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# Planar Chiral Phosphoric Acids with Biphenylene-Tethered Paracyclophane Scaffolds: Synthesis, Characterization, and Catalytic Screening

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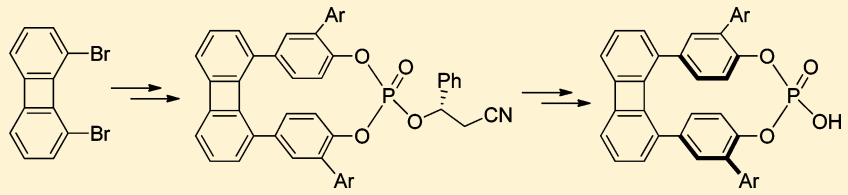
Supporting Information

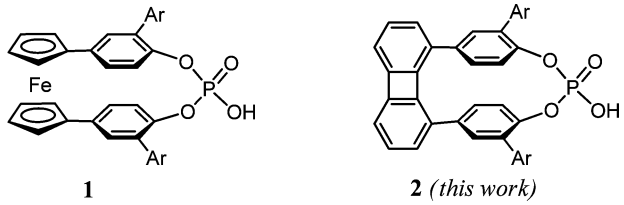



**ABSTRACT:** Phosphoric acids with planar chiral paracyclophane scaffolds have been prepared in optically pure form starting from 1,8-dibromobiphenylene, by means of a chiral phosphorodiamidate as the phosphorylating agent. Structural characterization and configurational assignment have been performed by X-ray diffraction studies. The acids promote the organocatalytic enantioselective H-transfer reduction of $\alpha$-arylquinolines with up to 90% enantiomeric excess.

## INTRODUCTION

The widespread uses of phosphoric acids and phosphates as chiral acids,[1] chiral anions, and ligands[2] are among the major achievements of modern enantioselective catalysis. In this field, the atropochiral Binol-derived phosphoric acids are privileged auxiliaries, but alternative scaffolds have also been developed, including Spinol[3] and Taddol[4] derivatives, which display axially chiral structures and stereogenic carbons, respectively.[5] The above series of chiral phosphoric acids might be suitably complemented by analogous derivatives exploiting planar chiral scaffolds. In this context, having noticed that only a single example of planar chiral phosphoric acids had been reported,[6] we have initiated a research project oriented toward the development of phosphoric acids of this class. In our previous papers[7] we have disclosed the first series of planar chiral phosphoric acids, represented hereafter by the general formula **1** (Figure 1).

These are paracyclophanes with 1,1′-ferrocenediyl and O−P−O units tethering the aromatic rings in their para positions. Two aryl substituents (Ar) generate the desired planar chirality while giving a formally $C_2$-symmetric scaffold. The 1,1′-ferrocenediyl unit had been targeted initially as a suitable linker, on the basis of DFT studies showing that it will give moderate ring strain, combined with satisfying configurational stability of the paracyclophane. Acids **1** proved to be good catalysts for the enantioselective H-transfer reduction of 2-substituted quinolines (ee values up to 92%). However, they displayed only moderate thermal stability, giving an estimated 10% decomposition rate after 18 h of heating at 60 °C. Their uses will be therefore reasonably restricted to catalytic reactions taking place at room temperature or lower. To hopefully overcome this limitation, we have turned our attention to analogous paracyclophane-type derivatives bearing different tethering chains. This paper reports on our studies oriented toward this goal and especially toward the use of a biphenylene-1,8-diyl unit as the tethering chain, as typified by compound **2** in Figure 1.




**1** **2** *(this work)*

**Figure 1.** Planar chiral phosphoric acids based on paracyclophane scaffolds.

## RESULTS AND DISCUSSION

In this work, with the aim of accessing new phosphoric acids with paracyclophane structures, we have envisioned the biphenylene-1,8-diyl unit as a possible paracyclophane tethering chain. In comparison to the previously used 1,1′-ferrocenediyl motif of **1**, the four-atom biphenylene tether is anticipated to give slightly longer C−C distances between the aromatic rings of the paracyclophane: *a* and *b* distances have been calculated indeed

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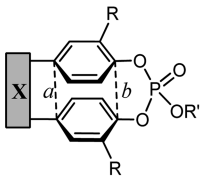
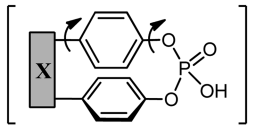



**1':** X = ferrocene-1,1'-diyl
R = H, R' = H
**1a:** X = ferrocene-1,1'-diyl
R = 4-Ph-$C_6H_4$,
R' = $OCH(Ph)CH_2CN$
**1b**: X = ferrocene-1,1'-diyl
R = Ph, R' = OCa
**2'**: X = biphenylene-1,8-diyl
R = H, R' = H

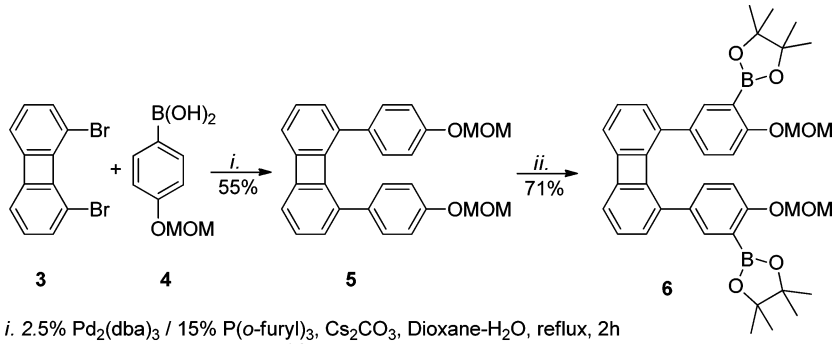
Rotation process for which $\Delta G^{\neq}$ values have been calculated:




| | *a* (Å) | *b* (Å) | $\Delta G^{\neq}$ |
|---|---|---|---|
| **Ferrocene-1,1'-diyl derived paracyclophanes, 1** | | | |
| Calculated values for **1'** | 3.51 | 3.09 | 216 kJ/mol |
| Experimental values for **1a**[7b] | 3.495 | 3.099 | |
| Experimental values for **1b**[7b] | 3.404 | 3.022 | |
| | | | |
| **Biphenylene-1,8-diyl derived paracyclophanes, 2** | | | |
| Calculated values for **2'** | 3.76 | 3.13 | 180 kJ/mol |

**Figure 2.** Calculated/experimental structural parameters and rotation barriers for paracyclophane-type phosphoric acids **1** and **2**.

**Scheme 1. Synthesis of the Bis-Boronate 6**




*i.* 2.5% $Pd_2(dba)_3$ / 15% P(*o*-furyl)$_3$, $Cs_2CO_3$, Dioxane-$H_2O$, reflux, 2h
*ii.* a) *n*-BuLi (6 equiv.), THF, -78°C to rt, 4h;
b) 2-(*i*PrO)-tetramethyl-1,3,2-dioxaborolane, -78°C to rt, 16h

at 3.76 and 3.13 Å, respectively, for **2**′ vs 3.51 and 3.09 Å for **1**′, at the M06/6-31G(d,p) DFT level (Figure 2). However, the ring strain energy has been calculated[8] to be slightly higher for **2**′ with respect to **1**′ (24 kJ/mol vs 17 kJ/mol), which is likely related to the rigidity of the biphenylene structure, in comparison to the flexible ferrocene scaffold. The activation energy required for the rotation of one of the two aromatic rings around the C- - -O axis ($\Delta G^{\ddagger}$ in Figure 2) has been calculated at 180 kJ/mol for **2**′: i.e., slightly lower than for the ferrocenic derivative **1**′ (216 kJ/mol) but still high enough to likely ensure the configurational stability of the molecule.

