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

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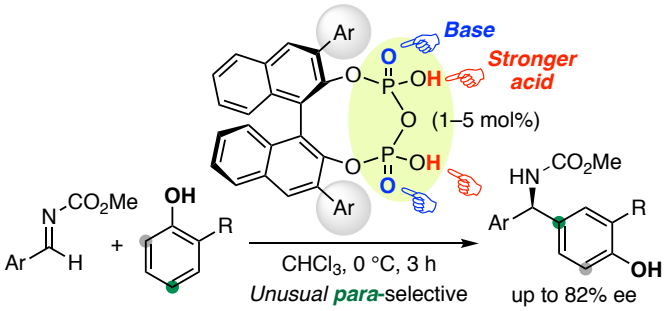

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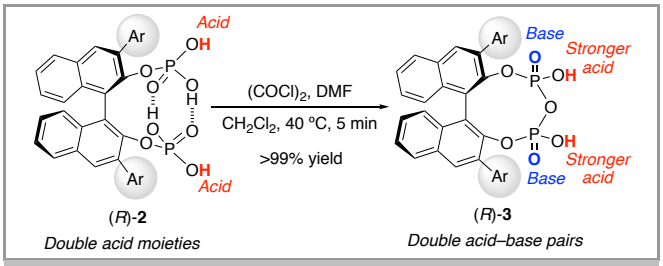
Abstract Chiral BINOL-derived pyrophosphoric acid catalysts were developed and used for the site- and enantioselective aza-Friedel–Crafts reaction of phenols with aldimines. *ortho/para*-Directing phenols could react at the *para*-position selectively with moderate to good enantioselectivities. Moreover,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

Key words Brønsted acid, phosphoric acid, pyrophosphoric acid, organocatalyst, aza-Friedel–Crafts reaction, phenol, site-selectivity

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**.

In this study, we developed a site- 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 site-selectivity of **5** (i.e., *para*- and *ortho*-control of **5** leading to **6** and

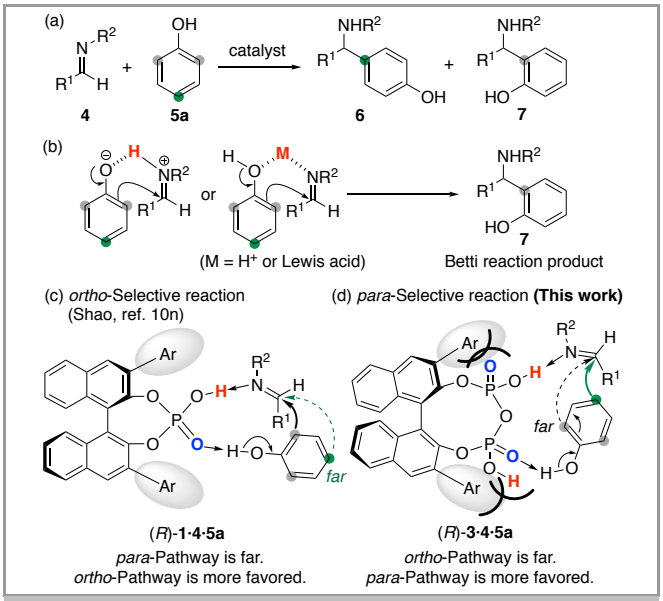
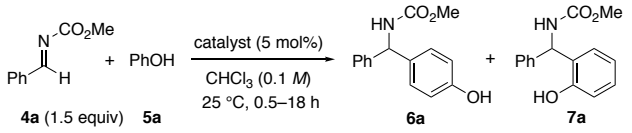


Figure 1 Strategy for the site- and enantioselective aza-Friedel–Crafts reaction of phenols with aldimines

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 site-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 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**.

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 (POH) but also a conjugate base function (P=O), did not give any byproducts, although the catalytic activity was moderate, and meaningful site-selectivity (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.

Table 1 Screening of Achiral Brønsted Acid Catalysts[a]

