8	(*R*)-**8**	0.5	50	3	26	11
9	(*R*)-**9**	0.5	61	2	12	10

[a] The reaction was carried out with catalyst (5 mol%), **4a** (1.5 equiv), and **5a** (1 equiv, 0.20 mmol) in chloroform (0.1 *M* based on **5a**) at 25 °C. [b] (*S*)-**6a** was obtained with 3% ee.

After further optimization of the reaction conditions,[20–22] a reaction in diluted chloroform (0.01 *M* based on **5a**) at lower temperature (0 °C) improved both the yield and enantioselectivity of **6a** up to 63% ee (Scheme 2a). Interestingly, the enantioselectivity was greatly improved when *o*-cresol **5b** was used instead of phenol **5a**, and *para*-adduct **6b** was obtained as a sole product in 93% yield with 82% ee without the generation of *ortho*-adduct **7b** (Scheme 2b). Notably, (*R*)-**3a** was detected almost intact in the resulting reaction mixture,[23] and recovered as (*R*)-**2a** through silica gel column chromatography. In contrast, (*R*)-**1a** and (*R*)-**2a** were not effective at that time, and the reaction hardly proceeded under the same reaction conditions or even at 25 °C (Scheme 2b). Moreover, as another control experiment, 100 mol% of trichloroacetic acid as an achiral catalyst also could not promote the reaction at 0 °C, and ultimately promoted the reaction at 25 °C. However, a meaningful regioselectivity for **6b** and **7b** was not observed as expected. Therefore, the observed *para*-selective reactions with (*R*)-**3a** did not depend on *ortho*-substituted phenol **5b**.

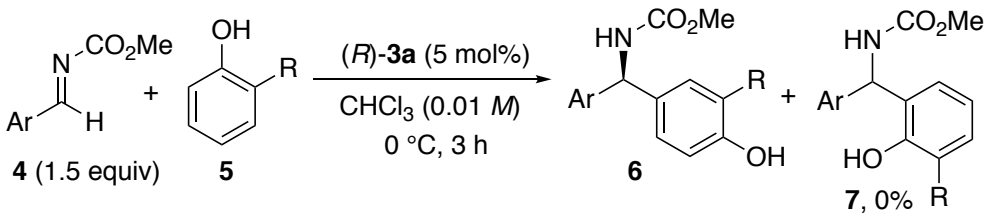
Scheme 2. Further optimization of the reaction conditions and the *para*-selective reaction with *o*-cresol **5b**.



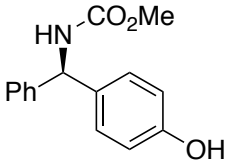
With the optimized reaction conditions in hand, we next examined the scope of phenols **5** with aldimines **4** (Scheme 3). As a result, not only phenyl-, but also *p*-tolyl- and 1-naphthylaldimines were used, and the corresponding *para*-adducts **6c** and **6d** were

exclusively obtained with 77% ee and 60% ee, respectively. Moreover, *o*-cresol **5b** and 2-allylphenol reacted with **4a**, and **6b** and **6e** were obtained with 82% ee and 76% ee,

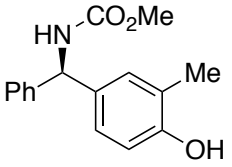
Scheme 3. Scope of substrates in the regio- and enantioselective aza-FC reaction of phenols.



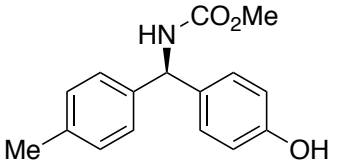
Products **6**, yield, and enantioselectivity:



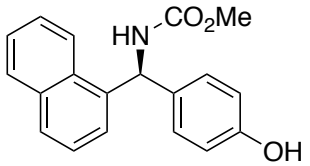
6a, 90%, 63% ee
[**6a**, 2%; **7a**, 14%][a]



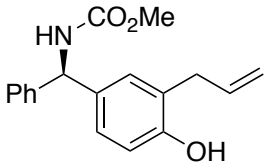
6b, 93%, 82% ee (90% ee)[b]
[**6b**, 31%; **7b**, 17%][a]
[**6b**, 78%, 79% ee][c]



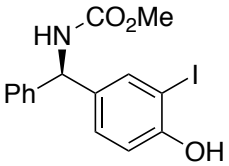
6c, 58%, 77% ee (86% ee)[b]
[**6c**, 20%; **7c**, 30%][a]



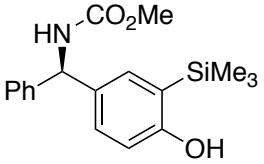
6d, 67%, 60% ee (90% ee)[b]
[**6d**, 9%; **7d**, 29%][a]



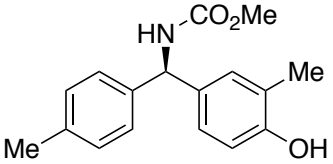
6e, 66%, 76% ee
[**6e**, 30%; **7e**, 20%][a]



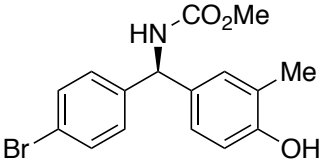
6f, 11%, 26% ee
[**6f**, 1%; **7f**, 21%][a]



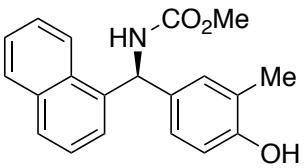
6g, 55%, 60% ee
[**6g**, 0%; **7g**, 5%][a]



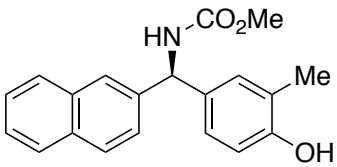
6h, 93%, 67% ee
[**6h**, 12%; **7h**, 5%][a]



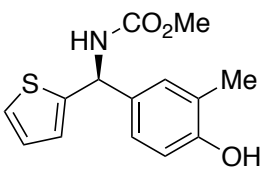
6i, 99%, 28% ee
[**6i**, 10%; **7i**, 4%][a]



6j, 82%, 77% ee
[**6j**, 31%; **7j**, 36%][a]



6k, 74%, 68% ee
[**6k**, 23%; **7k**, 23%][a]



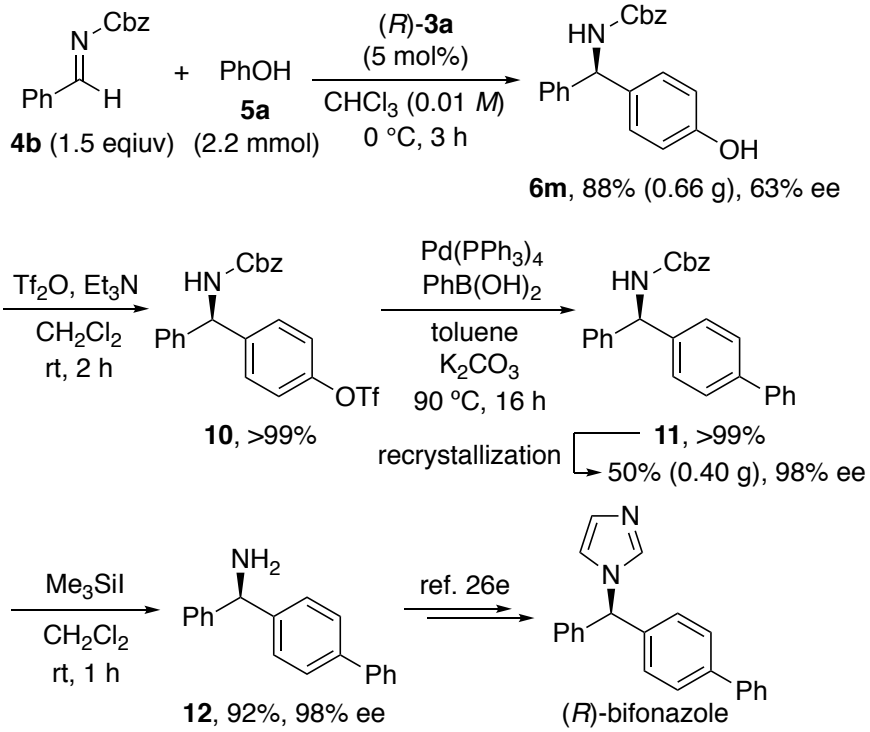
6l, 80%, 49% ee
[**6l**, 43%; **7l**, 7%][a]

Reaction conditions: (*R*)-**3a** (5 mol%), **4** (1.5 equiv), and **5** (1 equiv, 0.20 mmol) in chloroform (0.01 *M* based on **5**) at 0 °C for 3 h. [a] Data in brackets are the results with the use of CCl_3CO_2H (100 mol%) at 25 °C for 5 h. [b] Results after recrystallization. [c] 1 mol% of (*R*)-**3a** was used.

respectively. The amount of catalyst (*R*)-**3a** could be reduced to 1 mol%, and **6b** was then obtained in 78% yield with 79% ee. Unfortunately, 2-iodophenol gave **6f** in low yield with low enantioselectivity (26% ee). In contrast, bulky *o*-(trimethylsilyl)phenol was tolerable, and **6g** was obtained with moderate enantioselectivity (60% ee). Moreover, other aryl aldimines were also examined with the use of *o*-cresol **5b**. As a result, *p*-tolyl, 1-naphthyl, and 2-naphthyl substrates could be used, and good enantioselectivities (67–77% ee) were observed in the corresponding *para*-adducts **6h**, **6j**, and **6k**. On the other hand, 4-bromophenyl and 2-thienyl moieties decreased the enantioselectivities (see **6i** and **6l**). Some products in Scheme 3 were crystalline, and a single recrystallization effectively increased the enantiopurity (see parenthesis b for **6b**, **6c**, and **6d**).[24] Overall, the observed enantioselectivities in Scheme 3 were not excellent and further improvements are needed. However, it should be noted that *ortho*-adducts **7** were not obtained in any of the cases examined with (*R*)-**3a** in Scheme 3 (also see bracket a in Scheme 3 for the results with CCl_3CO_2H (100%) at 25 °C for 5 h),[25] and this might be a pioneering result for the normally difficult *para*-selective aza-FC reaction of phenols.[11]

To demonstrate the synthetic utility of the present catalytic system, we performed a formal total synthesis of (*R*)-bifonazole, which is a well-established antifungal agent for superficial mycoses

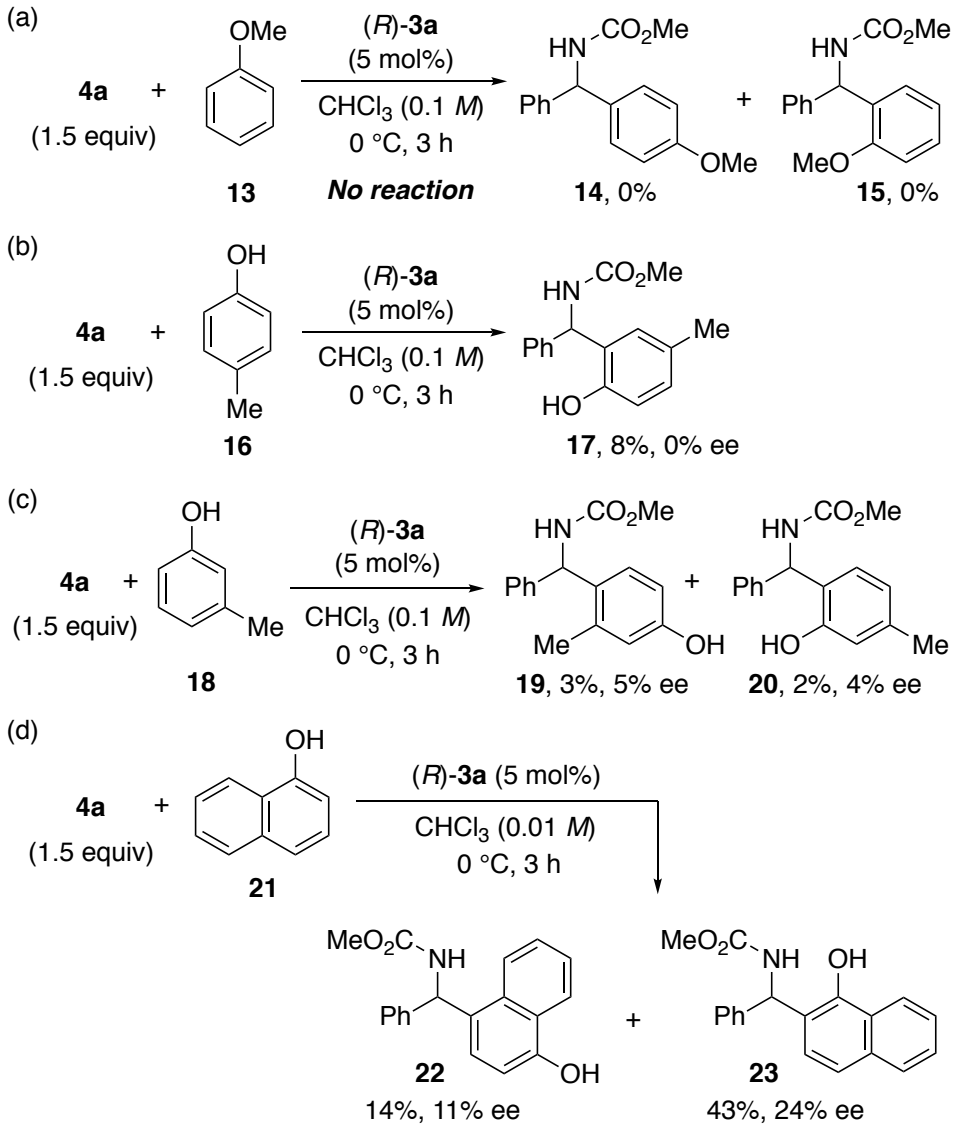
Scheme 4. Transformation toward (*R*)-bifonazole.