On the basis of these rather encouraging calculation results, we have investigated synthetic approaches to acids **2**. To this end, we have adopted the strategy previously used for the synthesis of **1**, which made use of two sequential Suzuki couplings to create both the ferrocene−aryl and the aryl−aryl bonds.[7b] On application to the synthesis of **2**, the method involves 1,8-dibromobiphenylene **3** as the starting material and the two Suzuki coupling steps shown in Schemes 1 and 2. The bis-boronate **6**, diol **8**, and chiral phosphates **10** in Scheme 3 are the key intermediates.

The synthetic procedure starts with a Suzuki coupling between 1,8-dibromobiphenylene (**3**)[9] and the arylboronic acid **4**,[10] which features a MOM-protected hydroxyl function in its para position. The reaction was carried out in a dioxane−water mixture, in the presence of a 2.5 mol % amount of $Pd_2(dba)_3$ and 15 mol % of tris(*o*-furyl)phosphine. The desired product **5** has been isolated in 55% yield on a 17 g scale. Other catalysts and conditions previously reported for the double arylation of **3** (e.g., $Pd(PPh_3)_4$)[11] did not afford improved yields.

Compound **5** has been converted into the corresponding bis-boronate **6** by a metalation−borylation reaction[12] taking advantage of the ortho-directing effect of the O-MOM functions: the addition of excess *n*-BuLi to **5** in THF afforded the dilithiated derivative, which was trapped with isopropyl pinacolborate. The bis-boronate **6** has been isolated in 71% yield on a 19 g scale. It should represent a useful platform for the introduction of various substituents to the aryl rings by coupling reactions. This was demonstrated by the synthesis of the highly hindered *m*-terphenyl-substituted diol **8** by palladium-catalyzed Suzuki coupling, under $Pd(PPh_3)_4$ catalysis (Scheme 2).

After in situ removal of the MOM protecting groups from the intermediate coupling product, the desired diol **8** was isolated in 69% yield. The $^1H$ and $^{13}C$ NMR spectra of **8** show single sets of signals that reveal unhindered rotation of the aryl substituents of the biphenylene unit.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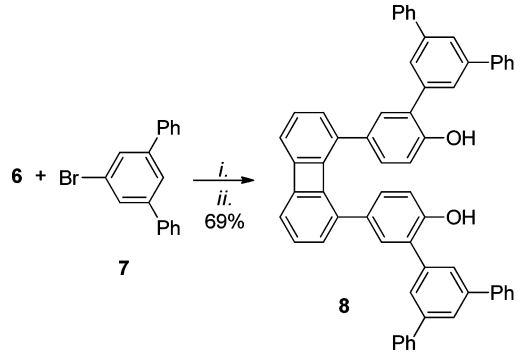
**Scheme 2. Synthesis of Diol 8**




The synthesis of the desired phosphoric acid in optically pure form was then carried out by reacting diol **8** with the chiral phosphinating agent (*S*)-**9**, according to our recently established procedure[7b,13] (Scheme 3). The cyclization reaction of diol **8** with phosphorodiamidite **9** in the presence of 1*H*-tetrazole, followed by oxidation of the resulting phosphites with *tert*-butyl hydroperoxide, afforded a 7:3 mixture of the corresponding cyclic phosphates **10a**,**b**. In principle, the cyclization reaction could also afford a third isomer with a nonchiral configuration of the paracyclophane scaffold, in which the two aryl substituents are located on the same face of the paracyclophane. This isomer was not detected in the reaction mixture. The mixture of phosphates **10a**,**b** was obtained in a high 86% yield over two steps. The cyclization step takes place here in much better yield than the analogous cyclization leading to the ferrocenic acids **1** (86% vs 40%). This is undoubtedly related to the rigid biphenylene unit, which forces the aromatic rings of **8** in a suitable, almost parallel arrangement.

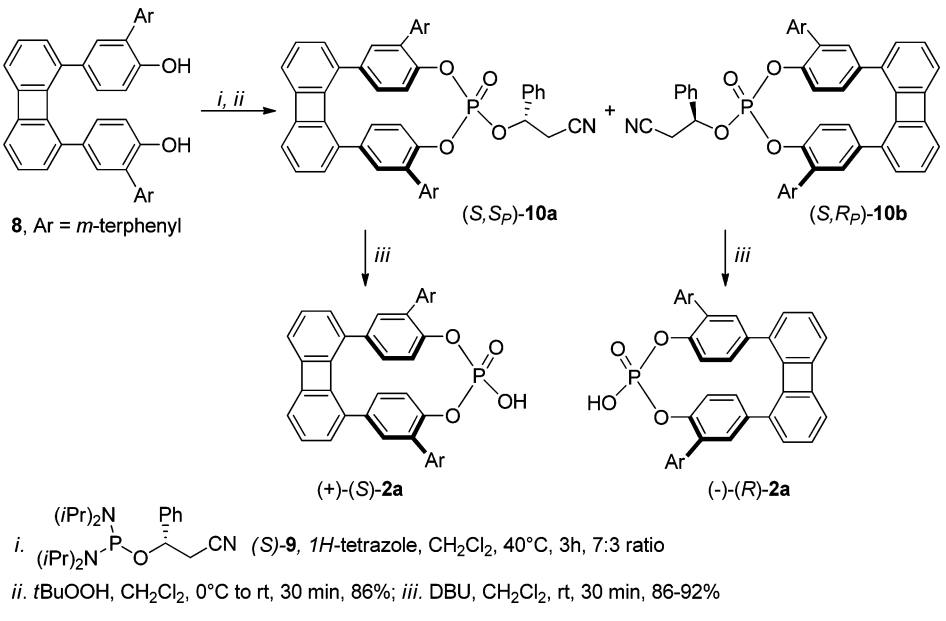
The two epimers of **10** could be separated easily by semipreparative HPLC (NW50 silica gel column, heptane/toluene/THF 4/95/1, retention times 10.0 min for ($S$,$S_P$)-**10a** ($[\alpha]_D$ = +68° ($c$ = 1, $CHCl_3$)) and 13.0 min for ($S$,$R_P$)-**10b** ($[\alpha]_D$ = −123° ($c$ = 1, $CHCl_3$)) and fully characterized. Thus, although the chiral auxiliary (*S*)-**9** induced only a moderate diastereoselectivity in this cyclization reaction, HPLC separation of the epimers afforded synthetically useful amounts of the pure compounds **10a**,**b**.

The configuration of the epimeric paracyclophanes has been assigned from the X-ray crystal structure of **10a**, shown in Figure 3 (CCDC 1014151). This epimer displays an $S_P$ configuration (relative configuration with respect to the known *S* configuration of the chiral auxiliary).[14] The structural parameters of ($S$,$S_P$)-**10a** from X-ray data are in good agreement with the calculated parameters in Figure 2. Notably, the key nonbonding *a* and *b* distances, which define the paracyclophane geometry and modulate the ring strain, have been measured at 3.794 and 3.197 Å, respectively, vs 3.76 and 3.13 Å for calculated values. With respect to the analogous ferrocene-tethered paracyclophane **1a**, the larger macrocyclic ring of **10a** generates a slightly larger O−P−O intracyclic bond angle (106.89° for **10a** vs 105.76° for phosphate **1a**[7b]), while the P−O distances measure about 1.60 Å in both series.