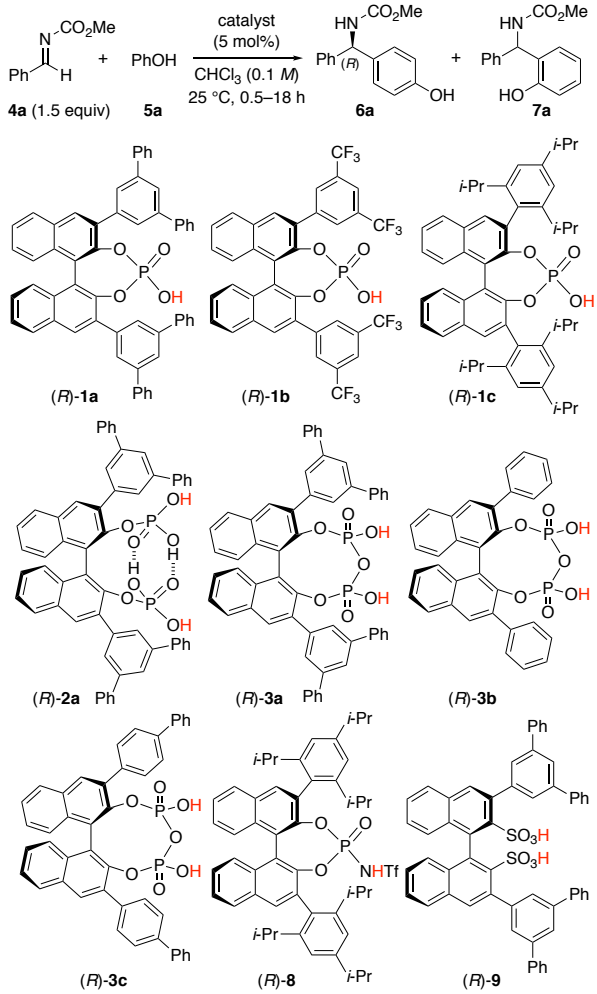


Entry	Catalyst	pK_a in H_2O	Reaction time (h)	Conversion (%) of **5a**	Yield (%) of **6a**	Yield (%) of **7a**
1	CH_3CO_2H	4.76	18	0	0	0
2	CH_2BrCO_2H	2.86	18	0	0	0
3	**$PhOP(=O)(OH)_2$**	1.42	18	**40**	**25**	**15**
4	CHF_2CO_2H	1.24	18	0	0	0
5	CCl_3CO_2H	0.65	18	16	2	14
6	**$(PhO)_2P(=O)OH$**	0.26	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.

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

Table 2 Screening of Chiral Brønsted Acid Catalysts[a]

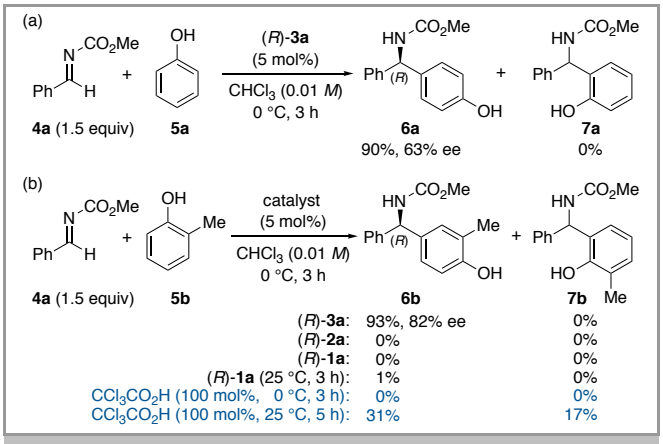


Entry	Catalyst	Reaction time (h)	Yield (%) of **6a**	ee (%) of **6a**	Yield (%) of **7a**	ee (%) of **7a**
1	(*R*)-**1a**	3	40	0	12	0
2	(*R*)-**1b**	3	16	4	7	7
3	(*R*)-**1c**	18	0	–	0	–
4	(*R*)-**2a**	3	15	23	10	0
5	(*R*)-**3a**	**0.5**	**82**	**52**	**1**	–
6	(*R*)-**3b**	0.5	41	4	0	–
7[b]	(*R*)-**3c**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

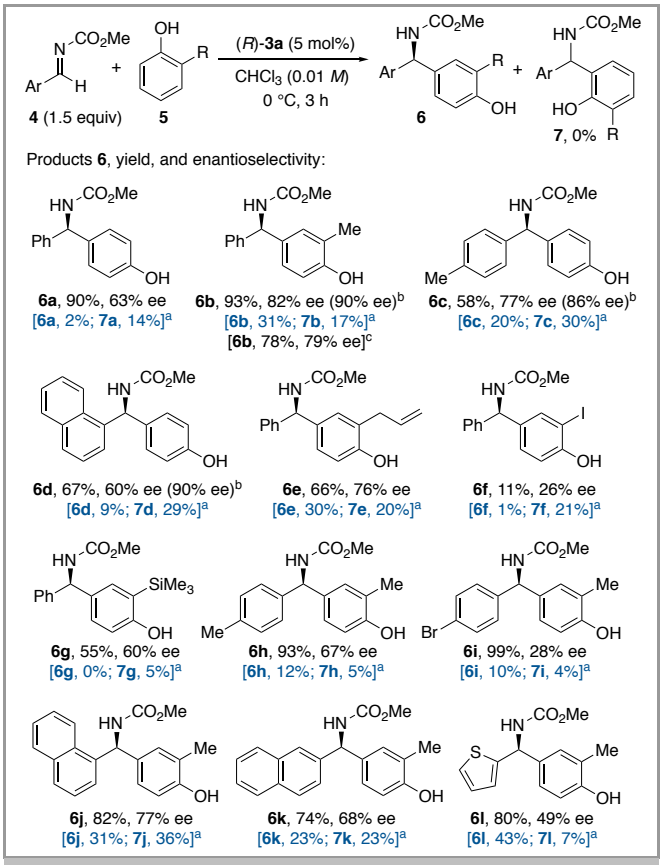
function, chiral pyrophosphoric acid (*R*)-**3a** dramatically facilitated the reaction, and **6a** was obtained in 82% yield with 52% ee within 30 min (entry 5). At that time, **7a** was provided in only 1% yield. The substituent effect at the 3,3'-positions of the binaphthyl backbone was important, 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]

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 site-selectivity 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**.