(Scheme 4).[25,26] Fortunately, more stable *N*-Cbz aldimine **4b** in place of less stable *N*-CO_2Me aldimine **4a** could be used in a scalable aza-FC reaction of **5a** (2.2 mmol), and the corresponding **6m** was obtained in 88% yield (0.66 g), although the enantioselectivity was still moderate (63% ee).[22] Treatment of **6m** with trifluoromethanesulfonic anhydride (Tf_2O) gave **10**, which was used in Suzuki–Miyaura coupling with $PhB(OH)_2$ to give **11** quantitatively. Recrystallization of **11** improved the optical purity to 98% ee. Finally, after deprotection of the *N*-Cbz moiety with the use of trimethylsilyl iodide, the desired key compound **12**[26e] was obtained in 92% yield.

To consider the reaction mechanism, particularly the *para*-selectivity of phenols, we performed several control experiments. When anisole **13**, instead of non-substituted phenol **5a**, was used

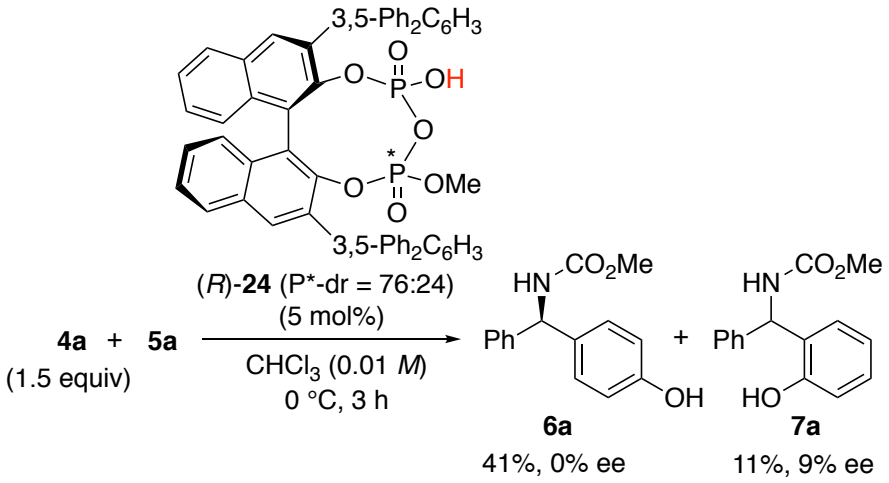
Scheme 5. Control experiments with other phenols and naphthols.



with **4a**, the reaction did not proceed (Scheme 5a). This result suggests that the deprotonation process of phenol might be necessary to promote the reaction. Moreover, when we used *p*-cresol **16**, the corresponding *ortho*-adduct **17** was obtained in only 8% yield with 0% ee (Scheme 5b). This result strongly suggests that regioselective *para*-activation might occur in our reaction system. Moreover, we also examined the reaction with *m*-cresol **18** (Scheme 5c). As a result, both *para*-adduct **19** and *ortho*-adduct **20** were obtained in very low yields. Moreover, the enantioselectivity of *para*-adduct **19** was low (5% ee), and thus *meta*-substituted phenols would not be suitable in the present reaction system, probably because the *para*-addition reaction is preferred due to steric reasons. Next, we examined whether or not 1-naphthol **21** could be used for the *para*-selective reaction (Scheme 5d). As a result, the reaction proceeded preferentially at the 2-position (i.e., *ortho*-position) of **21**, and compound **23** was obtained in 43% yield with 24% ee. However, 4(*para*)-adduct **22** was barely obtained in 14% yield with 11% ee, even though 1-naphthol **21** is strongly conjugated between the 1- and 2-positions and the 2(*ortho*)-adduct would usually be dominant.[28] Although the enantioselectivity of **22** was still low at this stage, *para*-addition-induced catalyst (*R*)-**3a** might show some resistance such as in the normally *ortho*-addition of 1-naphthol **21**.

To elucidate the function of the Brønsted acid parts of (*R*)-**3a**, we used (*R*)-**24** as a catalyst, which was prepared from (*R*)-**3a** by Me-protecting one of the P(=O)OH moieties (Scheme 6). (*R*)-**24** was used as an inseparable diastereomeric mixture based on the chiral P center (dr = 76:24). As a result, the reaction of **5a** with **4a** proceeded, and **6a** (41% yield with 0% ee) and **7a** (11% yield with 9% ee) were obtained. Neither regioselectivity nor enantioselectivity was effectively induced. Therefore, the double P(=O)OH moieties in (*R*)-**3a** should be essential for successful

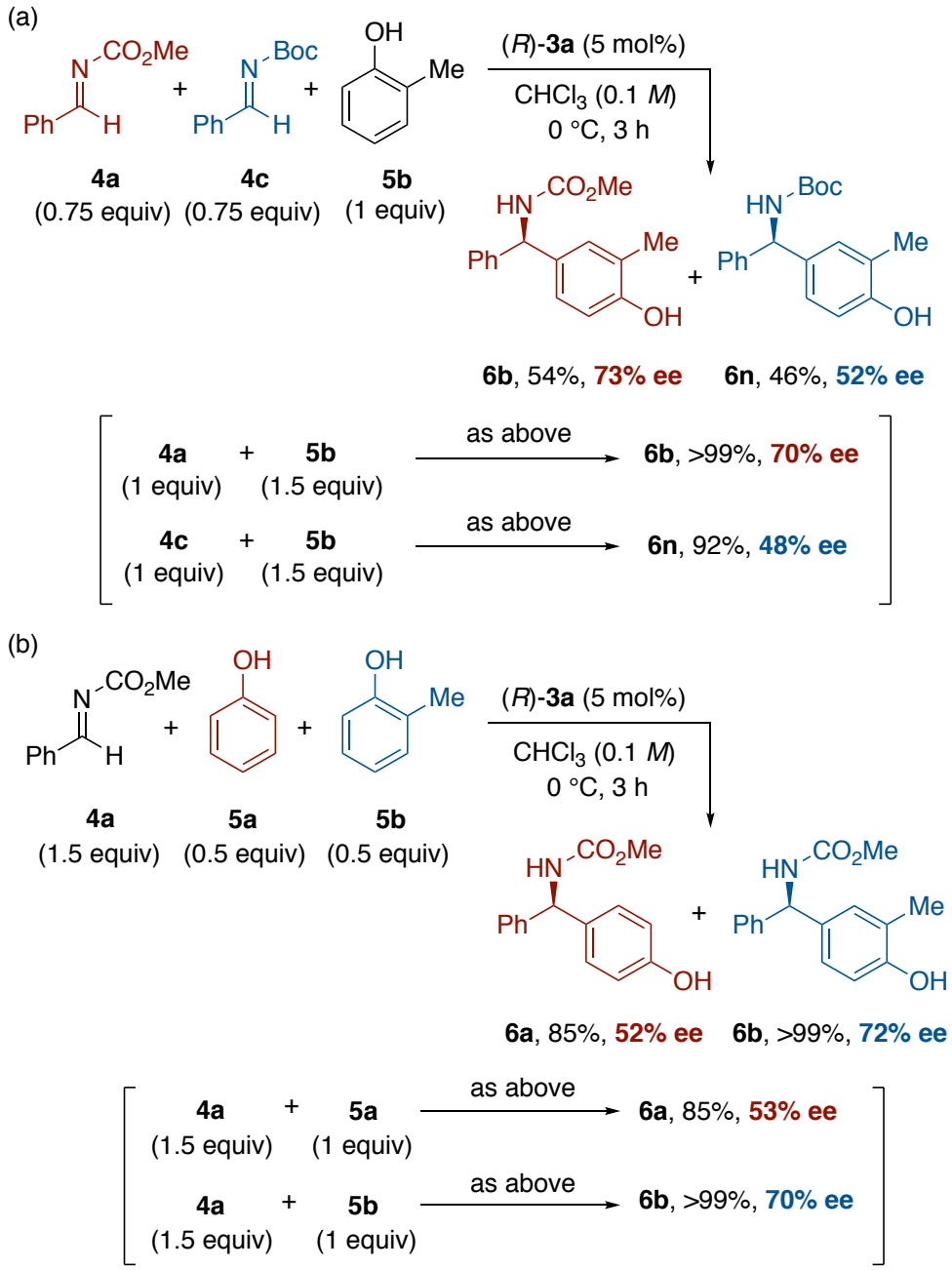
Scheme 6. Role of two P(=O)OH moieties of the catalysts.



activation of the aldimine and phenol.

As expected in Figure 1d, we considered an activation model. To support the consideration that aldimine **4** and phenol **5** might be activated independently by two acid–base moieties of (*R*)-**3a**, we performed preliminary competition experiments with either two different aldimines or phenols (Scheme 7). If a more complicated activation mechanism with the two acid–base moieties of (*R*)-**3a** is involved, the enantioselectivity of the products might be affected by the interaction among

Scheme 7. Control experiments with competitive substrates.



the competitive substrates. First, we examined a reaction with the use of two different aldimines **4a** and **4c** (Scheme 7a). As a result, the corresponding products **6b** and **6n** were obtained with almost the same enantioselectivities as in the case with each alone. Next, we examined a reaction with the use of two different phenols **5a** and **5b** (Scheme 7b). As a result, the corresponding products **6a** and **6b** were obtained with almost the same enantioselectivities as in the case with each alone. Overall, a possible activation mechanism might involve a (*R*)-**3a**:**4**:**5** ratio of 1:1:1, as shown in Figure 1d, and (*R*)-**3a**•**4**$_2$•**5**, (*R*)-**3a**•**4**•**5**$_2$, (*R*)-**3a**•**4**$_2$•**5**$_2$, or more complicated species might be unlikely.

Based on the above experimental results, Figure 2 shows a possible transition state through the use of (*R*)-**3a**•**4**•**5** as a working model. Due to the steric constraints of bulky aryl substituents at the 3,3'-positions, each aldimine **4a** and phenol **5** might be activated independently at two different P(=*O*)O*H* sites of (*R*)-**3a**. Phenol **5** would be deprotonated by a Brønsted base moiety (P=*O*) at one site, whereas aldimine **4a** would coordinate to the Brønsted acid center (PO*H*) at the other site. To avoid significant steric constraint due to the catalyst, the aryl moiety of **4a** might be oriented inward. Thus, a *para*-selective reaction pathway might be suitable, since the *para*-position of **5** would be close to the imino-carbon of **4a**, while the *ortho*-position of **5** would be far from the imino-carbon of **4a**. As a result, *si*-face attack of **5** to **4a** might proceed, and the corresponding (*R*)-isomer **6** might be provided with high regioselectivity and moderate to good enantioselectivities.

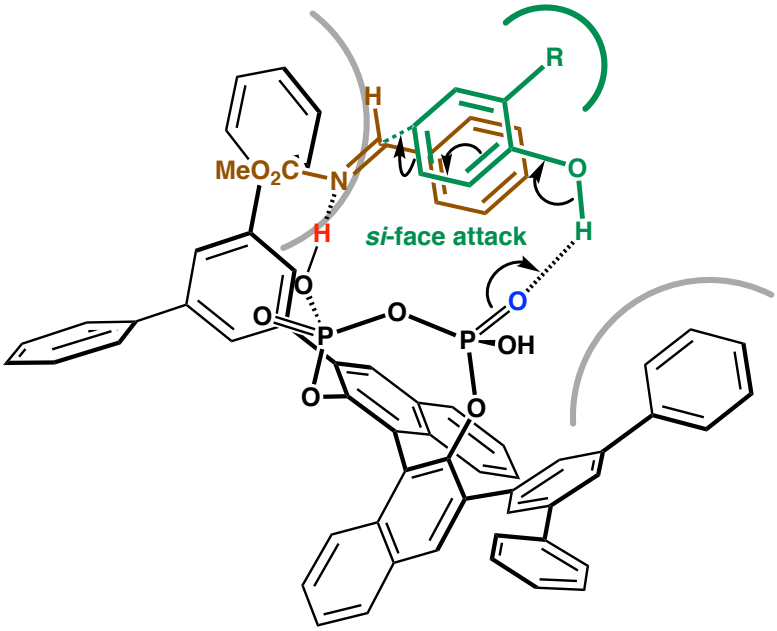


Fig. 2. A possible transition state

Some *ortho*-substituted phenols, which offered higher enantioselectivities than non-substituted phenol **5a**, might help to provide the favored transition state, since the *ortho*-substituent would direct outward, as shown in Figure 2. Moreover, an electrostatic π– π stacking interaction between **4** and **5** cannot be ruled out, where a not very bulky but electron-donating *ortho*-substituent on phenol might be effective, as shown in Scheme 3.

3-3 Conclusions

In summary, we have developed chiral BINOL-derived pyrophosphoric acid catalysts for the first time, which were effective for the *para*-selective and enantioselective aza-Friedel–Crafts reaction of phenols to aldimines. Since phenols have an *ortho*/*para*-orientation, exclusive *para*-addition is difficult and geometric remote control would be needed through the use of designer chiral catalysts. With the use of the present chiral pyrophosphoric acid catalysts, both aldimines and phenols would be activated cooperatively, and phenols could react at a *para*-position with moderate to good enantioselectivities. Moreover, transformation of a product into (*R*)-bifonazole was demonstrated on an enlarged scale. This is the first example of chiral pyrophosphoric acid catalysts, and the further application to asymmetric reactions is underway.