X-ray data highlight significantly different geometrical features for the ferrocene-based paracyclophane **1a** and the biphenylene analogue **10a**, with respect to their three-dimensional structures, in the solid state at least. Indeed, in the phosphate ($S$,$S_P$)-**10a** the dihedral angle between the parallel aryl planes and the biphenylene-tether plane measures 53.8°, while in the ferrocene-based paracyclophane **1a** the parallel aryl planes are almost orthogonal to the median plane of the ferrocene tether (83.03° dihedral angle). The observed differences in the geometrical features are anticipated to cause slightly different catalytic behaviors for the two series of paracyclophanic acids, **1** and **2**.

As shown in Scheme 3, phosphates ($S$,$S_P$)-**10a** and ($S$,$R_P$)-**10b** have been converted into the desired phosphoric acids (+)-(*S*)-**2a** ($[\alpha]_D$ = +90° ($c$ = 0.5, $CHCl_3$)) and (−)-(*R*)-**2a**, respectively, by removal of the 1-phenyl-2-cyanoethyl substituent in the presence of DBU and subsequent washing of the resulting DBU-phosphate with an 6 N HCl solution. The acids have been obtained in 86−92% yields on a 1−2 g scale, as colorless solids. The enantiomeric purity of these acids has been established by

**Scheme 3. Synthesis of the Planar Chiral Phosphoric Acids (+)-2a and (−)-2a**





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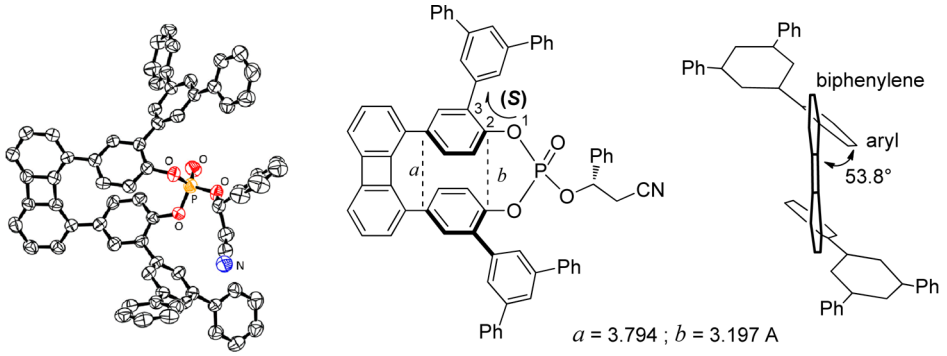
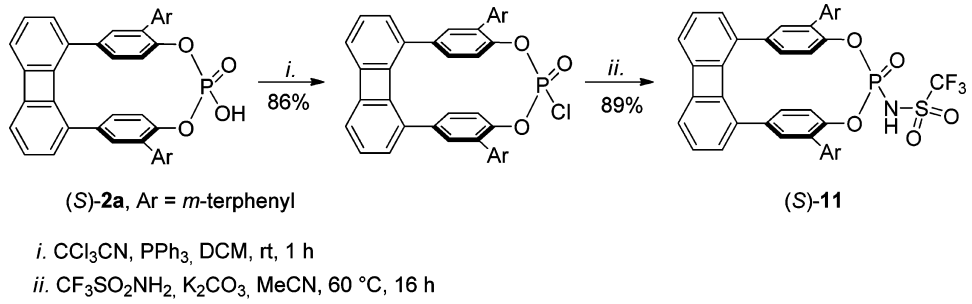



**Figure 3.** X-ray crystal structure of ($S$,$S_P$)-**10a**, stereochemical descriptor, and key geometrical features.

**Scheme 4. Synthesis of the Chiral *N*-Triflyl Phosphoramide (*S*)-11**



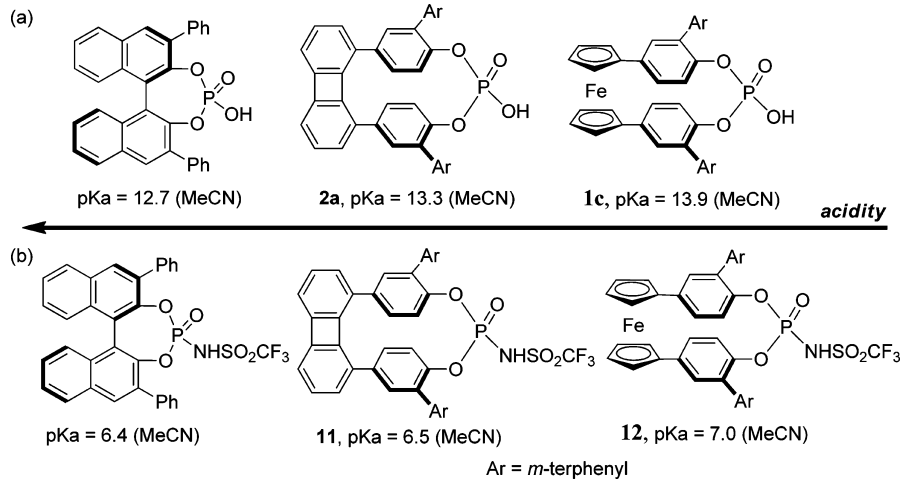




**Figure 4.** (a) p$K_a$ values for (a) the phosphoric acids **2a** and **1c** and a representative binol-derived acid[15] and (b) the corresponding sulfonimides.

HPLC on an ID column with heptane/THF/TFA/$Et_3N$ (40/60/0.5/0.3) as the eluent: retention times 3.9 and 5.9 min (ee >98%).

In order to ascertain the configurational stability of the biphenylene-based [4.3]-paracyclophane scaffold of **2a**, we have heated a sample of acid (*S*)-**2a** (>98% ee) at 110 °C in toluene. Chiral HPLC analysis did not show any epimerization after heating for 16 h. The sample did not show significant decomposition either, so that the experiment also demonstrates that acid **2a** is chemically more stable than the ferrocene-based acids **1**, which start to decompose at about 60 °C.[7b] Thus, the biphenylene-based acid **2a** has the potential of overcoming the limitations of the ferrocene-based acids in terms of thermal stability, while overall retaining the same key structural features related to planar chirality.

The range of biphenylene derived acids has been expanded through the synthesis of the corresponding *N*-triflyl phosphoramide (*S*)-**11** (Scheme 4).[16]

The synthesis involves conversion of the phosphoric acid (*S*)-**2a** into the corresponding acid chloride and subsequent reaction of this compound with triflamide under basic conditions. Both steps take place in high yields (86% and 89% isolated yields).

For comparison purposes, p$K_a$ values have been measured for the biphenylene-derived acid **2a** and the ferrocene-derived acid **1c**.