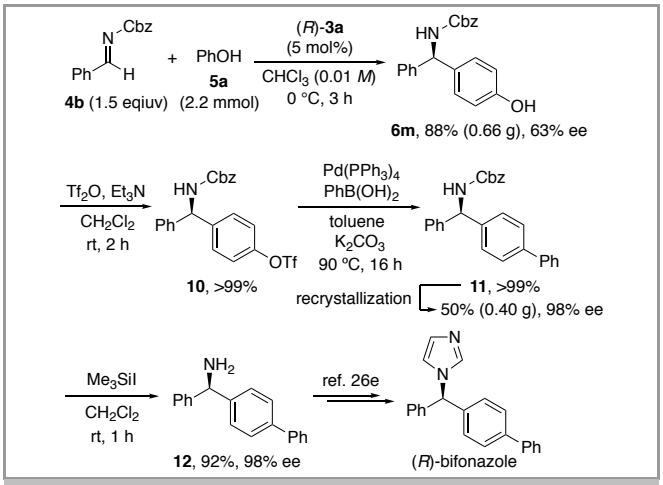
With the optimized reaction conditions in hand, we next examined the scope of phenols **5** with aldimines **4** (Scheme 3). As a result, not only phenyl-, but also *p*-tolyl- and 1-naphthylaldimines were used, and the corresponding *para*-adducts **6c** and **6d** were exclusively obtained with 77% ee and



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

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, 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]

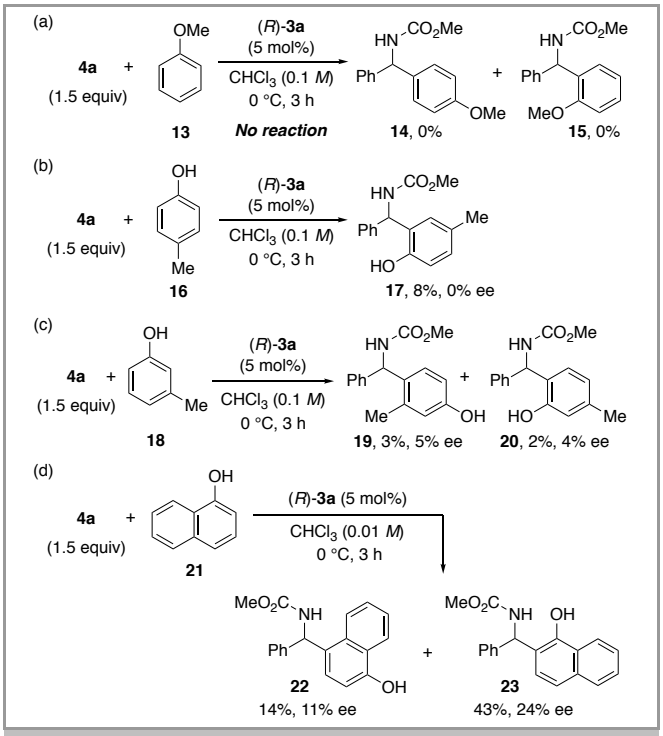
To demonstrate the synthetic utility of the present catalytic system, we performed a formal total synthesis of (*R*)-bifonazole,



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

which is a well-established antifungal agent for superficial mycoses (Scheme 4).[26,27] 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.

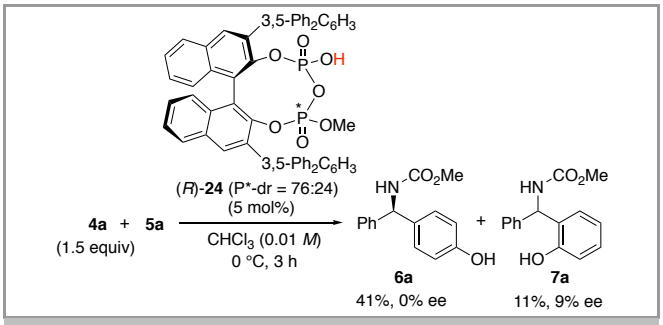
To consider the reaction mechanism, particularly the *para*-selectivity of phenols, we performed several control experiments. When anisole **13**, instead of non-substituted phenol **5a**, was used with **4a**, the reaction did not proceed (Scheme 5a). This result suggests that the deprotonation



Scheme 5 Control experiments with other phenols and naphthols.