3-4 Notes and Refrences

1. (a) Timperley, C. M. *Best Synthetic Methods: Organophosphorus(V) Chemistry*, Academic Press: Cambridge, **2014**. (b) Montchamp, J.-L. Ed. *Phosphorus Chemistry I: Asymmetric Synthesis and Bioactive Compounds (Topics in Current Chemistry)*, Springer: New York, **2015**. (c) Montchamp, J.-L. Ed. *Phosphorus Chemistry II, Synthetic Methods (Topics in Current Chemistry)*, Springer: New York, **2015**.
2. (a) Corbridge, D. In *Studies in Inorganic Chemistry*, vol. 20., *Chapter 3: Phosphates,* Elsevier Science B.V.: Amsterdam, **1995**, pp. 169–305. (b) Haynes, W. M. Ed. In *Handbook of Chemistry and Physics*, 96th ed., CRC Press: Boca Raton, **2015**, pp. 5-91–5-92.
3. For reviews. (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Synthesis* **2010**, *2010*, 1929. (e) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (f) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (g) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277. (h) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2017**, *117*, 10608. (i) Merad, J.; Lalli, C.; Bernadat, G.; Maury, J.; Masson, G. *Chem. Eur. J.* **2018**, *24*, 3925.
4. For seminal studies of chiral BINOL-derived phosphoric acids **1**, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
5. (a) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (b) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946. (c) Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 4050. (d) Guo, C.; Song, J.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 2676. (e) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504.
6. (a) Momiyama, N.; Konno, T.; Furiya, Y.; Iwamoto, T.; Terada, M. *J. Am. Chem. Soc.* **2011**, *133*, 19294. (b) Momiyama, N.; Narumi, T.; Terada, M. *Chem. Commun.* **2015**, *51*, 16976. (c) Momiyama, N.; Funayama, K.; Noda, H.; Yamanaka, M.; Akasaka, N.; Ishida, S.; Iwamoto, T.; Terada, M. *ACS Catal.* **2016**, *6*, 949.
7. (a) Ishihara, K.; Sakakura, A. *Japan Patent* JP2012-160092 (2012). (b) Hatano, M.; Okamoto, H.; Kawakami, T.; Toh, K.; Nakatsuji, H.; Sakakura, A.; Ishihara, K. *Chem.*

Sci. **2018**, *9*, 6361.

8. (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (b) Kondoh, A.; Ota, Y.; Komuro, T.; Egawa, F.; Kanomata, K.; Terada, M. *Chem. Sci.* **2016**, *7*, 1057.
9. Reviews and accounts for catalytic enantioselective FC reaction: (a) Jørgensen, K. A. *Synthesis* **2003**, *2003*, 1117. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (e) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608. (f) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635. (g) Zeng, M.; You, S.-L. *Synlett* **2010**, *2010*, 1289.
10. Selected papers for *ortho*-selective catalytic asymmetric FC reaction of phenols with α,β-unsaturated carbonyl compounds, nitro olefins, α-keto esters, aldimines, isatins, CF_3-ketimines, and so on: (a) Zhao, J.-L.; Liu, L.; Gu, C.-L.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2008**, *49*, 1476. (b) Lv, J.; Li, X.; Zhong, L.; Luo, S.; Cheng, J.-P. *Org. Lett.* **2010**, *12*, 1096. (c) Hajra, S.; Sinha, D. *J. Org. Chem.* **2011**, *76*, 7334. (d) Yoshida, M.; Nemoto, T.; Zhao, Z.; Ishige, Y.; Hamada, Y. *Tetrahedron: Asymmetry* **2012**, *23*, 859. (e) Suzuki, Y.; Nemoto, T.; Kakugawa, K.; Hamajima, A.; Hamada, Y. *Org. Lett.* **2012**, *14*, 2350. (f) Li, G.-X.; Qu, J. *Chem. Commun.* **2012**, *48*, 5518. (g) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2012**, *14*, 2579. (h) Bai, S.; Liu, X.; Wang, Z.; Cao, W.; Lin, L.; Feng, X. *Adv. Synth. Catal.* **2012**, *354*, 2096. (i) Kaur, J.; Kumar, A.; Chimni, S. S. *RSC Adv.* **2014**, *4*, 62367. (j) Zhao, Z.-L.; Xu, Q.-L.; Gu, Q.; Wu, X.-Y.; You, S.-L. *Org. Biomol. Chem.* **2015**, *13*, 3086. (k) Ren, H.; Wang, P.; Wang, L.; Tang, Y. *Org. Lett.* **2015**, *17*, 4886. (l) Zhou, D.; Huang, Z.; Yu, X.; Wang, Y.; Li, J.; Wang, W.; Xie, H. *Org. Lett.* **2015**, *17*, 5554. (m) Vetica, F.; Marcia de Figueiredo, R.; Cupioli, E.; Gambacorta, A.; Loreto, M. A.; Miceli, M.; Gasperi, T. *Tetrahedron Lett.* **2016**, *57*, 750. (n) Wang, Y.; Jiang, L.; Li, L.; Dai, J.; Xiong, D.; Shao, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 15142. (o) Shikora, J. M.; Chemler, S. R. *Org. Lett.* **2018**, *20*, 2133.
11. *para*-Selective catalytic asymmetric FC reaction of phenols have been very limited: (a) Zhao, J.-L.; Liu, L.; Gu, C.-L.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2008**, *49*, 1476. (b) Shao, L.; Hu, X.-P. *Org. Biomol. Chem.* **2017**, *15*, 9837.
12. (a) Ralston, A. W.; INGLE, A.; McCorkle, M. R.; Bauer, S. T. *J. Org. Chem.* **1940**, *5*, 645. (b) Ralston, A. W.; INGLE, A.; McCorkle, M. R. *J. Org. Chem.* **1942**, *7*, 457.

(c) Gore, P. H.; Smith, G. H.; Thorburn, S. *J. Chem. Soc. C.* **1971**, *0*, 650.

13. (a) Betti, M. *Gazz. Chim. Ital.* **1900**, *30II*, 301. (b) Betti, M. *Gazz. Chim. Ital.* **1900**, *30 II*, 310. (c) Betti, M. *Gazz. Chim. Ital.* **1903**, *33II*, 1. Also see a review: (d) Cardellicchio, C.; Capozzi, M. A. M.; Naso, F. *Tetrahedron: Asymmetry* **2010**, *21*, 507.
14. Very recently, Shao reported a catalytic enantioselective aza-FC reaction of phenols with aldimines with the use of chiral phosphoric acid catalysts. *ortho*-Adducts were selectively obtained with high enantioselectivities. See ref. 10n.
15. To determine whether or not overreaction/decomposition of **6a** and **7a** would occur with the use of strong acids, we used either isolated product **6a** or **7a** alone in the presence of *p*-TsOH. As a result, overreaction/decomposition was observed in both cases, and the same unknown compounds as were observed under the standard reaction conditions (Table 1, entry 8) were obtained.
16. Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424.
17. (a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2411. (c) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (d) Sai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2015**, *137*, 7091. (e) Zhou, F.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 8970.
18. (a) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (b) Hatano, M.; Hattori, Y.; Furuya, Y.; Ishihara, K. *Org. Lett.* **2009**, *11*, 2321. (c) Hatano, M.; Sugiura, Y.; Ishihara, K. *Tetrahedron: Asymmetry* **2010**, *21*, 1311. (d) Hatano, M.; Sugiura, Y.; Akakura, M.; Ishihara, K. *Synlett* **2011**, *2011*, 1247. (d) Hatano, M.; Ozaki, T.; Sugiura, Y.; Ishihara, K. *Chem. Commun.* **2012**, *48*, 4986. (f) Hatano, M.; Ozaki, T.; Nishikawa, K.; Ishihara, K. *J. Org. Chem.* **2013**, *78*, 10405. (g) Hatano, M.; Ishihara, K. *Asian J. Org. Chem.* **2014**, *3*, 352. (h) Hatano, M.; Nishikawa, K.; Ishihara, K. *J. Am. Chem. Soc.* **2017**, *139*, 8424. (i) Hatano, M.; Mochizuki, T.; Nishikawa, K.; Ishihara, K. *ACS Catal.* **2018**, *8*, 349. (j) Kurihara, T.; Satake, S.; Hatano, M.; Ishihara, K.; Yoshino, T.; Matsunaga, S. *Chem. Asian J.* **2018**, published on the web (**DOI:** org/10.1002/asia.201800341). (k) Satake, S.; Kurihara, T.; Nishikawa, K.; Mochizuki, T.; Hatano, M.; Ishihara, K.; Yoshino, T.; Matsunaga, S. *Nat. Catalysis* **2018**, published on the web (**DOI:** 10.1038/s41929-018-0106-5)
19. Unfortunately, we have not yet been able to synthesize chiral bis(phosphoric acid)s and thus the corresponding chiral pyrophosphoric acids with more bulky substituents (e.g.,

2,4,6-*i*-$Pr_3C_6H_2$) due to the steric constraints. With this regard, we have already discussed the synthetic difficulty of the bulky catalysts in our previous manuscript (ref. 7b).

20. A higher concentration (i.e., >0.1 *M* based on **5** in chloroform) gave much lower enantioselectivities, whereas a lower concentration gave almost the same enantioselectivity as with the optimal concentration (0.01 *M*). Moreover, the effect of the reaction temperature (–40, –20, 0, and 25 °C) was also investigated. As a result, 0 °C gave better results in terms of yield and enantioselectivity than the other temperatures.
21. Chloroform provided a better yield and enantioselectivity than other low-polarity solvents, such as dichloromethane, 1,2-dichloroethane, toluene, and benzotrifluoride. In contrast, no reaction occurred when polar solvents were used, such as diethyl ether, tetrahydrofuran, propionitrile, and nitroethane.
22. Aldimines with other *N*-protecting groups, such as CO_2t-Bu (Boc), showed lower enantioselectivities (see Scheme 7). Relatively stable *N*-CO_2CH_2Ph (Cbz) aldimines could be used but showed slightly lower yields with almost the same enantioselectivities as less stable *N*-CO_2Me aldimines. Moreover, no reaction occurred when *N*-CO_2CH_2(9-fluorenyl) (Fmoc), *N*-SO_2Ph, *N*-Ph, and *N*-Bn aldimines were used.
23. We performed the ^{31}P NMR ($CDCl_3$) analysis after the routine workup with triethylamine. As a result, (*R*)-**3a**·$(Et_3N)_n$ was observed as a sole peak at –19.7 ppm, which strongly suggests that (*R*)-**3a** was intact during the reaction (*cf.* ^{31}P NMR ($CDCl_3$) spectra; (*R*)-**3a**: –20.8 ppm; (*R*)-**2a**: –0.4 ppm.).
24. Compounds **6b**, **6c**, and **6d** were subjected to X-ray analysis. See the Experimental Section for details.
25. As seen in Table 2 and Scheme 2, the catalytic activity of (*R*)-**1a** was lower than that of (*R*)-**3a**, and (*R*)-**1a** did not promote the reactions of **5b** (0.01 *M* $CHCl_3$) effectively at 0 °C for 3 h. A mixture of the corresponding adducts **6** and **7** was obtained in <5% yield.
26. Synthesis of bifonazole: (a) Corelli, F.; Summa, V.; Brogi, A.; Monteagudo, E.; Botta, M. *J. Org. Chem.* **1995**, *60*, 2008. (b) Botta, M.; Corelli, F.; Gasparrini, F.; Messina, F.; Mugnaini, C. *J. Org. Chem.* **2000**, *65*, 4736. (c) Botta, M.; Corelli, F.; Manetti, F.; Mugnaini, C.; Tafi, A. *Pure Appl. Chem.* **2001**, *73*, 1477. (d) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (e) Castagnolo, D.; Giorgi, G.; Spinosa, R.; Corelli, F.; Botta, M. *Eur. J. Org. Chem.* **2007**, 3676. (f) Petrov, O.; Gerova, M.; Petrova, K.; Ivanova, Y. *J. Heterocyclic Chem.* **2009**, *46*, 44. (g) Hage,

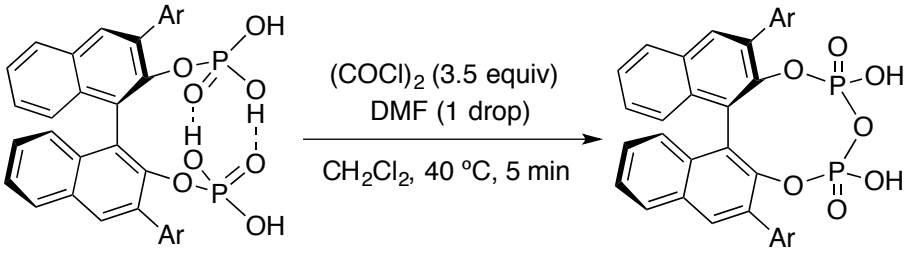
S. E.; Lajoie, B.; Feuillolay, C.; Roques, C.; Baziard, G. *Arch. Pharm. Chem. Life Sci.* **2011**, *344*, 402. (h) Syu, J.-F. Lin, H.-Y.; Cheng, Y.-Y.; Tsai, Y.-C.; Ting, Y.-C.; Kuo, T.-S.; Janmanchi, D.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Chem. Eur. J.* **2017**, *23*, 14515.