The p$K_a$ values have been obtained in MeCN, according to the published procedure.[15] With a p$K_a$ value of 13.3, the biphenylene-derived acid **2a** is slightly more acidic than the ferrocenic acid **1c** (p$K_a$ = 13.9), both of them being less acidic than the 3,3′-diphenyl-1,1′-binol derived phosphoric acid (p$K_a$ = 12.7) (Figure 4). However, as expected, the p$K_a$ values remain in the same


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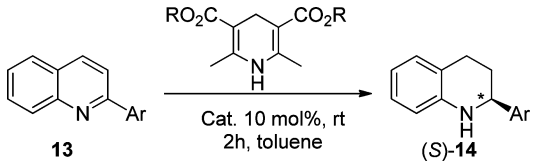
**Table 1. Enantioselective H-Transfer Hydrogenation of $\alpha$-Arylquinolines**




| entry | substrate[a] | Ar | cat. | R (Hantsch ester) | product | ee % |
|---|---|---|---|---|---|---|
| 1 | **13a** | Ph | (*S*)-**2a** | Et | **14a** | 77 |
| 2 | **13a** | Ph | (*R*)-**1c** | Et | **14a** | 60[7b] |
| 3 | **13a** | Ph | (*S*)-**2a** | $CH_2$(4-BnO-$C_6H_4$) | **14a** | 78 |
| 4 | **13a** | Ph | (*S*)-**1c** | $CH_2$(4-BnO-$C_6H_4$) | **14a** | 87[7b] |
| 5 | **13a** | Ph | (*S*)-**2a** | *t*-Bu | **14a** | **82** |
| 6 | **13a** | Ph | (*S*)-**1c** | *t*-Bu | **14a**[b] | 70[7b] |
| 7 | **13b** | 2-naphthyl | (*S*)-**2a** | *t*-Bu | **14b** | **90** |
| 8 | **13c** | *p*-biphenyl | (*S*)-**2a** | *t*-Bu | **14c** | **87** |
| 9 | **13d** | 4-MeO-$C_6H_4$ | (*S*)-**2a** | *t*-Bu | **14d** | **77** |
| 10 | **13e** | 3,5-$(CF_3)_2$-$C_6H_3$ | (*S*)-**2a** | *t*-Bu | **14e** | 60 |
| 11 | **13f** | 1-naphthyl | (*S*)-**2a** | *t*-Bu | **14f** | 47 |
| 12 | **13b** | 2-naphthyl | (*S*)-**11**[c] | *t*-Bu | **14b** | 69 |
| 13 | **13b** | 2-naphthyl | (*S*)-**12**[c] | $CH_2$(4-BnO-$C_6H_4$) | **14b** | 60 |

[a]Reactions performed on 0.05 mmol scale. [b]Reaction time 20 h. [c]Reaction time 3 h.

range. A decrease of the acidic character is observed also in the mixed phosphoric−sulfonic imides, on going from the Binol-derived *N*-triflyl phosphoramide (p$K_a$ = 6.4) to paracyclophanic imides with biphenylene (**11**; p$K_a$ = 6.5) and ferrocene tethers (**12**; p$K_a$ = 7.0).

The last step of this study has been to validate the catalytic efficiency of the newly designed acid **2a** by preliminary screenings in a model reaction: i.e. the organocatalytic H-transfer hydrogenation of the $\alpha$-arylquinolines **13** with Hantsch esters.[17] The results are shown in Table 1.

For the hydrogenation of **13a** (Ar = Ph) in the presence of acid (*S*)-**2a**, three different Hantsch esters have been tested as the H-transfer reagents (R = Et, $CH_2$(4-BnO-$C_6H_3$), *t*-Bu; entries 1, 3, and 5 in Table 1). In all of these experiments, the starting material has been converted quantitatively into the expected tetrahydroquinoline **14a** after 2 h at room temperature. Enantiomeric excesses of 77−78% were obtained by using the ethyl or the 4-benzyloxybenzyl esters, while the *tert*-butyl ester afforded the desired product in a slightly improved 82% ee. For comparison purposes, entries 2, 4, and 6 in Table 1 reproduce the results obtained previously in the same reactions by using the ferrocene derivative **1c** as the acid catalyst.

The *t*-Bu Hantsch ester and catalyst (*S*)-**2a** were used then in the reduction of a larger set of substrates. Good enantiomeric excesses were obtained for Ar = 2-naphthyl, *p*-biphenyl, 4-methoxyphenyl, with ee values between 77% and 90% (entries 7−9). The mixed amides (*S*)-**11** and (*S*)-**12** have been tested also in the reduction of the $\alpha$-2-naphthylquinoline **13b** (entries 12 and 13). In spite of their lower p$K_a$ values, these catalysts gave lower catalytic activity and also afforded lower enantiomeric excesses than the corresponding phosphoric acids.

## CONCLUSIONS

This work complements our previous studies by highlighting the biphenylene-based paracyclophanes **2** as a new series of planar chiral phosphoric acids giving promising levels of enantioselectivity in organocatalytic H-transfer hydrogenations. With respect to the analogous ferrocene framework of **1**, the biphenylene unit rigidifies the cyclophane conformation and gives advantages in terms of both synthetic availability and thermal stability of the corresponding phosphoric acids. This work corroborates the good potential of these paracyclophane scaffolds in enantioselective acid catalysis. Further studies on their catalytic applications are currently in progress.

## EXPERIMENTAL SECTION

Anhydrous solvents were obtained by filtration through drying columns (THF, toluene, $CH_2Cl_2$). All reagents and solvents were of commercial quality and were used without further purification. Analytical thin-layer chromatography (TLC) was performed on plates precoated with silica gel layers. Flash column chromatography was performed using 40−63 mesh silica. NMR spectra ($^1$H, $^{13}$C) were recorded with 500 and 300 MHz spectrometers. $^{13}$C assignments have been done on the basis of DEPT 135 experiments. Missing signals are possibly due to signal overlap. $^{19}$F NMR spectra have been recorded using TFA as the external reference. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode.

**1,8-Bis(4-(methoxymethoxy)phenyl)biphenylene (5).** 1,8-Dibromobiphenylene (**3**; 22.5 g, 72.7 mmol), [4-(methoxymethoxy)-phenyl]boronic acid (**4**; 29.12 g, 160.0 mmol) and tris(*o*-furyl)-phosphine (2.53 g, 10.9 mmol, 15 mol %) were dissolved in 1,4-dioxane (700 mL) under argon, and then a 1 M solution of $Cs_2CO_3$ (290 mL) was added. $Pd_2(dba)_3$ (1.67 g, 1.82 mmol, 2.5 mol %) was added, and the mixture was refluxed for 2 h and then cooled to room temperature and quenched with a saturated solution of $NH_4Cl$. The organic phase was extracted twice with EtOAc and dried over $MgSO_4$, and the solvents were removed under reduced pressure. The black residue was purified by column chromatography (heptane/EtOAc 95/5 to 9/1). Compound **5** ($R_f$ = 0.15 in heptane/EtOAc 7/3) was obtained as a pale yellow solid (17.0 g, 55%): mp 162 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.86−6.81 (m, 8H), 6.67−6.64 (m, 2H), 6.60 (d, $J$ = 8.3 Hz, 4H), 5.11 (s, 4H), 3.48 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 156.8 (C), 151.4 (C), 148.1 (C), 132.5 (C), 131.9 (C), 129.3 (CH), 128.8 (CH), 128.7 (CH), 115.5 (CH), 115.4 (CH), 94.7 ($CH_2$), 56.1 ($CH_3$) ppm; HRMS (ESI) calcd for $C_{28}H_{24}NaO_4$ $[M + Na]^+$ 447.1572, found 447.1563.