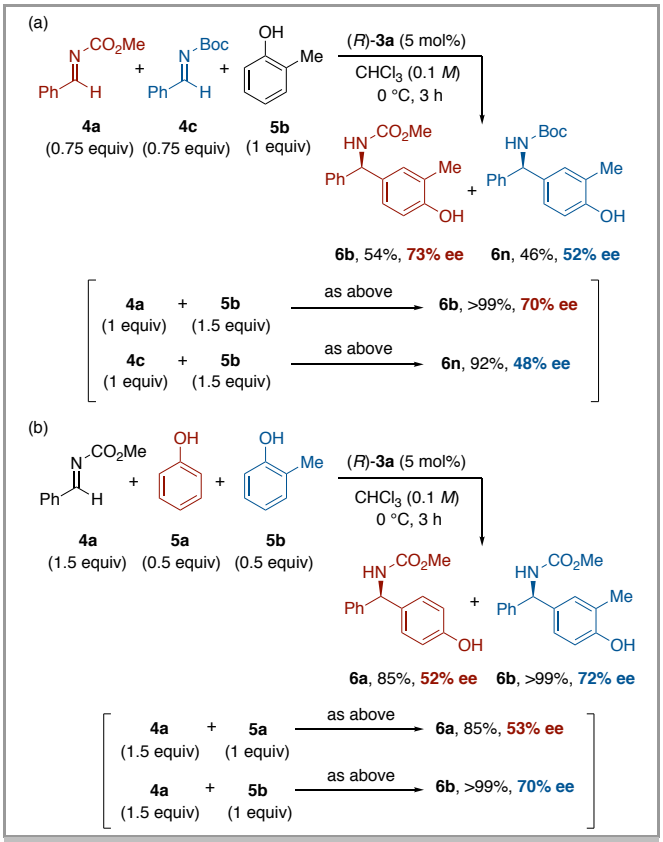
process of phenol might be necessary to promote the reaction. Moreover, when we used *p*-cresol **16**, the corresponding *ortho*-adduct **17** was obtained in only 8% yield with 0% ee (Scheme 5b). This result strongly suggests that site-selective *para*-activation might occur in our reaction system. 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 site-selectivity nor enantioselectivity was effectively induced. Therefore, the double P(=O)OH moieties in (*R*)-**3a** should be essential for successful activation of the aldimine and phenol.



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

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 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



Scheme 7 Control experiments with competitive substrates.

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

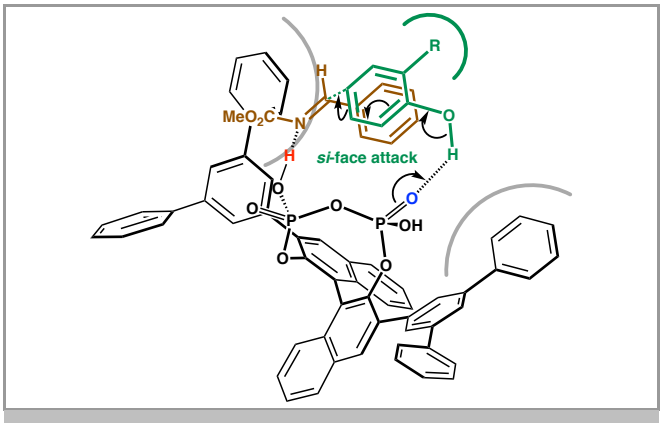


Figure 2 A possible transition state

of **4a** might be oriented inward. Thus, a site-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 site-selectivity and moderate to good enantioselectivities. 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.

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.

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^{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.[29] Phenols are commercially available, although 2-(trimethylsilyl)phenol was prepared from 2-bromophenol based on the literature procedure.[30]

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

To a solution of chiral bis(phosphoric acid) (*R*)-**2**[7] (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)

Pale yellow solid; Yield: 8.8 mg (99%).

IR (KBr) 3444, 2929, 1655, 1498, 1402, 1239, 1191, 1088, 1029 cm^{-1}.

^1H 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.

$[\alpha]_D^{23}$ = +60.0 (*c* 1.00, THF).

HRMS (ESI): *m/z* $[M–H]^-$ calcd for $C_{56}H_{37}O_7P_2$: 883.2009; found: 883.2008.

(*R*)-3,3'-Diphenyl-1,1'-binaphthyl-2,2'-pyrophosphoric acid ((*R*)-3b)

Pale yellow solid; Yield: 5.8 mg (99%).

IR (KBr) 3421, 3058, 1496, 1457, 1420, 1246, 1193, 993 cm^{-1}.

^1H 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.

$[\alpha]_D^{26}$ = +219.5 (*c* 1.00, THF).

HRMS (ESI): *m/z* $[M–H]^-$ calcd for $C_{32}H_{21}O_7P_2$: 579.0768; found: 579.0757.

(*R*)-3,3'-Di(4-biphenyl)-1,1'-binaphthyl-2,2'-pyrophosphoric acid ((*R*)-3c)

Pale yellow solid; Yield: 7.3 mg (99%).

IR (KBr) 3408, 3056, 2930, 1656, 1488, 1428, 1396, 1246, 1194, 1104, cm^{-1}.

^1H 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.