27. A review for catalytic enantioselective diarylmethylamine synthesis: (a) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454. Pharmacopphores of diarylmethylamines are well known, see: (b) Plobeck, N.; Delorme, D.; Wei, Z.-Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Yue, S. Y.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P.-E.; Projean, D.; Ducharme, J.; Roberts, E. *J. Med. Chem.*, **2000**, *43*, 3878. (c) Jolidon, S.; Alberati, D.; Dowle, A.; Fischer, H.; Hainzl, D.; Narquizian, R.; Norcross, R.; Pinard, E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5533. (d) Aiman, R.; Gharpure, M. B. *Curr. Sci.* **1949**, *18*, 303.
28. Recent selected papers for enantioselective Friedel–Crafts reaction of 1- and 2-naphthols: (a) Niu, L.-F.; Xin, Y.-C.; Wang, R.-L.; Jiang, F.; Xu, P.-F.; Hui, X.-P. *Synlett* **2010**, *2010*, 765. (b) Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 7299. (c) Liu, G.; Zhang, S.; Li, H.; Zhang, T.; Wang, W. *Org. Lett.* **2011**, *13*, 828. (d) Chauhan, P.; Chimni, S. S. *Eur. J. Org. Chem.* **2011**, 1636. (e) Jarava-Barrera, C.; Esteban, F.; Navarro-Ranninger, C.; Parra, A.; Alemán, J. *Chem. Commun.* **2013**, *49*, 2001. (f) Takizawa, S.; Hirata, S.; Murai, K.; Fujioka, H.; Sasai, H. *Org. Biomol. Chem.* **2014**, *12*, 5827. (g) Montesinos-Magraner, M.; Vila, C.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Catal.* **2015**, *357*, 3047. (h) Montesinos-Magraner, M.; Vila, C.; Cantón, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 6320. (i) Poulsen, P. H.; Feu, K. S.; Paz, B. M.; Jensen, F.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 8203. (j) Montesinos-Magraner, M.; Cantón, R.; Vila, C.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *RSC Adv.* **2015**, *5*, 60101. (k) kumari, P.; Barik, S.; Khan, N. H.; Ganguly, B.; Kureshy, R. I.; Abdi, S. H. R.; Bajaj; H. C. *RSC Adv.* **2015**, *5*, 69493. (l) Qin, L.; Wang, P.; Zhang, Y.; Ren, Z.; Zhang, X.; Da, C.-S. *Synlett* **2016**, *27*, 571. (m) Vila, C.; Rendón-Patiño, A.; Montesinos-Magraner, M.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Asv. Synth. Catal.* **2018**, *360*, 859. Also see an excellent review: (n) Montesinos-Magraner, M.; Vila, C.; Blay, G.; Pedro, J. R. *Synthesis* **2016**, *48*, 2151.

1. General methods

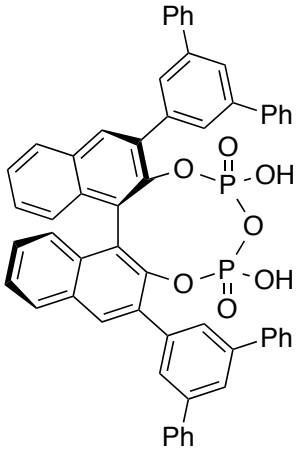
^{1}H NMR spectra were measured on a JEOL ECS400 (400 MHz) spectrometer at ambient temperature unless otherwise noted. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.10 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). ^{31}P NMR spectra were measured on a JEOL ECS-400 (161 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard (H_3PO_4 at 0 ppm). High resolution mass spectral analyses (HRMS) were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700 (FAB), JEOL JMS-T100GCV (EI), Bruker Daltonics micrOTOF-QII (ESI)). Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-M20A and chiral column of Daicel CHIRALCEL OD-H, OD-3 and CHIRALPAK AS-3, IA-3, IC-3. Optical rotations were measured on Rudolph Autopol IV digital polarimeter. X-ray analysis was performed by Rigaku PILATUS-200K. The products were purified by column chromatography on silica gel (Kanto Chemical Co., Inc. 37560). In experiments that required dry solvents such as chloroform were distilled in prior to use. Aldimines **4** were known compounds and were prepared based on the literature procedure.[1] Phenols are commercially available, although 2-(trimethylsilyl)phenol was prepared from 2-bromophenol based on the literature procedure.[2]

2. Preparation of chiral 1,1'-binaphthyl-2,2'-pyrophosphoric acids (*R*)-3 (Table 2)

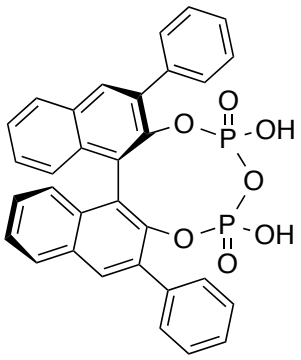


(*R*)-**2** (*R*)-**3**

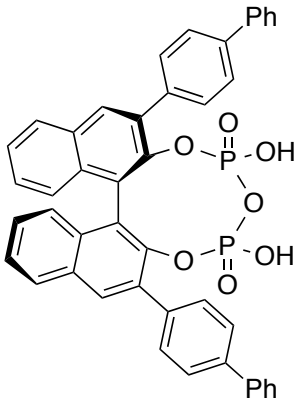
To a solution of chiral bis(phosphoric acid) (*R*)-**2**[3] (0.010 mmol) in dichloromethane (0.2 mL) was added one drop of *N*,*N*-dimethylformamide (DMF) Oxalyl chloride (3.0 μL, 0.035 mmol) was added at room temperature, and the mixture was warmed to 40 °C. The reaction mixture was stirred at 40 °C for 5 min. After the mixture was allowed to cool to room temperature, toluene (2 mL) was added. The volatiles were removed *in vacuo*, and the desired pyrophosphoric acid (*R*)-**3** was obtained, which was used for the catalysis without the further purification. A small amount of DMF and dichloromethane were usually involved.



(*R*)-3,3'-Di(3,5-terphenyl)-1,1'-binaphthyl-2,2'-pyrophosphoric acid ((*R*)-3a): 99% yield. Pale yellow solid. ^{1}H NMR (THF-d_8, 400 MHz) δ = 4.00-5.00 (br, 2H), 7.12 (d, J = 8.2 Hz, 2H), 7.26-7.35 (m, 6H), 7.37-7.50 (m, 10H), 7.75-8.10 (m, 16H), 8.31 (s, 2H). ^{13}C NMR (THF-d_8, 100 MHz) δ = 125.6 (2C), 126.0 (2C), 126.3 (2C), 126.8 (2C), 127.9 (2C), 128.0 (4C), 128.2 (8C), 128.3 (4C), 129.1 (2C), 129.5 (8C), 132.5 (2C), 132.7 (2C), 134.2 (2C), 135.4 (2C), 140.5 (2C), 142.3 (4C), 142.5 (4C), 146.5 (2C). ^{31}P NMR (THF-d_8, 160 MHz) δ = –21.2. IR (KBr) 3444, 2929, 1655, 1498, 1402, 1239, 1191, 1088, 1029 cm^{-1}. $[\alpha]_D^{23}$ = +60.0 (*c* 1.00, THF). HRMS (ESI–) calcd for $C_{56}H_{37}O_7P_2$ $[M–H]^-$ 883.2009, found 883.2008.

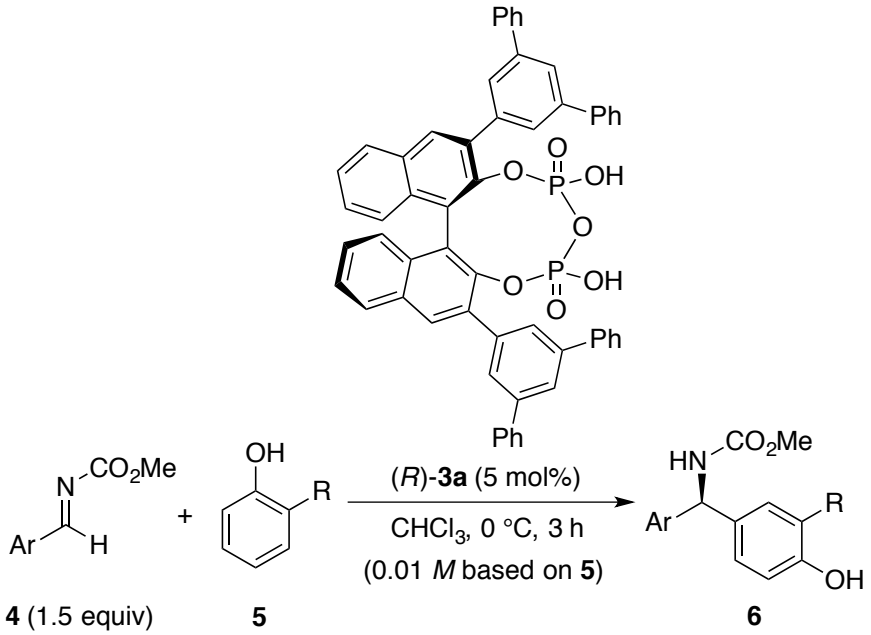


(*R*)-3,3'-Diphenyl-1,1'-binaphthyl-2,2'-pyrophosphoric acid ((*R*)-3b): 99% yield. Pale yellow solid. ^{1}H NMR (THF-d_8, 400 MHz) δ = 6.60-7.20 (br, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.26-7.34 (m, 4H), 7.38 (t, J = 7.3 Hz, 4H), 7.46 (t, J = 7.3 Hz, 2H), 7.67 (d, J = 7.3 Hz, 4H), 8.00 (d, J = 8.2 Hz, 2H), 8.10 (s, 2H). ^{13}C NMR (THF-d_8, 100 MHz) δ = 125.9 (2C), 126.2 (2C), 126.8 (2C), 127.7 (2C), 127.8 (2C), 128.7 (4C), 129.1 (2C), 130.4 (4C), 132.2 (2C), 132.7 (2C), 133.9 (2C), 135.8 (2C), 139.4 (2C), 146.3 (2C). ^{31}P NMR (THF-d_8, 160 MHz) δ = –20.8. IR (KBr) 3421, 3058, 1496, 1457, 1420, 1246, 1193, 993 cm^{-1}. $[\alpha]_D^{26}$ = +219.5 (*c* 1.00, THF). HRMS (ESI–) calcd for $C_{32}H_{21}O_7P_2$ $[M–H]^-$ 579.0768, found 579.0757.

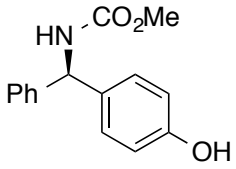


(*R*)-3,3'-Di(4-biphenyl)-1,1'-binaphthyl-2,2'-pyrophosphoric acid ((*R*)-3c): 99% yield. Pale yellow solid. ^{1}H NMR (THF-d_8, 400 MHz) δ = 7.13 (br, 2H), 7.28-7.35 (m, 4H), 7.37-7.52 (m, 6H), 7.60-7.82 (m, 12H), 8.01 (m, 2H), 8.15 (s, 2H) (Two P-OH moieties were not clearly observed.). ^{13}C NMR (THF-d_8, 100 MHz) δ = 125.9 (2C), 126.4 (2C), 126.8 (2C), 127.2 (4C), 127.7 (4C), 127.8 (2C), 127.9 (2C), 129.1 (2C), 129.5 (4C), 130.9 (4C), 132.1 (2C), 132.7 (2C), 134.0 (2C), 135.4 (2C), 138.6 (2C), 140.3 (2C), 141.7 (2C), 146.3 (2C). ^{31}P NMR (THF-d_8, 160 MHz) δ = –20.2. IR (KBr) 3408, 3056, 2930, 1656, 1488, 1428, 1396, 1246, 1194, 1104, cm^{-1}. $[\alpha]_D^{30}$ = +112.0 (*c* 1.00, THF). HRMS (ESI–) calcd for $C_{44}H_{29}O_7P_2$ $[M–H]^-$ 731.1383, found 731.1380.

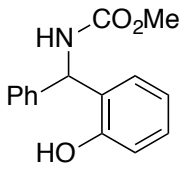
3. General procedure for the catalytic enantioselective aza-Friedel–Crafts reaction of phenols 5 with aldimines 4 (Scheme 3)



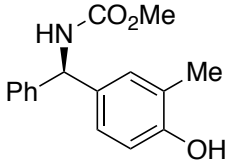
To a well-dried round-bottom flask (50 mL) with (*R*)-**3a** (8.8 mg, 0.010 mmol), which was prepared *in situ* in advance, were added chloroform (18 mL) and aldimine **4** (0.30 mmol) under a nitrogen atmosphere. The solution was cooled to 0 °C, and then a solution of phenol **5** (0.20 mmol) in chloroform (2 mL) was added. The resultant mixture was stirred at 0 °C for 3 h. To quench the reaction, triethylamine (0.20 mL, 1.44 mmol) was added at 0 °C and the mixture was stirred for 5 min. Brine (10 mL) was poured into the reaction mixture, and the product was extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give the desired product **6**. Hydrolyzed catalyst (*R*)-**2a** (partially, some metal salts of (*R*)-**2a**) could be recovered through the same silica gel column chromatography (eluent: $CHCl_3$:MeOH = 3:1) almost quantitatively. If the catalyst was to be reused for another reaction, further purification with washing by an aqueous solution of 1 *M* HCl was necessary. The enantiomeric purity of **6** was determined by HPLC analysis.



Methyl (*R*)-((4-hydroxyphenyl)(phenyl)methyl)carbamate (6a): 90% yield, 63% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.69 (s, 3H), 5.32 (br, 1H), 5.74 (br, 1H), 5.89 (br, 1H), 6.73 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 7.3 Hz, 2H), 7.20-7.28 (m, 3H), 7.21-7.34 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 52.6, 58.4, 115.6 (2C), 127.2 (2C), 127.5, 128.6 (2C), 128.7 (2C), 133.3, 141.8, 155.5, 156.7. IR (neat) 3326, 1698, 1508, 1456, 1362, 1233, 1038 cm^{-1}. $[\alpha]_D^{27}$ = –16.0 (*c* 1.00, $CHCl_3$, 63% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 210 nm, 0.6 mL/min, t_R = 21.7 min (minor, *S*), 25.9 min (major, *R*). HRMS (FAB+) calcd for $C_{15}H_{15}NNaO_3$ $[M+Na]^+$ 280.0950, found 280.0944.