**1,8-Bis-[(4-(methoxymethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)]biphenylene (6).** *n*-BuLi (2.5 M solution in hexane, 47.5 mL, 118 mmol) was added to a solution of 1,1′-bis[4-(methoxymethoxy)phenyl]biphenylene **5** (8.4 g, 19.8 mmol) in anhydrous THF (200 mL) at −78 °C. The mixture was warmed to room temperature and stirred for 4 h (after a few minutes at room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temperature the pale yellow solution turned into a dark brown solution and, after ca. 20 min, a white precipitate was formed). The suspension was cooled to −78 °C, and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (32.0 mL, 158.3 mmol) was added dropwise. The mixture was stirred overnight at room temperature, and then a saturated aqueous solution of $NH_4Cl$ and EtOAc was added. The phases were separated, and the aqueous phase was extracted with EtOAc. The organic phases were dried over $MgSO_4$, and the solvents were removed under reduced pressure. Flash chromatography on silica gel with toluene/EtOAc (9/1) afforded **6** as a pale yellow solid ($R_f$ = 0.42 in heptane/EtOAc 7/3; yield 9.5 g, 71%): mp 176 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 2.4 Hz, 2H), 6.84−6.81 (m, 4H), 6.75 (dd, $J$ = 8.5, 2.4 Hz, 2H), 6.63 (m, 2H), 6.42 (d, $J$ = 8.5 Hz, 2H), 5.12 (s, 4H), 3.51 (s, 6H), 1.30 (s, 24H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.4 (C), 151.3 (C), 148.1 (C), 135.5(CH), 132.4 (C), 132.1 (CH), 131.3 (C), 129.4 (CH), 128.4 (CH), 115.2 (CH), 114.2 (CH), 95.3 ($CH_2$), 83.3 (C), 56.1 ($CH_3$), 25.0 ($CH_3$), 24.9 ($CH_3$), 24.6 ($CH_3$) ppm; HRMS (ESI) calcd for $C_{40}H_{46}O_8B_2Na$ $[M + Na]^+$ 699.3276, found 699.3293.

**1,8-Bis-[4-(hydroxy)-3-[(3′,5′-diphenyl)phenyl]phenyl]biphenylene (8).** Bis-boronate **6** (17.1 g, 25.2 mmol), 1-bromo-3,5-diphenylbenzene (7; 16.0 g, 51.7 mmol), and $Ba(OH)_2{\cdot}8H_2O$ (31.8 g, 101 mmol) were dissolved in DME (200 mL) and water (55 mL). $Pd(PPh_3)_4$ (1.46 g, 1.26 mmol, 5 mol %) was added under argon. The mixture was refluxed for 18 h. The resulting white suspension was diluted with $CH_2Cl_2$ and washed with water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was taken up in 1,4-dioxane (500 mL)/MeOH (500 mL), 37% HCl was added dropwise until pH 1 (15 mL), and the mixture was heated to 60 °C for 4 h. A saturated aqueous solution of $NaHCO_3$ was added, the layers were separated, and the aqueous layer was extracted with EtOAc. After the extract was dried over $MgSO_4$, the solvents were removed under reduced pressure. The mixture was separated by flash chromatography on silica gel (toluene/EtOAc 97/3) to afford the desired product **8** as a pale yellow solid ($R_f$ = 0.35 in heptane/EtOAc 8/2, yield 13.7 g, 69%): mp 224 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.59 (bs, 2H), 7.46−7.45 (m, 8H), 7.36−7.32 (m, 16H), 6.98 (bs, 2H), 6.93 (d, $J$ = 8.1 Hz, 2H), 6.87−6.82 (m, 4H), 6.68 (d, $J$ = 6.5 Hz, 2H), 6.60 (d, $J$ = 8.0 Hz, 2H), 5.09 (bs, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 152.2 (C), 151.4 (C), 147.8 (C), 142.4 (C), 140.5 (C), 137.8 (C), 132.3 (C), 131.1 (C), 130.0 (CH), 129.6 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 126.6 (CH), 125.2 (CH), 115.5 (CH) ppm; HRMS (ESI) calcd for $C_{60}H_{41}O_2$ $[M + H]^+$ 793.3107, found 793.3104.

**Synthesis of the Epimeric Phosphates 10.** To a solution of bisphenol **8** (6.5 g, 8.2 mmol) and 1*H*-tetrazole (2.41 g, 34.4 mmol) in anhydrous DCM (410 mL) was added dropwise a solution of (*S*)-2-cyanoethyl-1-phenyl-*N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite ((*S*)-**9**; 3.71 g, 9.8 mmol) in anhydrous DCM (10 mL). The mixture was heated at 40 °C for 3 h and then quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM. The organic phase was dried over $MgSO_4$, and the solvents were removed under reduced pressure. The crude macrocyclic phosphites were obtained as a 7/3 mixture of diastereoisomers and engaged in the next step without purification: $^{31}$P NMR (200 MHz, $CDCl_3$) $\delta$ 130.0 (minor), 129.4 ppm (major); HRMS (ESI) calcd for $C_{69}H_{46}NO_3NaP$ $[M + Na]^+$ 990.3113, found 990.3148.

The crude phosphites were dissolved in DCM (20 mL), and TBHP (5.5 M in decane, 4.5 mL) was added to the solution at 0 °C. After 15 min, the reaction mixture was warmed to room temperature and stirred for 45 min. The mixture was treated with saturated aqueous $Na_2S_2O_3$, and the layers were separated, dried over $MgSO_4$, and concentrated in vacuo. The crude phosphates were purified by chromatography on silica gel (eluent toluene/EtOAc 7/3) to afford a mixture of phosphates **10a,b** (6.9 g, 86% over two steps) as a pale yellow solid. Phosphates ($S$,$S_P$)-**10a** and ($S$,$R_P$)-**10b** were then separated by semipreparative HPLC on a $SiO_2$ column (250 × 10 mm, 5 mic) with toluene/heptane/THF (95/4/1) as the eluent at a flow rate of 100 mL/min. Retention times: 10.0 min for ($S$,$S_P$)-**10a** and 13.0 min for ($S$,$R_P$)-**10b**.

($S$,$S_P$)-**10a** (major diastereoisomer), white solid (3.6 g, 45% yield): mp 251 °C; $^{31}$P NMR (200 MHz, $CDCl_3$) $\delta$ −17.2 ppm; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91 (bs, 1H), 7.78 (bs, 3H), 7.70 (d, $J$ = 7.4 Hz, 4H), 7.65−7.62 (m, 6H), 7.45−7.34 (m, 12H), 7.29 (d, $J$ = 7.5 Hz, 2H), 7.14 (t, $J$ = 7.5 Hz, 1H), 7.03 (t, $J$ = 7.6 Hz, 2H), 6.94−6.86 (m, 3H), 6.81−6.74 (m, 4H), 6.68−6.63 (m, 2H), 6.21 (dd, $J$ = 8.5, 2.2 Hz, 1H), 6.14 (d, $J$ = 8.5 Hz, 1H), 6.08 (dd, $J$ = 8.5, 2.2 Hz, 1H), 5.17 (ddd, $J_{H-P}$ = 7.7, $J$ = 6.5, 5.5 Hz, 1H), 2.44 (dd, $J$ = 16.5, 6.5 Hz, 1H), 2.34 (dd, $J$ = 16.5, 5.5 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.6 (C), 151.5 (C), 149.6 (C), 149.2 (C), 149.1 (d, $J_{C-P}$ = 5.9 Hz, C−O), 146.8 (d, $J_{C-P}$ = 8.3 Hz, C−O), 142.5 (C), 142.0 (C), 141.0 (C), 140.5 (C), 138.1 (C), 137.9 (C), 136.9 (C), 136.5 (C), 136.1 (d, $J_{C-P}$ = 3.9 Hz, C), 132.9 (C), 131.8 (C), 131.5 (C), 131.1 (C), 131.0 (C), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 125.9 (CH), 125.8 (CH), 125.6 (CH), 121.9 (CH), 118.9 (CH), 116.8 (CH), 114.9 (C), 76.7 (CH), 26.9 (d, $J_{C-P}$ = 7.7 Hz, $CH_2$) ppm; HRMS (ESI) calcd for $C_{69}H_{47}NO_4P$ 984.3243, found 984.3210; $[\alpha]_D^{20}$ = +68° ($c$ = 1, $CHCl_3$).