$[\alpha]_D^{30}$ = +112.0 (*c* 1.00, THF).

HRMS (ESI): *m/z* $[M–H]^-$ calcd for $C_{44}H_{29}O_7P_2$: 731.1383; found: 731.1380.

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)

Colorless oil; Yield: 46.4 mg (90%).

IR (neat) 3326, 1698, 1508, 1456, 1362, 1233, 1038 cm^{-1}.

^1H 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.

$[\alpha]_D^{27}$ = –16.0 (*c* 1.00, $CHCl_3$, 63% ee).

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{15}H_{15}NNaO_3$: 280.0950; found: 280.0944.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 210 nm, flow rate = 0.6 mL/min, t_R = 21.7 min (minor, *S*) and 25.9 min (major, *R*).

Methyl ((2-hydroxyphenyl)(phenyl)methyl)carbamate (7a)

Colorless oil; Yield: 7.7 mg (15%, Table 1, entry 3).

IR (neat) 3407, 1696, 1600, 1519, 1457, 1348, 1267, 1025 cm^{-1}.

^1H 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.

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{15}H_{15}NNaO_3$: 280.0950; found: 280.0942.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 210 nm, flow rate = 0.6 mL/min, t_R = 10.9 min and 60.5 min.

Methyl (*R*)-((4-hydroxy-3-methylphenyl)(phenyl)methyl)carbamate (6b)

Colorless solid; Yield: 50.5 mg (93%).

IR (KBr) 3394, 2924, 1699, 1509, 1267, 1118, 1039 cm^{-1}.

^1H 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.

$[\alpha]_D^{21}$ = –23.6 (*c* 1.00, $CHCl_3$, 82% ee).

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{16}H_{17}NNaO_3$: 294.1106; found: 294.1105.

M.p. 119-123 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 254 nm, flow rate = 0.6 mL/min, t_R = 17.8 min (minor, *S*) and 25.9 min (major, *R*).

Methyl ((2-hydroxy-3-methylphenyl)(phenyl)methyl)carbamate (7b)

Colorless oil; Yield: 9.5 mg (17%, Scheme 3b).

IR (neat) 3410, 1703, 1518, 1468, 1345, 1266, 1193, 1028 cm^{-1}.

^{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.

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{16}H_{17}NNaO_3$: 294.1106; found: 294.1108.

Methyl (*R*)-(4-hydroxyphenyl)(*p*-tolyl)methylcarbamate (6c)

Colorless solid; Yield: 31.8 mg (58%).

IR (KBr) 3361, 1664, 1542, 1512, 1439, 1266, 1039 cm^{-1}.

^{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.

$[\alpha]_D^{25}$ = –5.1 (*c* 0.87, $CHCl_3$, 77% ee).

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{16}H_{17}NNaO_3$: 294.1101; found: 294.1105.

M.p. 133-137 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALPAK IA-3, *n*-hexane/*i*-PrOH = 4/1, 210 nm, flow rate = 1.0 mL/min, t_R = 8.8 min (major, *R*) and 11.5 min (minor, *S*).

Methyl (*S*)-((4-hydroxyphenyl)(naphthalen-1-yl)methyl)carbamate (6d)

Colorless solid; Yield: 41.3 mg (67%).

IR (KBr) 3398, 3349, 1697, 1515, 1448, 1263, 1225, 1191, 1174, 1056 cm^{-1}.

^{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.

$[\alpha]_D^{26}$ = –26.8 (*c* 1.00, MeOH, 60% ee).

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{19}H_{17}NNaO_3$: 330.1101; found: 330.1093.

M.p. 208-222 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL ID-3, *n*-hexane/*i*-PrOH = 4/1, 284 nm, flow rate = 0.5 mL/min, t_R = 24.4 min (major, *S*) and 29.3 min (minor, *R*).

Methyl (*R*)-((3-allyl-4-hydroxyphenyl)(phenyl)methyl)carbamate (6e)

Colorless oil; Yield: 39.2 mg (66%).

IR (neat) 3326, 2923, 2855, 1698, 1267 cm^{-1}.

^{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.

$[\alpha]_D^{27}$ = –29.9 (*c* 1.00, $CHCl_3$, 76% ee).

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{18}H_{19}NNaO_3$: 320.12657; found: 320.1257.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 230 nm, flow rate = 0.6 mL/min, t_R = 13.3 min (minor, *S*) and 23.8 min (major, *R*).

Methyl (*R*)-((4-hydroxy-3-iodophenyl)(phenyl)methyl)carbamate (6f)

Colorless oil; Yield: 8.5 mg (11%).

IR (neat) 3305, 2919, 1691, 1268, 1225, 1040 cm^{-1}.

^{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.

$[\alpha]_D^{25}$ = –10.3 (*c* 1.00, $CHCl_3$, 26% ee).

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{15}H_{14}INNaO_3$: 405.9916; found: 405.9906.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 210 nm, flow rate = 0.6 mL/min, t_R = 16.9 min (minor, *S*) and 46.8 min (major, *R*).