Methyl ((2-hydroxyphenyl)(phenyl)methyl)carbamate (7a): 15% yield, 0% ee (Table 1, entry 3). Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.72 (s, 3H), 5.84 (br, 1H), 6.17 (br, 1H), 6.83-6.88 (m, 2H), 6.99 (br, 1H), 7.07 (br, 1H), 7.15 (td, *J* = 7.8, 1.4 Hz, 1H), 7.23-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 52.8, 54.8, 116.8, 120.4, 126.8 (2C), 127.3, 128.5 (2C), 128.8, 129.1 (2C), 140.8, 154.2, 157.6. IR (neat) 3407, 1696, 1600, 1519, 1457, 1348, 1267, 1025 cm^{-1}. HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 210 nm, 0.6 mL/min, t_R = 10.9 min, 60.5 min. HRMS (FAB+) calcd for $C_{15}H_{15}NNaO_3$ $[M+Na]^+$ 280.0950, found 280.0942.



Methyl (*R*)-((4-hydroxy-3-methylphenyl)(phenyl)methyl)carbamate (6b): 93% yield, 82% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.21 (s, 3H), 3.69 (s, 3H), 4.76 (s, 1H), 5.25 (br, 1H), 5.87 (br, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 7.23-7.28 (m, 3H), 7.32 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 16.0, 52.5, 58.4, 115.0, 124.4, 125.9, 127.2 (2C), 127.4, 128.6 (2C), 129.9, 133.3, 142.0, 153.7, 156.6. IR (KBr) 3394, 2924,

1699, 1509, 1267, 1118, 1039 cm^{-1}. M.p. 119-123 °C. $[\alpha]_D^{21}$ = –23.6 (*c* 1.00, $CHCl_3$, 82% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 254 nm, 0.6 mL/min, t_R = 17.8 min (minor, *S*), 25.9 min (major, *R*). HRMS (FAB+) calcd for $C_{16}H_{17}NNaO_3$ $[M+Na]^+$ 294.1106, found 294.1105.

Crystal data of 6b (Figure S1): Compound **6b** was recrystallized in diethyl ether for X-ray analysis. Formula $C_{16}H_{17}NO_3$, colorless, crystal dimensions 0.30 × 0.25 × 0.10 mm^3, monoclinic, space group *P2₁* (#4), *a* = 4.8284(19) Å, *b* = 14.582(6) Å, *c* = 9.948(4) Å, α = 90.00 °, β = 98.700(8) °, γ = 90.00 °, *V* = 692.4(5) $Å^3$, *Z* = 2, ρ_{calc} = 1.301 g cm^{-3}, F(000) = 288, μ(MoKα) = 0.090 mm^{-1}, *T* = 123 K. 5805 reflections collected, 2791 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.556 °), and 195 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0348 and wR_2 = 0.0777. GOF = 1.039. Absolute stereo configuration could not be determined by flack's parameter due to a lack of heavy atoms. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1513098. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk; Web page: http://www.ccdc.cam.ac.uk/pages/Home.aspx].

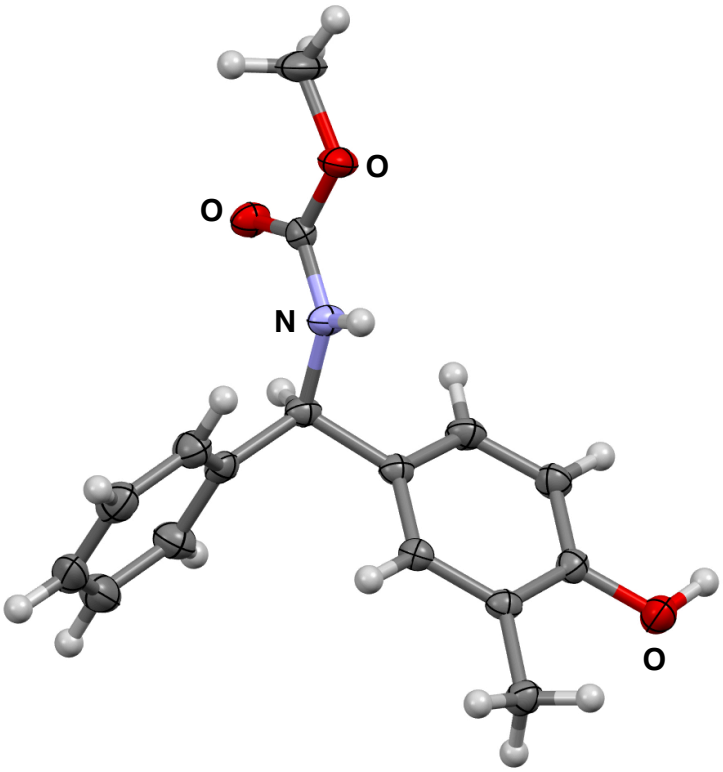
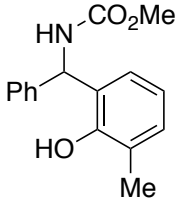
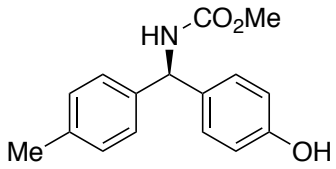


Figure S1. ORTEP drawing of **6b**.



Methyl ((2-hydroxy-3-methylphenyl)(phenyl)methyl)carbamate (7b): 17% yield, 0% ee (Scheme 3b). Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.26 (s, 3H), 3.72 (s, 3H), 5.72 (br, 1H), 6.20 (d, *J* = 8.2 Hz, 1H), 6.60 (br, 1H), 6.78 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 7.25-7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 16.1, 52.8, 54.7, 120.6, 125.6, 126.8 (2C), 126.9, 127.5, 128.3, 128.7 (2C), 130.6, 140.7, 152.6, 157.7. IR (neat) 3410, 1703, 1518, 1468, 1345, 1266, 1193, 1028 cm^{-1}. HRMS (FAB+) calcd for $C_{16}H_{17}NNaO_3$ $[M+Na]^+$ 294.1106, found 294.1108.



Methyl (*R*)-(4-hydroxyphenyl)(*p*-tolyl)methylcarbamate (6c): 58% yield, 77% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.33 (s, 3H), 3.69 (s, 3H), 4.92 (s, 1H), 5.22 (br, 1H), 5.86 (br, 1H), 6.76 (dt, *J* = 8.7, 2.7 Hz, 2H) 7.07-7.15 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.2, 52.6, 58.2, 115.6 (2C), 127.2 (2C), 128.6 (2C), 129.4 (2C), 133.5, 137.3, 139.0, 155.4, 156.6. IR (KBr) 3361, 1664, 1542, 1512, 1439, 1266, 1039 cm^{-1}. M.p. 133-137 °C. $[\alpha]_D^{25}$ = –5.1 (*c* 0.87, $CHCl_3$, 77% ee). HPLC analysis; IA-3, *n*-hexane/*i*-PrOH = 4/1, 210 nm, 1.0 mL/min, t_R = 8.8 min (major, *R*), 11.5 min (minor, *S*). HRMS (ESI+) calcd for $C_{16}H_{17}NNaO_3$ $[M+Na]^+$ 294.1101, found: 294.1105.

Crystal data of 6c (Figure S2): Compound **6c** was recrystallized in dichloromethane/methanol/*n*-hexane for X-ray analysis. Formula $C_{16}H_{17}NO_3$, colorless, crystal dimensions 0.20 × 0.18 × 0.10 mm^3, monoclinic, space group $P2_1$ (#4), *a* = 4.7609(19) Å, *b* = 15.097(6) Å, *c* = 9.928(4) Å, α = 90.00 °, β = 102.347(8) °, γ = 90.00 °, *V* = 697.1(5) Å^3, *Z* = 2, ρ_{calc} = 1.293 g cm^{-3}, F(000) = 288, μ(MoKα) = 0.089 mm^{-1}, *T* = 103 K. 5704 reflections collected, 2902 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.336 °), and 195 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0295 and wR_2 = 0.0818. GOF = 1.072. Absolute stereo configuration could not be determined by flack's parameter due to a lack of heavy atoms. Crystallographic data for the structure reported

in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1849652. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk; Web page: http://www.ccdc.cam.ac.uk/pages/Home.aspx].

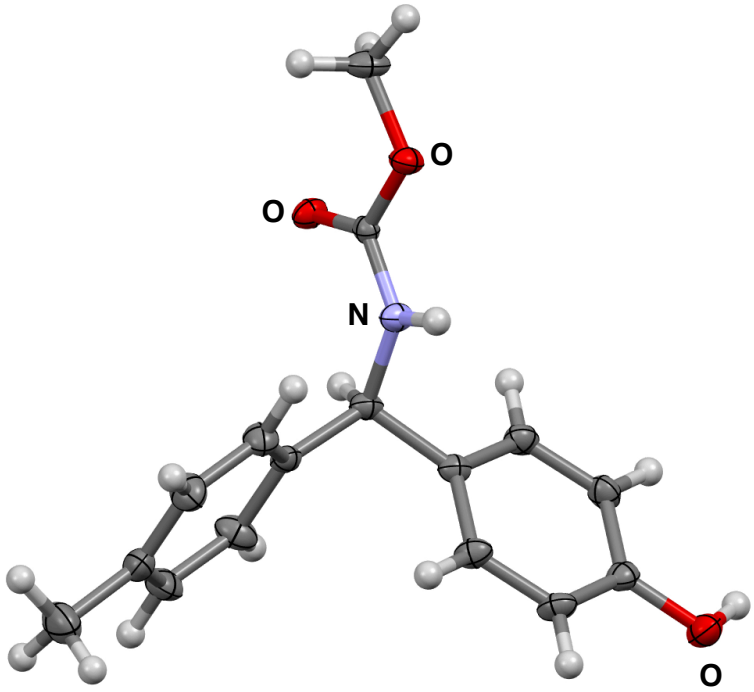
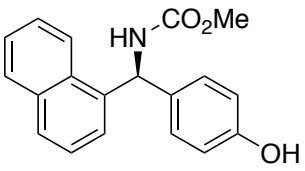


Figure S2. ORTEP drawing of **6c**.



Methyl (*S*)-((4-hydroxyphenyl)(naphthalen-1-yl)methyl)carbamate (6d): 67% yield, 60% ee. Colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz, 40 °C) δ = 3.56 (s, 3H), 6.50 (d, J = 9.2 Hz, 1H), 6.68 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.3 Hz, 2H), 7.45 (t, J = 7.3 Hz, 1H), 7.48-7.51 (m, 3H), 7.84 (d, J = 7.8 Hz, 1H), 7.93 (m, 1H), 8.00 (m, 1H), 8.13 (br, 1H), 9.28 (br, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, 40 °C) δ = 51.3, 54.2, 115.0 (2C), 123.4, 124.3, 125.2, 125.4, 126.1, 127.4, 128.5, 128.7 (2C), 130.4, 132.1, 133.3, 138.4, 155.9, 156.3. IR (KBr) 3398, 3349, 1697, 1515, 1448, 1263, 1225, 1191, 1174, 1056 cm^{-1}. M.p. 208-222 °C. $[\alpha]_D^{26}$ = –26.8 (*c* 1.00, MeOH, 60% ee).

HPLC analysis; ID-3, *n*-hexane/*i*-PrOH = 4/1, 284 nm, 0.5 mL/min, t_R = 24.4 min (major, *S*), 29.3 min (minor, *R*). HRMS (ESI+) calcd for $C_{19}H_{17}NNaO_3$ $[M+Na]^+$ 330.1101, found 330.1093.

Crystal data of 6d (Figure S3): Compound **6d** was recrystallized in chloroform/methanol/*n*-hexane for X-ray analysis. Formula $C_{19}H_{17}NO_3$, colorless, crystal dimensions 0.20 × 0.20 × 0.20 mm^3, orthorhombic, space group $P2_12_12_1$ (#19), a = 9.116(2) Å, b = 11.311(3) Å, c = 14.553(3) Å, α = 90.00 °, β = 90.00 °, γ = 90.00 °, V = 1500.6(6) $Å^3$, Z = 4, ρ_{calc} = 1.360 g cm^{-3}, F(000) = 648, μ(MoKα) = 0.092 mm^{-1}, T = 123 K. 12688 reflections collected, 3391 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.399 °), and 218 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0259 and wR_2 = 0.0668. GOF = 1.045. Absolute stereo configuration could not be determined by flack's parameter due to a lack of heavy atoms. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1849239. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk; Web page: http://www.ccdc.cam.ac.uk/pages/Home.aspx].

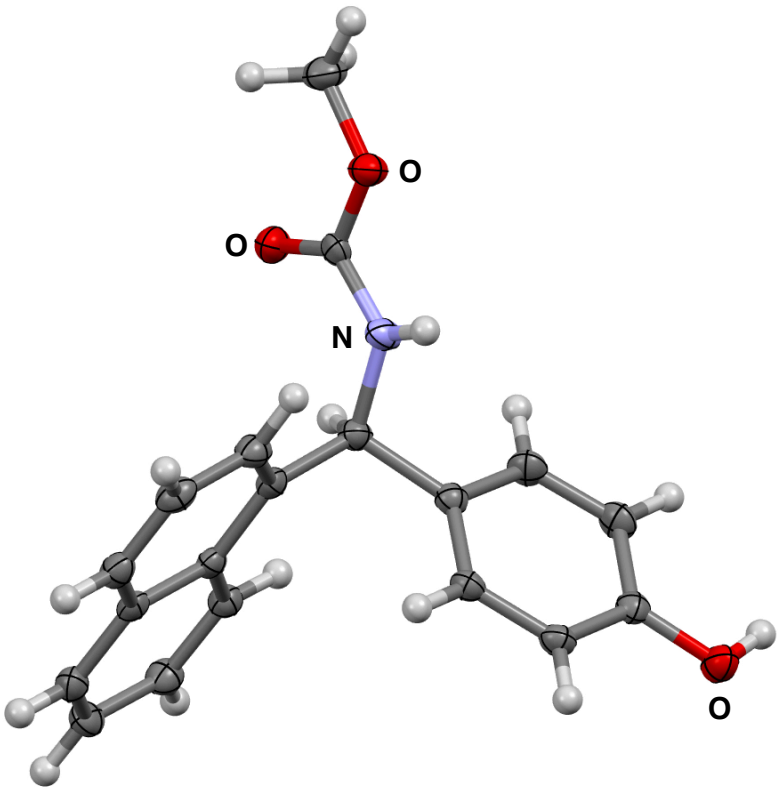
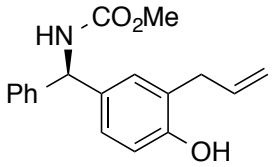
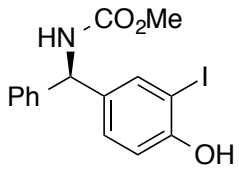


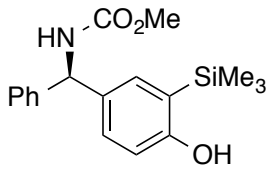
Figure S3. ORTEP drawing of **6d**.