($S$,$R_P$)-**10b** (minor diastereoisomer), white solid (1.8 g, 22% yield): mp 253 °C; $^{31}$P NMR (200 MHz, $CDCl_3$) $\delta$ −17.7 ppm; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.90 (bs, 1H), 7.81 (d, $J$ = 1.4 Hz, 2H), 7.77 (bs, 1H), 7.71 (d, $J$ = 7.6 Hz, 4H), 7.65 (d, $J$ = 7.6 Hz, 6H), 7.48−7.30 (m, 14H), 7.16−7.10 (m, 1H), 7.02−6.96 (m, 4H), 6.81−6.77 (m, 4H), 6.68−6.64 (m, 2H), 6.60 (d, $J$ = 8.4 Hz, 1H), 6.15−6.10 (m, 2H), 6.02 (dd, $J$ = 8.4, 2.1 Hz, 1H), 5.40 (ddd, $J_{H-P}$ = 8.2, $J$ = 8.2, 4.6 Hz, 1H), 2.57 (dd, $J$ = 16.6, 4.6 Hz, 1H), 2.37 (dd, $J$ = 16.6, 8.2 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.5 (C), 149.4 (C), 148.2 (d, $J_{C-P}$ = 8.3 Hz, C), 147.8 (d, $J_{C-P}$ = 8.9 Hz, C), 142.6 (C), 142.2 (C), 141.1 (C), 140.5 (C), 138.0 (C), 137.6 (C), 136.9 (C), 136.7 (C), 135.6 (d, $J_{C-P}$ = 6.0 Hz, C), 132.2 (C), 132.1 (C), 131.6 (C), 131.1 (C), 131.0 (C), 129.7 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH), 126.3 (CH), 126.0 (CH), 125.7 (CH), 120.7 (CH), 120.0 (CH), 116.8 (CH), 115.0 (C), 76.1 (d, $J_{C-P}$ = 5.6 Hz, CH), 26.0 (d, $J_{C-P}$ = 4.3 Hz, $CH_2$) ppm; HRMS (ESI) calcd for $C_{69}H_{47}NO_4P$ $[M + H]^+$ 984.3243, found 984.3212; $[\alpha]_D^{20}$ = −123° ($c$ = 1, $CHCl_3$).

**Phosphoric Acid (*S*)-2a.** DBU (920 μL, 6.1 mmol) was added to a solution of phosphate ($S$,$S_P$)-**10a** (3.0 g, 3.0 mmol) in DCM (15 mL). After 30 min at room temperature, the crude DBU phosphate salt was purified by column chromatography (eluent MeOH/DCM 0:100 to 5:95) to remove cinnamonitrile. The fractions were concentrated in vacuo, and the residue was diluted in DCM (15 mL). The solution was treated with 6 N HCl (3 × 15 mL). The layers were separated, and the organic layer was concentrated in vacuo to afford the chiral phosphoric acid (*S*)-**2a** as a white solid (2.4 g, 92% yield): mp 306 °C; $^{31}$P (125 MHz, $CDCl_3$) $\delta$ −11.4; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.66 (bs, 2H), 7.65 (bs, 4H), 7.61 (d, $J$ = 7.7 Hz, 8H), 7.44 (d, $J$ = 1.7 Hz, 2H), 7.34 (t, $J$ = 7.7 Hz, 8H), 7.24 (t, $J$ = 7.7 Hz, 4H), 6.93−6.89 (m, 4H), 6.77 (dd, $J$ = 5.1, 2.4 Hz, 2H), 6.39 (d, $J$ = 8.5 Hz, 2H), 6.02 (1H), 6.00 (dd, $J$ = 8.5, 1.7 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 151.9 (C), 149.7 (C), 148.2 (d, $J_{C-P}$ = 7.6 Hz, C), 142.5 (C), 141.3 (C), 137.8 (C), 136.5 (C), 132.0 (C), 131.9 (d, $J_{C-P}$ = 5.9 Hz, C), 129.0 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.1 (CH), 126.0 (CH), 120.8 (CH), 116.8 (CH) ppm; HRMS (ESI) calcd for $C_{60}H_{38}O_4P$ $[M - H]^+$ 853.2508, found 853.2493; $[\alpha]_D^{20}$ = +90° ($c$ = 0.5, $CHCl_3$).

Phosphoric acid (*R*)-**2a** was prepared by following the same procedure as for (*S*)-**2a**: starting from ($S$,$R_P$)-**10b** (1.8 g, 1.9 mmol), the reaction afforded 1.4 g of (*R*)-**2a** (1.6 mmol, 86% yield). For spectroscopic data, see (*S*)-**2a**. $[\alpha]_D^{20}$ = −88° ($c$ = 0.5, $CHCl_3$).

**Representative Procedure for the Synthesis of the *N*-Triflyl Phosphoramides.** *(a). Conversion of (S)-2a into the corresponding Chlorophosphate.* A solution of triphenylphosphine (105 mg, 0.40 mmol) in anhydrous dichloromethane (1.5 mL) was added dropwise to a solution of phosphoric acid (*S*)-**2a** (171 mg, 0.20 mmol) and 2,2,2-trichloroacetonitrile (40 μL, 0.40 mmol) in anhydrous dichloromethane (1.5 mL). The mixture was stirred for 1 h at room temperature, and then the solvent was evaporated under reduced pressure and the residue was purified on silica gel (heptane/ethyl acetate 9/1 to 8/2) to afford the desired chlorophosphate as a white solid ($R_f$ = 0.5 in heptane/ethyl acetate 8/2, yield 150 mg, 86%); mp 282 °C; $^{31}$P NMR (200 MHz, $CDCl_3$) $\delta$ −14.0 ppm; $^1$H NMR (500.1 MHz, $CDCl_3$) $\delta$ 7.87 (t, $J$ = 1.6 Hz, 1H), 7.85 (t, $J$ = 1.6 Hz, 1H), 7.81 (d, $J$ = 1.6 Hz, 2H), 7.79 (d, $J$ = 1.6 Hz, 2H), 7.75 (d, $J$ = 8.0 Hz, 4H), 7.73 (d, $J$ = 8.0 Hz, 4H), 7.54 (bs, 2H),


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7.52−7.48 (m, 8H), 7.41 (t, $J$ = 8.0 Hz, 2H), 7.39 (t, $J$ = 8.0 Hz, 2H), 6.92−6.86 (m, 4H), 6.77 (d, $J$ = 7.0 Hz, 2H), 6.63 (d, $J$ = 8.5 Hz, 1H), 6.61 (d, $J$ = 8.5 Hz, 1H), 6.29 (dd, $J$ = 8.5, 2.1 Hz, 1H), 6.26 (dd, $J$ = 8.5, 2.1 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 151.6 (C), 149.5 (C), 149.4 (C), 148.6 (d, $J_{C-P}$ = 12.2 Hz, C), 148.2 (d, $J_{C-P}$ = 12.2 Hz, C), 142.7 (C), 142.6 (C), 141.1 (C), 140.9 (C), 137.6 (C), 137.5 (C), 137.0 (C), 132.2 (d, $J_{C-P}$ = 6.4 Hz, C), 131.5 (C), 131.4 (C), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 126.5 (CH), 126.3 (CH), 121.2 (CH), 119.2 (CH), 117.0 (CH) ppm; HRMS (ESI) calcd for $C_{60}H_{39}O_3ClP$ $[M + H]^+$ 873.2325, found 873.2340; $[\alpha]_D^{20}$ = +89° ($c$ = 1, $CHCl_3$).