Methyl (*R*)-((4-hydroxy-3-(trimethylsilyl)phenyl)(phenyl)methyl)carbamate (6g)

Colorless oil; Yield: 36.2 mg (55%).

IR (neat) 3335, 2953, 1699, 1508, 1405, 1243, 1074 cm^{-1}.

^{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.

$[\alpha]_D^{25}$ = –22.8 (*c* 1.00, $CHCl_3$, 60% ee).

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{18}H_{23}NNaO_3Si$: 352.1345; found: 352.1335.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 210 nm, flow rate = 0.6 mL/min, t_R = 7.5 min (minor, *S*) and 10.0 min (major, *R*).

Methyl (*R*)-((4-hydroxy-3-methylphenyl)(*p*-tolyl)methyl)carbamate (6h)

Colorless oil; Yield: 53.0 mg (93%).

IR (neat) 3334, 2921, 1697, 1511, 1268, 1117, 1039 cm^{-1}.

^{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.

$[\alpha]_D^{27}$ = –8.0 (*c* 1.00, $CHCl_3$, 67% ee).

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{17}H_{19}NNaO_3$: 308.1257; found: 308.1261.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 280 nm, flow rate = 0.6 mL/min, t_R = 16.3 min (major, *R*) and 19.8 min (minor, *S*).

Methyl (*R*)-((4-bromophenyl)(4-hydroxy-3-methylphenyl)methyl)carbamate (6i)

Colorless oil; Yield: 70.0 mg (99%).

IR (neat) 3327, 2922, 1697, 1511, 1266, 1118, 1071, 1039, 1011 cm^{-1}.

^1H 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.

$[\alpha]_D^{23}$ = –2.8 (*c* 1.00, $CHCl_3$, 28% ee).

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{16}H_{16}BrNNaO_3$: 372.0206; found: 372.0197.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALPAK AS-3, *n*-hexane/*i*-PrOH = 3/1, 230 nm, flow rate = 1.0 mL/min, t_R = 9.8 min (minor, *S*) and 11.0 min (major, *R*).

Methyl (*S*)-((4-hydroxy-3-methylphenyl)(naphthalen-1-yl)methyl)carbamate (6j)

Colorless oil; Yield: 52.7 mg (82%).

IR (neat) 3335, 2975, 1698, 1508, 1260, 1118 cm^{-1}.

^1H 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.

$[\alpha]_D^{26}$ = –7.6 (*c* 1.00, $CHCl_3$, 77% ee).

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{19}NNaO_3$: 344.1263; found: 344.1263.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 230 nm, flow rate = 0.6 mL/min, t_R = 21.7 min (minor, *R*) and 32.0 min (major, *S*).

Methyl (*R*)-((4-hydroxy-3-methylphenyl)(naphthalen-2-yl)methyl)carbamate (6k)

Colorless oil; Yield: 47.7 mg (74%).

IR (neat) 3330, 1696, 1508, 1265, 1114, 1040 cm^{-1}.

^1H 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.

$[\alpha]_D^{25}$ = –28.6 (*c* 1.00, $CHCl_3$, 68% ee).

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{19}NNaO_3$: 344.1263; found: 344.1257.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 254 nm, flow rate = 0.6 mL/min, t_R = 20.2 min (major, *R*) and 29.3 min (minor, *S*).

Methyl (*S*)-((4-hydroxy-3-methylphenyl)(thiophen-2-yl)methyl)carbamate (6l)

Colorless solid; Yield: 44.5 mg (80%).

IR (KBr) 3398, 2918, 1509, 1256, 1118, 1044 cm^{-1}.

^1H 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.

$[\alpha]_D^{25}$ = –9.6 (*c* 1.00, $CHCl_3$, 49% ee).

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{14}H_{15}NNaO_3S$: 300.0670; found: 300.0666.

M.p. 42-45 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 230 nm, flow rate = 0.6 mL/min, t_R = 15.4 min (minor, *R*) and 18.6 min (major, *S*).

Large scale synthesis of benzyl (*R*)-((4-hydroxyphenyl)(phenyl)methyl)carbamate (6m) (Scheme 4)

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; Yield: 663 mg (88%).

IR (neat) 3321, 1696, 1661, 1517, 1356, 1297, 1265, 1237, 1041 cm^{-1}.

^1H 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.

$[\alpha]_D^{27}$ = –13.6 (*c* 1.00, $CHCl_3$, 63% ee).

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{19}NNaO_3$: 356.1263; found: 356.1261.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALPAK IC-3, *n*-hexane/*i*-PrOH = 85/15, 230 nm, flow rate = 1.0 mL/min, t_R = 14.1 min (minor, *S*), 20.9 min (major, *R*).

(*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; Yield: 930 mg (>99%).

IR (KBr) 3315, 3033, 1696, 1499, 1424, 1140, 1040 cm^{-1}.

^1H 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-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.

$[\alpha]_D^{26}$ = +18.4 (*c* 1.00, $CHCl_3$, 62% ee).