Methyl (*R*)-((3-allyl-4-hydroxyphenyl)(phenyl)methyl)carbamate (6e): 66% yield, 76% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.36 (d, *J* = 6.4 Hz, 2H), 3.69 (s, 3H), 5.08-5.20 (m, 2H), 5.30 (br, 1H), 5.40 (br, 1H), 5.89 (d, *J* = 7.3 Hz, 1H), 5.96 (m, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.97 (s, 1H), 7.22-7.27 (m, 3H), 7.30-7.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.3, 52.5, 58.4, 116.0, 116.7, 125.7, 126.8, 127.2 (2C), 127.5, 128.7 (2C), 129.5, 134.0, 136.3, 142.0, 153.7, 156.4. IR (neat) 3326, 2923, 2855, 1698, 1267 cm^{-1}. $[\alpha]_D^{27}$ = –29.9 (*c* 1.00, $CHCl_3$, 76% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 230 nm, 0.6 mL/min, t_R = 13.3 min (minor, *S*), 23.8 min (major, *R*). HRMS (FAB+) calcd for $C_{18}H_{19}NNaO_3$ $[M+Na]^+$ 320.12657, found 320.1257.

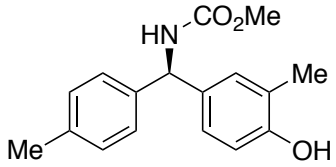


Methyl (*R*)-((4-hydroxy-3-iodophenyl)(phenyl)methyl)carbamate (6f): 11% yield, 26% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.70 (s, 3H), 5.24 (br, 1H), 5.42 (s, 1H), 5.87 (br, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 7.10 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.21 (d, *J* = 6.9 Hz, 2H), 7.27-7.38 (m, 3H), 7.54 (d, *J* = 2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 52.6, 57.7, 85.8, 115.1, 127.3 (2C), 127.8, 128.9 (2C), 129.2, 135.4, 137.0, 141.2, 154.4, 156.3. IR (neat) 3305, 2919, 1691, 1268, 1225, 1040 cm^{-1}. $[\alpha]_D^{25}$ = –10.3 (*c* 1.00, $CHCl_3$, 26% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 210 nm, 0.6 mL/min, t_R = 16.9 min (minor, *S*), 46.8 min (major, *R*). HRMS (FAB+) calcd for $C_{15}H_{14}INNaO_3$ $[M+Na]^+$ 405.9916, found 405.9906.

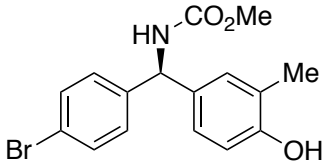


Methyl (*R*)-((4-hydroxy-3-(trimethylsilyl)phenyl)(phenyl)methyl)carbamate (6g): 55% yield, 60% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.26 (s, 9H), 3.69 (s, 3H), 5.19 (br, 1H), 5.28 (br, 1H), 5.90 (br, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 6.99 (br, 1H), 7.20 (s, 1H), 7.22-7.28 (m, 3H),

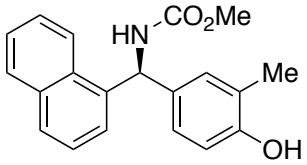
7.32 (t, J = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = –1.0 (3C), 52.5, 58.6, 114.6, 125.8, 127.1 (2C), 127.4, 128.6 (2C), 129.7, 133.0, 134.4, 142.0, 156.5, 160.2. IR (neat) 3335, 2953, 1699, 1508, 1405, 1243, 1074 cm^{-1}. $[\alpha]_D^{25}$ = –22.8 (*c* 1.00, $CHCl_3$, 60% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 210 nm, 0.6 mL/min, t_R = 7.5 min (minor, *S*), 10.0 min (major, *R*). HRMS (FAB+) calcd for $C_{18}H_{23}NNaO_3Si$ $[M+Na]^+$ 352.1345, found 352.1335.



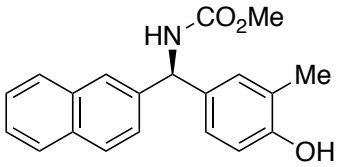
Methyl (*R*)-((4-hydroxy-3-methylphenyl)(*p*-tolyl)methyl)carbamate (6h): 93% yield, 67% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.20 (s, 3H), 2.32 (s, 3H), 3.68 (s, 3H), 4.90 (br, 1H), 5.23 (br, 1H), 5.83 (br, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.98 (s, 1H), 7.12 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 16.0, 21.1, 52.4, 58.2, 115.0, 124.3, 125.8, 127.1 (2C), 129.3 (2C), 129.9, 133.7, 137.1, 139.1, 153.5, 156.5. IR (neat) 3334, 2921, 1697, 1511, 1268, 1117, 1039 cm^{-1}. $[\alpha]_D^{27}$ = –8.0 (*c* 1.00, $CHCl_3$, 67% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 280 nm, 0.6 mL/min, t_R = 16.3 min (major, *R*), 19.8 min (minor, *S*). HRMS (FAB+) calcd for $C_{17}H_{19}NNaO_3$ $[M+Na]^+$ 308.1257, found 308.1261.



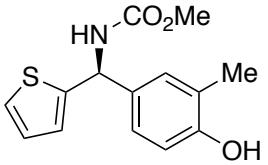
Methyl (*R*)-((4-bromophenyl)(4-hydroxy-3-methylphenyl)methyl)carbamate (6i): 99% yield, 28% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.19 (s, 3H), 3.69 (s, 3H), 5.22 (m, 2H), 5.80 (br, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.93 (s, 1H), 7.12 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 16.0, 52.6, 58.0, 115.1, 121.3, 124.6, 126.0, 128.8 (2C), 130.0, 131.7 (2C), 132.8, 141.1, 153.8, 156.5. IR (neat) 3327, 2922, 1697, 1511, 1266, 1118, 1071, 1039, 1011 cm^{-1}. $[\alpha]_D^{23}$ = –2.8 (*c* 1.00, $CHCl_3$, 28% ee). HPLC analysis; AS-3, *n*-hexane/*i*-PrOH = 3/1, 230 nm, 1.0 mL/min, t_R = 9.8 min (minor, *S*), 11.0 min (major, *R*). HRMS (FAB+) calcd for $C_{16}H_{16}BrNNaO_3$ $[M+Na]^+$ 372.0206, found 372.0197.



Methyl (*S*)-((4-hydroxy-3-methylphenyl)(naphthalen-1-yl)methyl)carbamate (6j): 82% yield, 77% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.19 (s, 3H), 3.70 (s, 3H), 4.86 (d, *J* = 9.6 Hz, 1H), 5.31 (d, *J* = 8.2 Hz, 1H), 6.62 (br, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.93 (br, 1H), 7.04 (s, 1H), 7.33 (m, 1H), 7.41-7.48 (m, 3H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.87 (m, 1H), 7.97 (br, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 16.0, 52.6, 55.3, 115.0, 123.8, 124.4, 124.9, 125.3, 125.8, 125.9, 126.5, 128.4, 128.8, 130.0, 131.0, 133.0, 134.0, 137.4, 153.6, 156.4. IR (neat) 3335, 2975, 1698, 1508, 1260, 1118 cm^{-1}. $[\alpha]_D^{26}$ = –7.6 (*c* 1.00, $CHCl_3$, 77% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 230 nm, 0.6 mL/min, t_R = 21.7 min (minor, *R*), 32.0 min (major, *S*). HRMS (FAB+) calcd for $C_{20}H_{19}NNaO_3$ $[M+Na]^+$ 344.1263, found 344.1263.

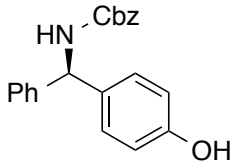


Methyl (*R*)-((4-hydroxy-3-methylphenyl)(naphthalen-2-yl)methyl)carbamate (6k): 74% yield, 68% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.18 (s, 3H), 3.71 (s, 3H), 5.22 (s, 1H), 5.37 (br, 1H), 6.03 (br, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.43-7.52 (m, 2H), 7.71 (s, 1H), 7.75-7.83 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 15.9, 52.5, 58.5, 115.1, 124.4, 125.5 (2C), 126.0, 126.1, 126.3, 127.7, 128.1, 128.5, 130.2, 132.7, 133.3, 133.5, 139.4, 153.6, 156.5. IR (neat) 3330, 1696, 1508, 1265, 1114, 1040 cm^{-1}. $[\alpha]_D^{25}$ = –28.6 (*c* 1.00, $CHCl_3$, 68% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 254 nm, 0.6 mL/min, t_R = 20.2 min (major, *R*), 29.3 min (minor, *S*). HRMS (FAB+) calcd for $C_{20}H_{19}NNaO_3$ $[M+Na]^+$ 344.1263, found 344.1257.

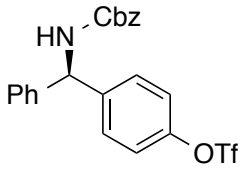


Methyl (*S*)-((4-hydroxy-3-methylphenyl)(thiophen-2-yl)methyl)carbamate (6l): 80% yield, 49% ee. Colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.23 (s, 3H), 3.70 (s, 3H), 5.02 (s,

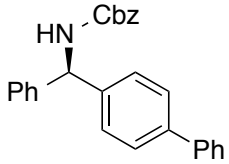
1H), 5.36 (br, 1H), 6.06 (br, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.81 (dm, J = 3.7 Hz, 1H), 6.93 (dd, J = 5.3, 3.7 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 7.08 (br, 1H), 7.22 (dd, J = 5.3, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 16.0, 52.5, 54.6, 115.1, 124.3, 125.2, 125.6, 125.7, 126.9, 129.7, 133.4, 146.5, 153.8, 156.2. IR (KBr) 3398, 2918, 1509, 1256, 1118, 1044 cm^{-1}. M.p. 42-45 °C. $[\alpha]_D^{25}$ = –9.6 (*c* 1.00, $CHCl_3$, 49% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 230 nm, 0.6 mL/min, t_R = 15.4 min (minor, *R*), 18.6 min (major, *S*). HRMS (FAB+) calcd for $C_{14}H_{15}NNaO_3S$ $[M+Na]^+$ 300.0670, found 300.0666.



Large scale synthesis of benzyl Benzyl (*R*)-((4-hydroxyphenyl)(phenyl)methyl)carbamate (6m): To a well-dried round-bottom flask (500 mL) with (*R*)-**3a** (99.4 mg, 0.113 mmol), which was prepared *in situ* in advance, were added chloroform (200 mL) and aldimine **4b** (810 mg, 3.39 mmol) under a nitrogen atmosphere. The solution was cooled to 0 °C, and then a solution of phenol **5a** (213 mg, 2.26 mmol) in chloroform (23 mL) was added. The resultant mixture was stirred at 0 °C for 3 h. To quench the reaction, triethylamine (0.20 mL, 1.44 mmol) was added at 0 °C and the mixture was stirred for 5 min. Brine (100 mL) was poured into the reaction mixture, and the product was extracted with ethyl acetate (100 mL × 2). The combined extracts were washed with brine (100 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give the desired product **6m** (663 mg, 88% yield) as colorless oil. Hydrolyzed catalyst (*R*)-**2a** (partially, some metal salts of (*R*)-**2a**) could be recovered through the same silica gel column chromatography (eluent: $CHCl_3$:MeOH = 3:1) almost quantitatively. The enantiomeric purity of **6m** was determined by HPLC analysis. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.11 (s, 2H), 5.41 (br, 1H) 5.80 (br, 1H), 5.90 (br, 1H), 6.66-6.72 (m, 2H), 7.03 (d, J = 7.3 Hz, 2H), 7.21-7.34 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 58.5, 67.3, 115.6 (2C), 127.2 (2C), 127.5, 128.3/128.5/128.6 (9C), 133.2, 136.1, 141.7, 155.5, 156.0. IR (neat) 3321, 1696, 1661, 1517, 1356, 1297, 1265, 1237, 1041 cm^{-1}. $[\alpha]_D^{27}$ = –13.6 (*c* 1.00, $CHCl_3$, 63% ee). HPLC analysis; IC-3, *n*-hexane/*i*-PrOH = 85/15, 230 nm, 1.0 mL/min, t_R = 14.1 min (minor, *S*), 20.9 min (major, *R*). HRMS (FAB+) calcd for $C_{21}H_{19}NNaO_3$ $[M+Na]^+$ 356.1263, found 356.1261.