*(b). Synthesis of the N-Triflyl Phosphoramide* ***11****.* A solution of chlorophosphate (105 mg, 0.12 mmol) in anhydrous dichloromethane/acetonitrile (0.5 mL/2.5 mL) was added to a solution of potassium carbonate (33 mg, 0.24 mmol) and trifluoromethanesulfonamide (36 mg, 0.24 mmol) in anhydrous acetonitrile (2.5 mL) at room temperature. The mixture was heated at 60 °C for 16 h. The solvent was evaporated, and the residue was purified on silica gel (eluent: heptane/ethyl acetate gradient, from 8/2 to 5/5). The fractions were concentrated in vacuo, and the residue was diluted in DCM (5 mL). This solution was treated with 6 N HCl (3 × 5 mL). The layers were separated, and the organic layer was concentrated in vacuo to afford **11** as a white solid ($R_f$ = 0.6 in heptane/ethyl acetate 1/1, yield 105 mg, 89%): mp 235 °C; $^{31}$P NMR (202.5 Hz, $CDCl_3$) $\delta$ −18.8 ppm; $^{19}$F NMR (282.4 Hz, $CDCl_3$) $\delta$ −77 ppm; $^1$H NMR (300.2 MHz, $CDCl_3$) $\delta$ 7.91 (bs, 1H), 7.77 (bs, 4H), 7.73 (d, $J$ = 7.7 Hz, 4H), 7.65 (bs, 1H), 7.62 (d, $J$ = 7.7 Hz, 4H), 7.55 (bs, 1H), 7.52 (bs, 1H), 7.45−7.31 (m, 12H), 7.04−6.83 (m, 6H), 6.74 (d, $J$ = 8.5 Hz, 1H), 6.51 (d, $J$ = 8.5 Hz, 1H), 6.29 (dd, $J$ = 8.5, 2.1 Hz, 1H), 6.25 (dd, $J$ = 8.5, 2.1 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 151.7 (C), 149.8 (C), 149.4 (C), 149.3 (d, $J_{C-P}$ = 8.8 Hz, C), 144.6 (d, $J_{C-P}$ = 8.8 Hz, C), 142.5 (C), 142.4 (C), 141.3 (C), 141.0 (C), 137.9 (C), 137.5 (C), 137.1 (C), 136.8 (C), 132.9 (C), 132.0 (C), 131.8 (d, $J_{C-P}$ = 8.2 Hz, C), 131.6 (C), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH),128.2 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 127.0 (CH), 126.3 (CH), 125.9 (CH), 122.2 (CH), 119.1 (q, $J_{C-F}$ = 321.2 Hz, $CF_3$), 118.5 (CH), 117.0 (CH); HRMS (ESI) calcd for $C_{61}H_{40}NO_5F_3PS$ $[M - H]^+$ 986.2317, found 986.2324; $[\alpha]_D^{20}$ = +99° ($c$ = 1, $CHCl_3$).

*(c). N-Triflyl Phosphoramide* ***12****.* This compound was prepared by following the same two-step procedure as for **11**. With 0.27 g (0.30 mmol) of the ferrocenic phosphoric acid **I** (Ar = *m*-terphenyl; Figure 1) as the starting material, the two steps occurred in 85% and 92% yields, respectively, leading to 245 mg (0.24 mmol) of the *N*-triflyl phosphoramide **12**: $^{31}$P NMR (202.5 MHz, $CDCl_3$) $\delta$ −10.5 ppm; $^{19}$F NMR (282.4 MHz, $CDCl_3$) −78 ppm; $^1$H NMR (500.1 MHz, DMSO-$d_6$, −90 °C): 7.91−7.87 (m, 10H), 7.81−7.80 (m, 2H), 7.71−7.64 (m, 2H), 7.53−7.48 (m, 8H), 7.39 (t, $J$ = 7.1 Hz, 4H), 7.25−7.22 (m, 3H), 6.52 (d, $J$ = 8.2 Hz, 1H), 6.43 (d, $J$ = 8.2 Hz, 1H), 6.36 (d, $J$ = 8.2 Hz, 1H), 4.90 (s, 1H), 4.87 (s, 1H), 4.68 (s, 1H), 4.62 (s, 1H), 4.40 (s, 2H), 4.37 (s, 2H); $^{13}$C NMR (125.7 MHz, DMSO-$d_6$, −90 °C) $\delta$ 148.0 (d, $J_{C-P}$ = 7.2 Hz, C), 146.4 (d, $J_{C-P}$ = 9.2 Hz, C), 140.0 (C), 139.7 (C), 138.2 (C), 137.5 (C), 131.8 (C), 131.4 (C), 129.3 (d, $J_{C-P}$= 9.0 Hz, C), 128.6 (C), 127.6 (CH), 127.5 (2CH), 127.4 (CH), 127.1 (C), 126.2 (CH), 126.1 (CH), 126.0 (CH), 125.8 (CH), 125.7 (CH), 125.6 (2CH), 124.7 (CH), 124.2 (CH), 123.1 (CH), 122.8 (CH), 122.5 (CH), 118.7 (CH), 85.4 (C), 85.2 (C), 67.8 (2CH), 67.1 (2CH), 65.4 (CH), 65.0 (CH), 64.4 (2CH); HRMS (ESI) calcd for $C_{59}H_{40}NF_3FeO_5PS$ $[M - H]^-$ 1018.1666, found 1018.1647; $[\alpha]_D^{20}$ = +747° ($c$ = 1, $CHCl_3$).

**Representative Procedure for the Catalytic Reduction of α-Arylquinolines.** A solution of 2-phenylquinoline **13a** (11 mg, 0.05 mmol), Hantzsch dihydropyridine (0.12 mmol), and the acid catalyst (*S*)-**2a** (0.005 mmol) in toluene (1 mL) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was purified on silica gel with toluene as the eluent. 2-Phenyl-1,2,3,4-tetrahydroquinoline (**14a**) was obtained as a colorless oil. NMR data are in good agreement with the literature.[18] The enantiomeric excess was determined by HPLC using a CHIRALPAK IB column with -PrOH/*n*-heptane 5/95 as eluent, at a flow rate of 1 mL/min (detection at 275 nm). Retention times: 6.7 min for (*S*)-**14a** and 8.2 min for (*R*)-**14a** (lit.[18] (*S*)-**14a**: $[\alpha]_D$ = −35.7° ($c$ = 0.8, $CHCl_3$)).

The same procedure was applied to the reduction of quinolines **13b−f**. Spectral data for the corresponding tetrahydroquinolines **14b−f** and conditions for ee measurements by HPLC have been reported previously (**14b**,[18] **14c**,[17a] **14d**,[18] **14e**,[7b] **14f**[21]).

**Computational Methods.** Calculations were carried out with the Gaussian09 package of programs.[19] All of the structures were optimized at the DFT level by means of the M06 functional.[20] The 6-31G(d,p) basis set was applied for all atoms. This level of calculation was shown previously to provide reliable structures for phosphoric acid derivatives.[7b] To get accurate geometries and energies, the SCF convergence criterion was systematically tightened to $10^{-8}$ au, and the force minimizations were carried out until the rms force became smaller than (at least) $1 \times 10^{-5}$ au. The optimized geometries were characterized by harmonic analysis, and the nature of the stationary points was determined according to the number of negative eigenvalues of the Hessian matrix.