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{22}H_{18}F_3NNaO_5S$: 488.0755; found: 488.0755.

M.p. 112-114 °C.

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; Yield: 783 mg (>99%).

IR (KBr) 3322, 3031, 1686, 1519, 1489, 1231, 1134, 1040 cm^{-1}.

^1H 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.

$[\alpha]_D^{25}$ = –5.7 (*c* 1.00, $CHCl_3$, 98% ee).

HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{23}NNaO_2$: 416.1626; found: 416.1626.

M.p. 109-116 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALPAK AD-H, *n*-hexane/*i*-PrOH = 4/1, 280 nm, flow rate = 1.0 mL/min, t_R = 12.9 min (minor, *S*) and 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, ^1H NMR, ^{13}C NMR, and HRMS data were consistent with previously reported values.[31]

Colorless solid; Yield: 33.4 mg (92%).

IR (KBr) 3378, 3027, 2922, 2850, 1598, 1487, 1448, 1417, 1213, 1147 cm^{-1}.

^1H 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.

$[\alpha]_D^{26}$ = +19.6 (*c* 1.00, $CHCl_3$, 98% ee) [lit.[31b] $[\alpha]_D^{22}$ = +8.9 (*c* 2.45, $CHCl_3$, 66% ee)].

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{19}H_{17}N$: 259.1361; found: 259.1369.

M.p. 69-74 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH/Et_2NH = 10/1/0.1, 254 nm, flow rate = 1.0 mL/min, t_R = 35.0 min (major, *R*) and 40.1 min (minor, *S*) [lit.[31b] HPLC analysis (66% ee): Daicel CHIRALCEL 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*) and 28.2 min (minor, *S*)].

Methyl ((2-hydroxy-5-methylphenyl)(phenyl)methyl)carbamate (17)

Colorless solid; Yield: 4.5 mg (8%).

IR (KBr) 3421, 3322, 2958, 1689, 1509, 1450, 1334, 1274, 1238, 1121, 1038 cm^{-1}.

^1H 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.

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{16}H_{17}NNaO_3$: 294.1101; found: 294.1091.

M.p. 148-152 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-3, *n*-hexane/*i*-PrOH = 9/1, 230 nm, flow rate = 1.0 mL/min, t_R = 12.2 min and 17.4 min.

Methyl ((4-hydroxy-2-methylphenyl)(phenyl)methyl)carbamate (19)

Colorless oil; Yield: 1.6 mg (3%).

IR (neat) 3332, 2923, 1695, 1610, 1504, 1453, 1358, 1232, 1097, 1027 cm^{-1}.

^1H 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, = 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.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{16}H_{17}NNaO_3$: 294.1101; found: 294.1100.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALPAK IC-3, *n*-hexane/*i*-PrOH = 85/15, 210 nm, flow rate = 0.4 mL/min, t_R = 33.8 min (minor) and 37.4 min (major).

Methyl ((2-hydroxy-4-methylphenyl)(phenyl)methyl)carbamate (20)

Colorless oil; Yield: 1.2 mg (2%).

IR (neat) 3319, 1694, 1618, 1516, 1452, 1421, 1347, 1291, 1232, 1120, 1028 cm^{-1}.

^1H 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.

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{16}H_{17}NNaO_3$: 294.1106; found: 294.1116.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALPAK IC-3, *n*-hexane/*i*-PrOH = 4/1, 230 nm, flow rate = 0.4 mL/min, t_R = 18.5 min (major), 23.8 min (minor).

Methyl ((4-hydroxynaphthalen-1-yl)(phenyl)methyl)carbamate (22)

Colorless solid; Yield: 8.7 mg (14%).

IR (KBr) 3335, 2946, 1699, 1528, 1391, 1339, 1274, 1237, 1053 cm^{-1}.

^{1}H 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

$[\alpha]_D^{25}$ = +5.9 (*c* 0,54, $CHCl_3$, 11% ee).

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{19}H_{17}NNaO_{3+}$: 330.1101; found: 330.1100.

M.p. 212-222 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALPAK IC-3, *n*-hexane/*i*-PrOH = 9/1, 240 nm, flow rate = 1.0 mL/min, t_R = 23.1 min (minor), 35.4 min (major).

Methyl (*R*)-((1-hydroxynaphthalen-2-yl)(phenyl)methyl)carbamate (23)

Colorless solid; Yield: 26.6 mg (43%).

IR (KBr) 3313, 3058, 1695, 1511, 1356, 1244, 1189, 1081 cm^{-1}.

^{1}H 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.

$[\alpha]_D^{25}$ = –23.3 (*c* 0,98, $CHCl_3$, 24% ee).

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{19}H_{17}NNaO_{3+}$: 330.1101; found: 330.1107.

M.p. 115-122 °C.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALPAK IC-3, *n*-hexane/*i*-PrOH = 9/1, 230 nm, flow rate = 1.0 mL/min, t_R = 12.8 min (major) and 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).[7] (*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; Yield: 9.0 mg (99%).