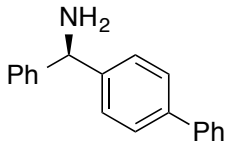


(*R*)-4-((((Benzyloxy)carbonyl)amino)(phenyl)methyl)phenyl trifluoromethanesulfonate (10): To a solution of **6m** (663 mg, 1.99 mmol, 62% ee) and triethylamine (0.70 mL, 4.98 mmol) in dichloromethane (5 mL) was added trifluoromethanesulfonic anhydride (721 μL, 4.38 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with ethyl acetate (10 mL) and brine (10 mL). The product was extracted with ethyl acetate (20 mL × 2) and washed with brine. The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure to give compound **10** (930 mg, >99% yield) as a colorless solid. This crude product was used in the next step without further purification. Colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.11 (s, 2H), 5.41 (br, 1H), 6.00 (br, 1H), 7.19-7.24 (m, 4H), 7.28-7.37 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 58.3, 67.3, 118.7 (q, $J_{C\text{-}F}$ = 319 Hz), 121.5 (2C), 127.4 (2C), 128.1, 128.3 (3C), 128.6 (2C), 129.0 (2C), 129.1 (2C), 136.1, 140.6, 142.3, 148.7, 155.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ = –72.7 ppm. IR (KBr) 3315, 3033, 1696, 1499, 1424, 1140, 1040 cm^{-1}. M.p. 112-114 °C. $[\alpha]_D^{26}$ = +18.4 (*c* 1.00, $CHCl_3$, 62% ee). HRMS (FAB+) calcd for $C_{22}H_{18}F_3NNaO_5S$ $[M+Na]^+$ 488.0755, found 488.0755.

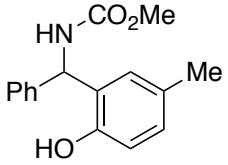


Benzyl (*R*)-(1,1'-biphenyl-4-yl(phenyl)methyl)carbamate (11): To a solution of compound **10** (containing impurities from the previous step, 1.99 mmol) in toluene (40 mL), phenylboronic acid (388 mg, 3.2 mmol), K_2CO_3 (340 mg, 2.46 mmol), and tetrakis(triphenylphosphine)palladium(0) (236 mg, 0.20 mmol) were added. The mixture was heated to 90 °C, and stirred at that temperature for 16 h. The resulting mixture was diluted with ethyl acetate (20 mL) and a 1.0 *M* aqueous solution of HCl. The product was extracted with ethyl acetate (20 mL × 2) and washed with brine (20 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: *n*-hexane:EtOAc = 5:1 to 3:1) to give **11** (783 mg, >99% yield) as a colorless solid.

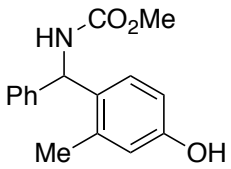
Recrystallization of the compound from *n*-hexane/Et_2O improved the optical purity to 98% ee (400 mg, 50% recovery). The enantiomeric purity of **11** was determined by HPLC analysis. Colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.13 (s, 2H), 5.43 (br, 1H), 6.03 (br, 1H), 7.25-7.40 (m, 13H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.52-7.59 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 58.7, 67.0, 127.1 (2C), 127.3 (2C), 127.4 (4C), 127.6, 127.7 (2C), 128.2 (2C), 128.5 (2C), 128.7 (2C), 128.8 (2C), 136.3, 140.4, 140.6, 140.7, 141.6, 155.7. IR (KBr) 3322, 3031, 1686, 1519, 1489, 1231, 1134, 1040 cm^{-1}. M.p. 109-116 °C. $[\alpha]_D^{25}$ = –5.7 (*c* 1.00, $CHCl_3$, 98% ee). HRMS (FAB+) calcd for $C_{27}H_{23}NNaO$ $[M+Na]^+$ 416.1626, found 416.1626. HPLC analysis; AD-H, *n*-hexane/*i*-PrOH = 4/1, 280 nm, 1.0 mL/min, t_R = 12.9 min (minor, *S*), 14.7 min (major, *R*).



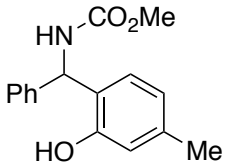
(*R*)-1,1'-Biphenyl-4-yl(phenyl)methanamine (12): To a solution of **11** (55.9 mg, 0.14 mmol) in dichloromethane (0.56 mL) was added trimethylsilyl iodide (74 μL, 0.52 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then quenched with MeOH (5 mL). Volatiles were removed *in vacuo*, and the resulting residue was dissolved in 30% aqueous acetic acid and washed with ether (5 mL). The aqueous layer was then neutralized with 1 *M* aqueous solution of NaOH, and extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure to give **12** (33.4 mg, 92% yield) as a colorless solid. The enantiomeric purity of **12** was determined by chiral HPLC analysis (98% ee). IR, ^{1}H NMR, ^{13}C NMR, and HRMS data were consistent with previously reported values.[4] Colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.80 (br, 2H), 5.27 (s, 1H), 7.23 (m, 1H), 7.30-7.36 (m, 3H), 7.39-7.50 (m, 6H), 7.52-7.58 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 59.6, 127.0 (2C), 127.1 (4C), 127.2 (2C), 127.3 (2C), 128.6 (2C), 128.8 (2C), 140.0, 140.9, 144.7, 145.5. IR (KBr) 3378, 3027, 2922, 2850, 1598, 1487, 1448, 1417, 1213, 1147 cm^{-1}. M.p. 69-74 °C. $[\alpha]_D^{26}$ = +19.6 (*c* 1.00, $CHCl_3$, 98% ee) [lit.[4b] $[\alpha]_D^{22}$ = +8.9 (*c* 2.45, $CHCl_3$, 66% ee)]. HPLC analysis; OD-H, *n*-hexane/*i*-PrOH/Et_2NH = 10/1/0.1, 254 nm, 1.0 mL/min, t_R = 35.0 min (major, *R*), 40.1 min (minor, *S*) [lit.[4b] HPLC analysis (66% ee); OD-H, *n*-hexane/*i*-PrOH/Et_2NH = 100/10/0.1, 254 nm, 1.0 mL/min, t_R = 25.9 min (major, *R*), 28.2 min (minor, *S*)]. HRMS (EI+) calcd for $C_{19}H_{17}N$ $[M]^+$ 259.1361, found 259.1369.



Methyl ((2-hydroxy-5-methylphenyl)(phenyl)methyl)carbamate (17): 8% yield, 0% ee. Colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.23 (s, 3H), 3.71 (s, 3H), 5.89 (br, 1H), 6.11 (br, 1H), 6.61 (br, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 1H), 6.95 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.22-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.6, 52.7, 55.4, 116.5, 126.7 (2C), 127.1, 127.4, 128.4 (2C), 129.4 (2C), 129.5, 141.2, 151.8, 157.5. IR (KBr) 3421, 3322, 2958, 1689, 1509, 1450, 1334, 1274, 1238, 1121, 1038 cm^{-1}. M.p. 148-152 °C. HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 9/1, 230 nm, 1.0 mL/min, t_R = 12.2 min, 17.4 min. HRMS (ESI+) calcd for $C_{16}H_{17}NNaO_3$ $[M]^+$ 294.1101, found 294.1091.

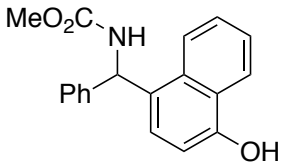


Methyl ((4-hydroxy-2-methylphenyl)(phenyl)methyl)carbamate (19): 3% yield, 5% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 40 °C) δ = 2.24 (s, 3H), 3.69 (s, 3H), 5.04 (s, 1H), 5.18 (br, 1H), 6.06 (br, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.62 (s, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J*= 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, 40 °C) δ = 19.6, 52.5, 55.4, 112.9, 117.7, 127.4 (2C), 127.5, 128.2, 128.7 (2C), 132.1, 138.0, 141.5, 155.0, 156.3. IR (neat) 3332, 2923, 1695, 1610, 1504, 1453, 1358, 1232, 1097, 1027 cm^{-1}. HPLC analysis; IC-3, *n*-hexane/*i*-PrOH = 85/15, 210 nm, 0.4 mL/min, t_R = 33.8 min (minor), 37.4 min (major). HRMS (ESI+) calcd for $C_{16}H_{17}NNaO_3$ $[M+Na]^+$ 294.1101, found 294.1100.

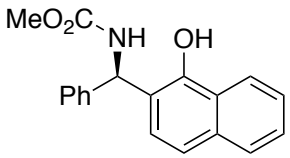


Methyl ((2-hydroxy-4-methylphenyl)(phenyl)methyl)carbamate (20): 2% yield, 4% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 40 °C) δ = 2.28 (s, 3H), 3.72 (s, 3H), 5.76 (d, *J* = 9.2 Hz, 1H), 6.14 (d, *J* = 8.2 Hz, 1H), 6.54 (br, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.69 (s, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 7.26-7.28 (m, 3H), 7.33 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, 40 °C) δ

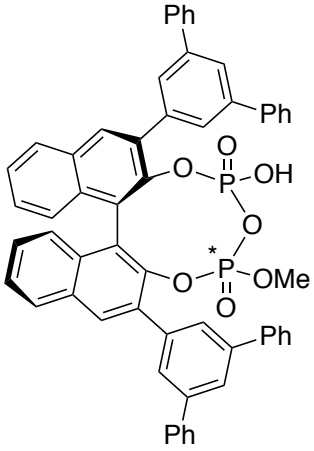
= 21.1, 52.8, 54.9, 117.3, 121.1, 124.9, 126.8 (2C), 127.1, 128.4 (2C), 128.7, 139.1, 141.2, 154.1, 157.6. IR (neat) 3319, 1694, 1618, 1516, 1452, 1421, 1347, 1291, 1232, 1120, 1028 cm^{-1}. HPLC analysis; IC-3, *n*-hexane/*i*-PrOH = 4/1, 230 nm, 0.4 mL/min, t_R = 18.5 min (major), 23.8 min (minor). HRMS (FAB+) calcd for $C_{16}H_{17}NNaO_3$ $[M+Na]^+$ 294.1106, found 294.1116.



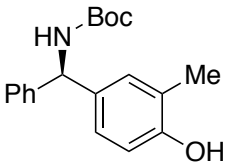
Methyl ((4-hydroxynaphthalen-1-yl)(phenyl)methyl)carbamate (22): 14% yield, 11% ee. Colorless solid. ^1H NMR (DMSO-d_6, 400 MHz) δ = 3.56 (s, 3H), 6.48 (d, *J* = 9.2 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.24 (m, 1H), 7.28-7.34 (m, 4H), 7.44 (t, *J* = 7.3 Hz, 1H) 7.50 (t, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 2H), 10.1 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 51.3, 54.3, 107.0, 122.6, 123.2, 124.3, 124.8, 125.8, 126.5, 126.9, 127.5 (2C), 128.1, 128.2 (2C), 131.9, 142.5, 152.7, 156.1. IR (KBr) 3335, 2946, 1699, 1528, 1391, 1339, 1274, 1237, 1053 cm^{-1}. M.p. 212-222 °C. $[\alpha]_D^{25}$ = +5.9 (*c* 0.54, $CHCl_3$, 11% ee). HPLC analysis; IC-3, *n*-hexane/*i*-PrOH = 9/1, 240 nm, 1.0 mL/min, t_R = 23.1 min (minor), 35.4 min (major). HRMS (ESI+) calcd for $C_{19}H_{17}NNaO_3$ $[M+Na]^+$ 330.1101, found 330.1100.



Methyl (*R*)-((1-hydroxynaphthalen-2-yl)(phenyl)methyl)carbamate (23): 43% yield, 24% ee. Colorless solid. ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.72 (s, 3H), 5.78 (br, 1H), 6.49 (d, *J* = 9.6 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 7.22-7.40 (m, 6H), 7.45-7.51 (m, 2H), 7.73 (d, *J* = 8.2 Hz, 1H), 8.33 (d, *J* = 7.4 Hz, 1H) 8.47 (br, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 53.1, 53.2, 120.6, 122.5, 122.9, 125.7, 125.8, 126.2, 126.7, 126.8 (2C), 127.5, 127.7, 128.8 (2C), 134.2, 139.5, 150.8, 158.8. IR (KBr) 3313, 3058, 1695, 1511, 1356, 1244, 1189, 1081 cm^{-1}. M.p. 115-122 °C. $[\alpha]_D^{25}$ = –23.3 (*c* 0.98, $CHCl_3$, 24% ee). HRMS (FAB+) calcd for $C_{19}H_{17}NNaO_3$ $[M+Na]^+$ 330.1101, found 330.1107. HPLC analysis; IC-3, *n*-hexane/*i*-PrOH = 9/1, 230 nm, 1.0 mL/min, t_R = 12.8 min (major), 14.7 min (minor).



(*R*)-24: Following the general procedure for (*R*)-**3** afforded (*R*)-**24** from methyl ester of (*R*)-**2a** (9.2 mg 0.010 mmol).[3] (*R*)-**24** was obtained (9.0 mg, 99%) as *P*-diastereomers (76:24; pale yellow solid), which were not separable from each other, and the diastereomeric mixture was used for subsequent analysis and the reaction. A small amount of toluene was used under azeotropic conditions, but a small amount of DMF and dichloromethane were involved. Pale yellow solid. ^{1}H NMR (THF-d_8, 400 MHz) Many peaks were overlapped, and two P-OH moieties were not clearly observed. δ = 3.22 (d, $J_{H–P}$ = 11.9 Hz), 7.06-7.27 (m), 7.28-7.65 (m), 7.74-8.16 (m), 8.32 (s), 8.35 (s). ^{13}C NMR (THF-d_8, 100 MHz) Many peaks were overlapped. δ = 56.3 (d, $J_{C–P}$ = 5.8 Hz), 125.5, 125.8, 125.9, 126.0, 127.2, 128.1, 128.2, 128.3, 128.4, 128.7, 128.9, 129.2, 129.5, 129.7, 132.6, 132.7, 132.8, 134.0, 134.1, 135.3, 135.4, 135.6, 138.4, 139.5, 140.2, 142.2 (d, $J_{C–P}$ = 6.7 Hz), 142.5 (d, $J_{C–P}$ = 5.8 Hz), 146.2 (d, $J_{C–P}$ = 8.6 Hz), 146.5 (d, $J_{C–P}$ = 10.5 Hz). ^{31}P NMR ($CDCl_3$, 160 MHz) δ = –20.8 (d, J = 26.0 Hz, minor), –20.6 (d, J = 25.8 Hz, major), –20.2 (d, J = 26.0 Hz, major), –19.7 (d, J = 25.9 Hz, minor). IR (KBr) 3408, 3056, 2930, 1656, 1488, 1428, 1396, 1246, 1194, 1104, cm^{-1}. $[\alpha]_D^{30}$ = +112.0 (*c* 1.00, THF). HRMS (ESI–) calcd for $C_{57}H_{39}O_7P_2$ $[M–H]^-$ 897.2177, found 897.2169.