**X-ray Crystallographic analysis of Compound 10a.** Small colorless plates of compound **10a** were obtained by slow evaporation of an ethyl acetate solution kept at room temperature. The diffraction data were collected using a Rigaku MM007 HF copper rotating-anode generator with Osmic CMF optics and a rapid II curved imaging plate ($\lambda$ = 1.54187 Å). Crystallographic data for **10a** (193 K): $C_{69}H_{46}NO_4P \cdot 2.3C_4H_8O_2$ ($M_r$ =1186.67) orthorhombic, $P2_12_12_1$, $a$ = 12.0216(2) Å, $b$ = 18.9542(3) Å, $c$ = 27.6717(19) Å, $V$ = 1463.5(2) Å$^3$, R1 = 0.0780 (6329, $I > 2\sigma(I)$), wR2 = 0.2406 (all 11193 data), GOF on $F^2$, $S$ = 1.033, Flack parameter using 1984 quotients $x$ = 0.075(12). In addition to one solvent molecule of ethyl acetate sensibly modeled with rigid-bond restraints (DELU), the PLATON SQUEEZE procedure was used to treat other regions of diffuse solvent. Their contribution to the diffraction pattern was removed and modified $F_o^2$ values written to a new HKL file. The number of electrons thus located, 260 per unit cell, was included in the formula, formula weight, calculated density, $\mu$, and $F(000)$. The residual electron density was assigned to 1.3 molecules of ethyl acetate.

CCDC 1014151 contains supplementary crystallographic data for **10a**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ U.K.; fax (+44) 1223-336033 or deposit@ccdc.cam.ac.uk).

## ■ ASSOCIATED CONTENT

### Supporting Information

Text, figures, tables, and a CIF file giving $^1$H, $^{13}$C, and $^{31}$P NMR spectra, X-ray crystal data for **10a**, and details of p$K_a$ measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES


(1) (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Terada, M. *Synthesis* **2010**, 1929. (d) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (e) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156.

(2) (a) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (b) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603. (c) Lv, J.; Luo, S. *Chem. Commun.* **2013**, *49*, 847. (d) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. (e) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534.

(3) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581.

(4) (a) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523. (b) Lam, H. W. *Synthesis* **2011**, 2011. (c) Gratzer, K.; Gururaja, G. N.; Waser, M. *Eur. J. Org. Chem.* **2013**, 4471. (d) Seebach, D.; Beck, A. K.; Bichsel, H.-U.; Pichota, A.; Sparr, C.; Wünsch, R.; Schweizer, W. B. *Helv. Chim. Acta* **2012**, *95*, 1303.

(5) For recent references on the use of chiral phosphoric acids in catalysis, see: (a) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370. (b) Xing, C.-H.; Liao, Y.-X.; Ng, J.; Hu, Q.-S. *J. Org. Chem.* **2011**, *76*, 4125. (c) Chen, Z.; Wang, B.; Wang, Z.; Zhu, G.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2027. (d) Li, X.; Zhao, Y.; Qu, H.; Mao, Z.; Lin, X. *Chem. Commun.* **2013**, *49*, 1401. (e) Huang, D.; Li, X.; Xu, F.; Li, L.; Lin, X. *ACS Catal.* **2013**, *3*, 2244. (f) Caruana, L.; Fochi, M.; Ranieri, S.; Mazzanti, A.; Bernardi, L. *Chem. Commun.* **2013**, *49*, 880. (g) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3964. (h) Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12932. (i) Wang, Z.; Law, W. K.; Sun, J. *Org. Lett.* **2013**, *15*, 5964. (j) Xie, W.; Jiang, G.; Liu, H.; Hu, J.; Pan, X.; Zhang, H.; Wan, X.; Lai, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12924. (k) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Org. Lett.* **2013**, *15*, 5890. (l) He, L.; Laurent, G.; Retailleau, P.; Folléas, B.; Brayer, J.-L.; Masson, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11088. (m) Kimura, T.; Sekine, M.; Takahashi, D.; Toshima, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 12131. (n) Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 1268. (o) Kano, T.; Takechi, R.; Kobayashi, R.; Maruoka, K. *Org. Biomol. Chem.* **2014**, *12*, 724. (p) Tang, W.; Johnston, S.; Li, C.; Iggo, J. A.; Bacsa, J.; Xiao, J. *Chem. Eur. J.* **2013**, *19*, 14187. (q) Calleja, J.; González-Pérez, A. B.; De Lera, A. R.; Álvarez, R.; Fañanás, F. J.; Rodriguez, F. *Chem. Sci.* **2014**, *5*, 996. (r) Dagousset, G.; Erb, W.; Zhu, J.; Masson, G. *Org. Lett.* **2014**, *16*, 2554. (s) Makiguchi, K.; Yamanaka, T.; Kakuchi, T.; Terada, M.; Satoh, T. *Chem. Commun.* **2014**, *50*, 2883. (t) Mori, K.; Wakazawa, M.; Akiyama, T. *Chem. Sci.* **2014**, *5*, 1799. (u) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Chem. Eur. J.* **2014**, *20*, 2367. (v) Terada, M.; Komuro, T.; Toda, Y.; Korenaga, T. *J. Am. Chem. Soc.* **2014**, *136*, 7044. (w) Tian, X.; Hofmann, N.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2997. (x) Wilent, J.; Petersen, K. S. *J. Org. Chem.* **2014**, *79*, 2303. (y) Cai, X.-F.; Guo, R.-N.; Feng, G.-S.; Wu, B.; Zhou, Y.-G. *Org. Lett.* **2014**, *16*, 2680. (z) Zhang, Y.; Lim, C.-S.; Sim, D. S. B.; Pan, H.-J.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 1399.

(6) Enders, D.; Ludwig, M.; Raabe, G. *Chirality* **2012**, *24*, 215.

(7) (a) Stemper, J.; Isaac, K.; Duret, V.; Retailleau, P.; Voituriez, A.; Betzer, J.-F.; Marinetti, A. *Chem. Commun.* **2013**, *49*, 6084. (b) Stemper, J.; Isaac, K.; Pastor, J.; Frison, G.; Retailleau, P.; Voituriez, A.; Betzer, J.-F.; Marinetti, A. *Adv. Synth. Catal.* **2013**, *355*, 3613.

(8) The ring strain energies have been calculated from isodesmic exchange reactions on the Binol-derived acid, as in ref 7b.

(9) Kabir, S. M. H.; Iyoda, M. *Synthesis* **2000**, 1839.

(10) Selepe, M. A.; Drewes, S. E.; van Heerden, F. R. *J. Nat. Prod.* **2010**, *73*, 1680.

(11) (a) Lunazzi, L.; Mancinelli, M.; Mazzanti, A. *J. Org. Chem.* **2008**, *73*, 2198. (b) Harvey, P. D.; Brégier, F.; Aly, S. M.; Szmytkowski, J.; Paige, M. F.; Steer, R. P. *Chem. Eur. J.* **2013**, *19*, 4352.

(12) Grubbs, R. A.; Lewis, M. M.; Owens-Vance, C.; Gay, E. A.; Jassen, A. K.; Mailman, R. B.; Nichols, D. E. *Bioorg. Med. Chem.* **2004**, *12*, 1403.

(13) Isaac, K.; Stemper, J.; Retailleau, P.; Betzer, J.-F.; Marinetti, A. *Eur. J. Org. Chem.* **2014**, 4099.

(14) The stereochemical description follows the Cahn–Ingold–Prelog nomenclature with the aryl ring as the reference plane and P as the pilot atom: Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed.* **1966**, *5*, 385.

(15) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 11569.

(16) For catalytic uses of *N*-triflyl phosphoramides, see: (a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 9730. (c) Wang, S.-G.; Han, L.; Zeng, M.; Sun, F.-L.; Zhang, W.; You, S.-L. *Org. Biomol. Chem.* **2012**, *10*, 3202.

(17) (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (b) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, 852. (c) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498.

(18) Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2012**, *134*, 2442.

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, V.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, revision B.01*; Gaussian Inc., Wallingford, CT, 2010.

(20) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.

(21) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891.