IR (KBr) 3408, 3056, 2930, 1656, 1488, 1428, 1396, 1246, 1194, 1104, cm^{-1}.

^{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).

$[\alpha]_D^{30}$ = +112.0 (*c* 1.00, THF).

HRMS (ESI): *m/z* [M–H]$^-$ calcd for $C_{57}H_{39}O_7P_2$: 897.2177; found: 897.2169.

***tert*-Butyl (*R*)-((4-hydroxy-3-methylphenyl)(phenyl)methyl)carbamate (6n)**

Colorless oil; Yield: 57.6 mg (92%).

IR (neat) 3337, 2977, 1685, 1613, 1508, 1367, 1269, 1164, 1117 cm^{-1}.

^{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.

$[\alpha]_D^{27}$ = –13.6 (*c* 1.00, $CHCl_3$, 48% ee).

HRMS (FAB): *m/z* [M+Na]$^+$ calcd for $C_{19}H_{23}NNaO_3$: 336.1570; found: 336.1566.

The enantiomeric purity of the product was determined by HPLC analysis: Daicel CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 4/1, 230 nm, flow rate = 0.6 mL/min, t_R = 25.1 min (minor, *S*) and 30.0 min (major, *R*).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-xxxxxxx.

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(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.

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(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 Supporting Information 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.

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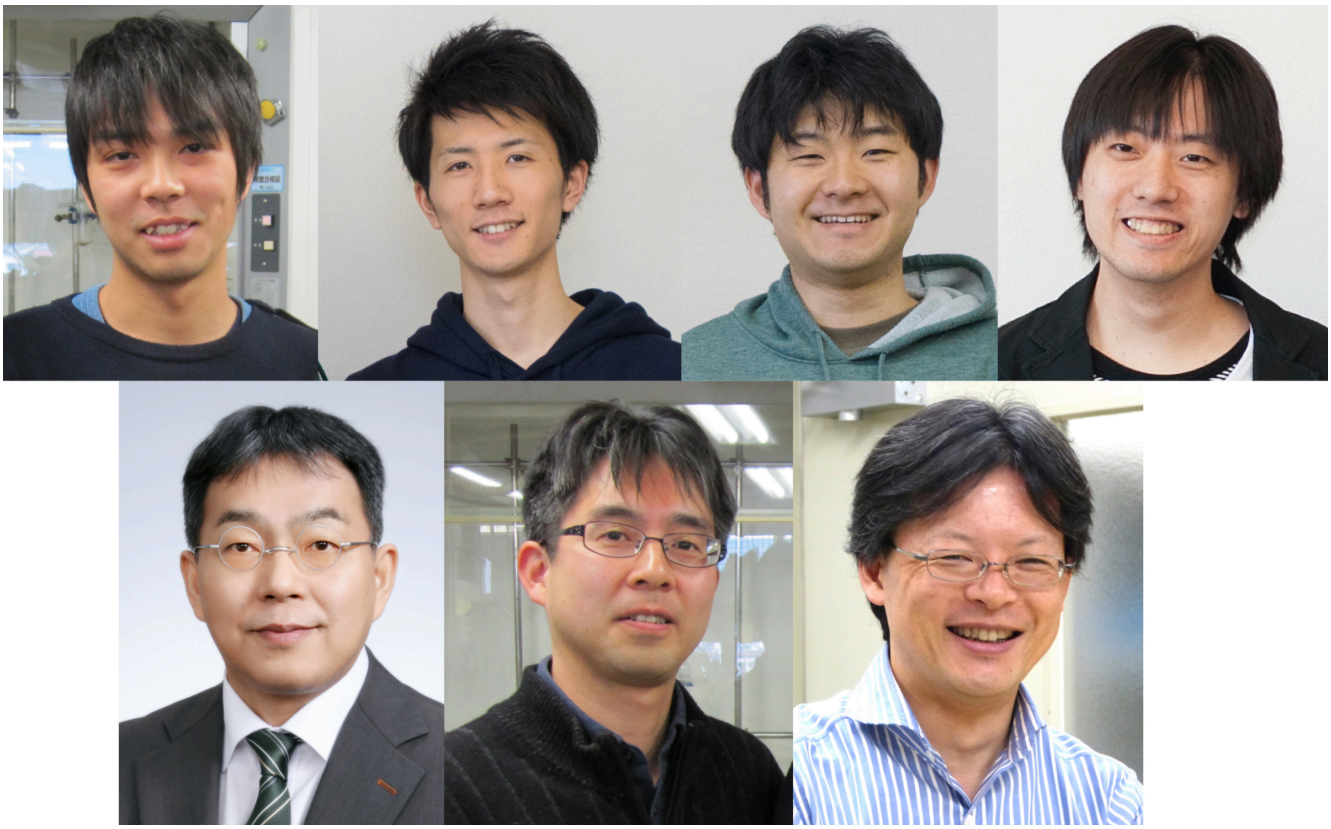

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Biosketches

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