***tert*-Butyl (*R*)-((4-hydroxy-3-methylphenyl)(phenyl)methyl)carbamate (6n):** 46% yield, 52% ee. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.44 (s, 9H), 2.18 (s, 3H), 5.13 (br, 1H), 5.24 (br, 1H), 5.80 (br, 1H), 6.65 (m, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.96 (s, 1H), 7.21-7.27 (m, 3H), 7.30 (t, J = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 16.0, 28.5 (3C), 58.0, 80.0, 115.0, 124.3,

125.8, 127.1 (2C), 127.2, 128.6 (2C), 129.9, 133.7, 142.5, 153.5, 155.2. IR (neat) 3337, 2977, 1685, 1613, 1508, 1367, 1269, 1164, 1117 cm^{-1}. $[\alpha]_D^{27} = -13.6$ (*c* 1.00, $CHCl_3$, 48% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 4/1, 230 nm, 0.6 mL/min, t_R = 25.1 min (minor, *S*), 30.0 min (major, *R*). HRMS (FAB+) calcd for $C_{19}H_{23}NNaO_3$ $[M+Na]^+$ 336.1570, found 336.1566.

4. Refrences

1. (a) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691. (b) Trost, B. M.; Jonasson, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 2063. (c) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191.
2. Bronner, B. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 13966.
3. (a) Ishihara, K.; Sakakura, A. *Japan Patent* JP2012-160092 (2012). (b) Hatano, M.; Okamoto, H.; Kawakami, T.; Toh, K.; Nakatsuji, H.; Sakakura, A.; Ishihara, K. *Chem. Sci.* **2018**, *9*, 6361.
4. (a) Castagnolo, D.; Giorgi, G.; Spinosa, R.; Corelli, F.; Botta, M. *Eur. J. Org. Chem.* **2007**, 3676. (b) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128.

Research Achievement

Publications

(1) "Enantioselective Aza-Friedel–Crafts Reaction of Furan with α-Ketimino Esters Induced by a Conjugated Double Hydrogen Bond Network of Chiral Bis(phosphoric Acid) Catalysts"
Hatano, M.; Okamoto, H.; Kawakami, T.; Toh, K.; Nakatsuji, H.; Sakakura, A.; Ishihara, K.
Chem. Sci., **2018**, *9*, 6361.

(2) "Chiral Pyrophosphoric Acid Catalysts for the *para*-Selective and Enantioselective Aza-Friedel–Crafts Reaction of Phenols"
Okamoto, H.; Toh, K.; Mochizuki, T.; Nakatsuji, H.; Sakakura, A.; Hatano, M.; Ishihara, K.
Synthesis, **2018**, accepted.

Conference Presentation

Oral Presentation

(1) “1,1’-ビナフチルピロリン酸ジエステルの合成とキラル Brønsted 酸触媒への展開”
○岡本 遼, 仲辻 秀文, 坂倉 彰, 石原 一彰
日本化学会第 93 春季年会, 3E5-07, 立命館大学, 2013 年 3 月

(2) “高活性キラル二塩基酸触媒の開発：光学活性ピロリン酸ジエステルの合成”
○岡本 遼, 波多野 学, 石原 一彰
日本化学会第94春季年会, 1B6-16, 名古屋大学, 2014年3月

(3) “キラルビナフチル-2,2’-ビス(リン酸モノエステル)触媒を用いるイミノエステルとフェノールの位置及びエナンチオ選択的アザ-Friedel–Crafts 反応”
○岡本 遼, 波多野 学, 石原 一彰
日本化学会第95春季年会, 2E3-02, 日本大学, 2015年 3月

(4) “キラル C_2 対称ビナフチル-2,2’-(ビスリン酸エステル)触媒を用いるイミン類のエナンチオ選択的アザ-Friedel–Crafts 反応”
○岡本 遼, 波多野 学, 石原 一彰
日本化学会第 96 春季年会, 1H2-39, 同志社大学, 2016 年 3 月

(5) “キラル C_1 対称ビナフチル-2,2’-(ビスリン酸エステル)触媒を用いるα-ケチミノエステルとフランのエナンチオ選択的アザ-Friedel–Crafts 反応”
○川上 太郎, 岡本 遼, 波多野 学, 石原 一彰
日本化学会第96春季年会, 1H2-40, 同志社大学, 2016年3月

(6) “Enantioselective Aza-Friedel–Crafts Reaction with Imines Catalyzed by Chiral Bis(phosphoric acid)s and Chiral Pyrophosphoric Acids”
○岡本 遼, 波多野 学, 石原 一彰
日本化学会第 97 春季年会, 4E6-23, 慶應義塾大学, 2017 年 3 月

(7) “キラルビスリン酸触媒を用いるα-ケチミノエステルと 2-メトキシフランのエナンチオ選択的アザ-Friedel–Crafts 反応”
○川上 太郎, 岡本 遼, 波多野 学, 石原 一彰
日本化学会第 97 春季年会, 4E6-26, 慶應義塾大学, 2017 年 3 月

(8) “キラルビスリン酸触媒を用いるα-ケチミノエステルと 2-メトキシフランのエナンチオ選択的アザ-Friedel–Crafts 反応”
〇波多野 学, 岡本 遼, 川上 太郎, 石原 一彰
第10回有機触媒シンポジウム, 東北大学, 2017年11・12月

Poster Presentation

(1) “新規キラル BINOL ピロリン酸触媒の設計開発”
〇岡本 遼, 坂倉 彰, 石原 一彰
第 47 回有機反応若手の会 夏の学校 2012, P-28 岡山, 2012 年 8 月

(2) “1,1’-ビナフチルピロリン酸触媒の合成とキラルブレンステッド酸触媒への展開”
〇岡本 遼, 仲辻 秀文, 坂倉 彰, 波多野 学, 石原 一彰
第 48 回天然物談話会 夏の学校 2013, B-15 滋賀, 2013 年 7 月

(3) “Development of High Active Chiral Dibasic Catalysts: Synthesis of Optically Active Pyrophosphate Diesters”
〇岡本 遼, 仲辻 秀文, 波多野 学, 石原 一彰
IGER Annual meeting 2013, G-30, 名古屋大学, 2014 年 1 月, ポスター発表

(4) “キラルビナフチル-2,2’-ビス(リン酸モノエステル)触媒を用いるイミノエステルとフェノールの位置及びエナンチオ選択的アザ-Friedel–Crafts 反応”
〇岡本 遼, 波多野 学, 石原 一彰
第 49 回天然物化学談話会, P64, せとうち児島ホテル, 2014 年 7 月

(5) “光学活性ピロリン酸触媒を用いる高次選択的アザ-Friedel–Crafts 反応”
〇岡本 遼, 波多野 学, 石原 一彰
第 4 回企業と博士人材交流会, 名古屋大学, 2014 年 8 月

(6) “Development of High Active Chiral Dibasic Catalysts: Synthesis of Optically Active Pyrophosphate Diesters”
○岡本 遼, 波多野 学, 石原 一彰
IGER Annual meeting 2014, G-52, 名古屋大学, 2014 年 12 月

(7) “キラルピロリン酸触媒及びキラルビス(リン酸モノエステル)触媒を用いる高次選択的アザ-Friedel–Crafts 反応”
○岡本 遼, 波多野 学, 石原 一彰
第 5 回企業と博士人材交流会, 名古屋大学, 2015 年 9 月

(8) “キラルビス(リン酸モノエステル)触媒を用いるイミノエステルへの高エナンチオ選択的アザ-Friedel–Crafts 反応”
○岡本 遼, 波多野 学, 石原 一彰
第 46 回中部化学関係協会支部連合連秋季大会, 2P02, 三重大学, 2015 年 11 月

(9) “キラルビス(リン酸モノエステル)触媒を用いるイミノエステルへの高エナンチオ選択的アザ Friedel–Craftsh 反応”
○岡本 遼, 波多野 学, 石原 一彰
名古屋大学グリーン自然科学国際教育研究プログラム・分子科学研究所リトリート研修「分子研・知られざる有機合成の世界」, P11, 分子科学研究所, 2015 年 11 月

(10) “Enantioselective Aza-Friedel–Crafts Reaction of alpha-Ketimino Esters with Furan Catalyzed by Chiral Binaphthyl-2,2’-bis(phosphate)s”
○岡本 遼, 波多野 学, 石原 一彰
IGER Annual meeting 2015, G-16, 名古屋大学, 2016 年 1 月

(11) “キラルビナフチル-2,2’-ビス(リン酸エステル)触媒を用いるα-イミノエステルとフランのエナンチオ選択的アザ-Friedel－Crafts 反応”
○岡本 遼, 波多野 学, 石原 一彰
第 33 回有機合成化学セミナー, P12, ヒルトンニセコビレッジ(北海道), 2016 年 9 月

(12) “Enantioselective Aza-Friedel–Crafts Reaction of Furan with α-Ketimino Esters Catalyzed by Chiral Bis(phosphate)s”
○岡本 遼, 波多野 学, 石原 一彰
IGER Annual meeting 2016, G-23, 名古屋大学, 2017 年 1 月

(13) “キラルビスリン酸触媒を用いるケチミノエステルとフランのエナンチオ選択的アザ-Friedel–Crafts 反応”
〇川上 太郎, 岡本 遼, 波多野 学, 石原 一彰
日本化学会秋季事業第 7 回 CSJ 化学フェスタ, P9-028, タワーホール堀越, 2017 年 10 月

Award

(1) “キラルビス(リン酸モノエステル)触媒を用いるイミノエステルへの高エナンチオ選択的アザFriedel–Crafts反応”
平成27年　名古屋大学グリーン自然科学教育研究プログラム　国際教育研究　分子科学研究所リトリート研修「分子研知られざる有機合成の世界」, P11, 分子科学研究所(愛知), 2015年11月, ポスター発表, 査読有, 優秀ポスター発表賞受賞

(2) “キラルビス(リン酸モノエステル)触媒を用いるイミノエステルへの高エナンチオ選択的アザ-Friedel–Crafts反応”
第46 回中部化学関係学協会支部連合秋季大会, 2P02, 三重大学(三重), 2015年11月, ポスター発表, 査読有, ポスター優秀賞受賞

(3) “Enantioselective Aza-Friedel–Crafts Reaction of Furan with α-Ketimino Esters Catalyzed by Chiral Bis(phosphate)s”
IGER Annual meeting 2016, G-23, Nagoya University(Aichi), January 2017, Poster Award

Acknowledgements

I would like to express my grateful acknowledgments to my supervisors, Professor Kazuaki Ishihara, Professor Akira Sakakura (Okayama University), and Associate Professor Manabu Hatano, whose encouragements and helpful suggestions have been indispensable to the completion of the present thesis. The excitement with which they approach the synthesis and their dedication to the goal of producing good science always inspired me. Their teaching style in the laboratory and positive attitudes for the research study motivated me to be engaged in chemistry. It has been a privilege to work under tutelage of them.

I am indebted to Assistant Professors Muhammet Uyanik and Takahiro Horibe for their practical and fruitful discussions. I am also very grateful to Dr. Hidefumi Nakatsuji, Mr. Takuya Mochizuki, Mr. Taro Kawakami, and Mr. Kohei Toh as my helpful research colleagues. It is pleasant to express my appreciation to the former and present colleagues, especially Assistant Professors Atsuto Izumiseki (Institute for Molecular Science) and Takeshi Yasui (Nagoya University), Drs. Keisuke Nishikawa, Kazushi Hayashi, Lu Yao, Yoshiki Koshikari, Masayuki Sakuma, Tomokazu Tamaoki, Masahiro Hori, Hiroki Yamada, Niiha Sasakura, Daisuke Suzuki, Yasuhiro Sawamura, Yoshihiro Ogura, Hiroki Hayashi, Yuta Goto, Tatsuya Mutsuga, Kenji Yamashita, Katsuya Yamakawa, and Yanhui Lu. Ms. Risa Hirako, Mr. Takahiro Suzuki, Mr. Dai Nagata, Mr. Tatsuhiro Sakamoto, Ms. Mai Mizuno, Ms. Yurika Yoshida, Mr. Hideyuki Ishihara, Mr. Yuji Tabata, Mr. Kousuke Nishio are also acknowledged as my colleagues in Ishihara group. I also would like to express my gratitude to Ms. Atsuko Nakao and Ms. Michiko Yoshimura for their dedicated supports in administrative work.

I am very grateful to the Fellowships from the Nagoya University Program for Leading Graduate Schools “Integrative Graduate Education and Research in Green Natural Science”, MEXT.

I would like to express special thanks to Professors Takashi Ooi, Toshio Nishikawa, and Yoshihiko Yamamoto for serving on my discussion committee.

Finally, I would like to thank my friends and especially my parents for their true regard and unwavering supports throughout my Ph.D study.

August 2018

Haruka Okamoto