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Development of Chiral Phosphoric Acids based on Ferrocene-Bridged Paracyclophane Frameworks

Jérémy Stemper,[a] Kévin Isaac,[a] Julien Pastor,[b] Gilles Frison,[b] Pascal Retailleau,[a] Arnaud Voituriez,[a] Jean-François Betzer,[a,*] and Angela Marinetti[a,*]

[a] Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Centre de Recherche de Gif, 91198 Gif-sur-Yvette, France
Fax: (+33)-1-6907-7247; e-mail: jean-francois.betzer@cnrs.fr or angela.marinetti@cnrs.fr
[b] Laboratoire des Mécanismes Réactionnels, Department of Chemistry, Ecole Polytechnique and CNRS, 91128 Palaiseau, France

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Abstract: This work deals with the development of a new family of planar chiral phosphoric acids based on a ferrocenophane/paracyclophane scaffold. The synthetic approach has been improved by taking advantage of a chiral phosphorylating agent to access enantiomerically enriched acids *via* diastereomers separation. These phosphoric acids have been used as catalysts for the enantioselective H-transfer reduction of α-substituted quinolines with Hantzsch esters. Optimization of both the catalyst and the Hantzsch reductant allowed *ee* values in the range 82–92% to be attained starting from α-arylquinolines.

Keywords: chiral phosphorodiamidites; organocatalysis; paracyclophanes; phosphoric acids; planar chirality

Introduction

The use of chiral phosphoric acids in organocatalytic processes has experienced an exponential growth following the seminal work of Terada[1] and Akiyama[2] on enantioselective Mannich-type reactions. Among the most classical applications, Biginelli, Pictet–Spengler, Friedel–Crafts, ene-type and Diels–Alder reactions can be mentioned.[3] Moreover, several unprecedented uses have been reported recently which include the desymmetrization of tetrasubstituted biaryls by asymmetric bromination,[4] the oxyfluorination of enamides,[5] the asymmetric protonation of ketene dithioacetals and silyl ketene imines[6] and others.[7] The privileged phosphoric acids for these applications are mainly based on chiral BINOL, SPINOL,[8] VANOL and VAPOL[9] derivatives, that is, C_2-symmetrical, axially chiral diols. Surprisingly, planar chirality has not been exploited so far for building phosphoric acids, although planar chiral structural units are known to afford efficient auxiliaries in other fields.[10] In the case of phosphoric acids, it can be expected that planar chiral scaffolds would create completely different asymmetric environments, with respect to axially chiral frameworks. They might generate, therefore, complementary properties in terms of stereoselection and offer new opportunities for catalytic applications. This hypothesis led us to design phosphoric acids based on planar chiral paracyclophane scaffolds as potentially relevant targets. Preliminary results from these studies have been disclosed in a short communication.[11] In this paper we present (i) more detailed information on our design of planar chiral phosphoric acids, (ii) an improved synthetic approach to optically pure compounds, based on the use of a chiral phosphorylating agent, (iii) more extensive investigations on the use of the new acids as organocatalysts in the enantioselective H-transfer reduction of α-substituted quinolines.

Results and Discussion

At the start of our studies, our aim was to develop a new series of phosphoric acids, based on planar chiral paracyclophane scaffolds. As far as we know, the literature reports only one compound of this class, the Enders acid **A** (Figure 1), in which a phosphoric acid function is embedded in the five-atom chain tethering an unsymmetrical [2.2]paracyclophane unit. This Brønsted acid catalyst had been evaluated in Man-

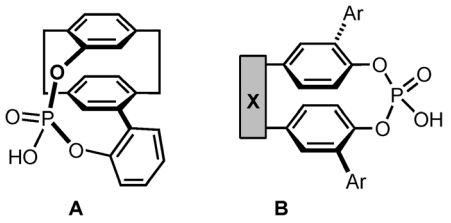


Figure 1. Enders' planar chiral phosphoric acid (**A**) and targeted structures from this work (**B**).

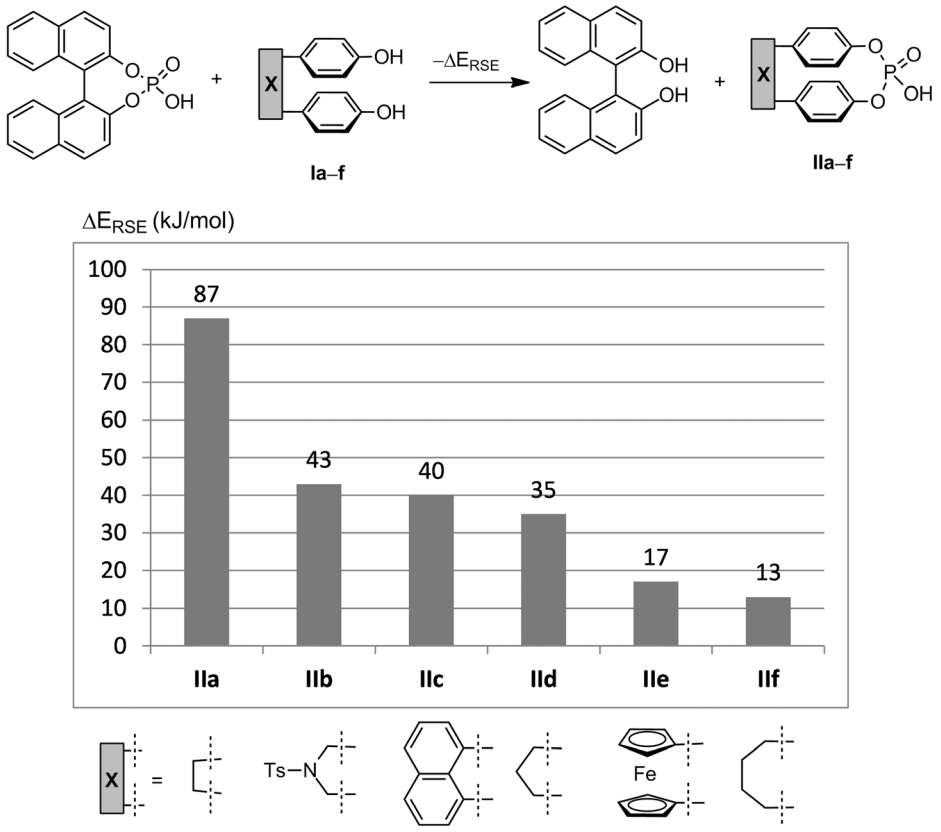
nich-type reactions affording moderate enantiomeric excesses (*ee*s up to 38%).[12]

Our target structures (**B**, Figure 1) differ from the Enders acid in as far as the O–P–O bridge itself would be a constitutive fragment of the C_2-symmetrical paracyclophane framework. In **B**, planar chirality is generated by the two aryl substituents (Ar) on opposite edges of the paracyclophane. The only previous report on related paracyclophanes and ferrocenophanes are due to Nifant′ev[13] and Herberhold[14] who synthesized racemic macrocyclic bis-phosphoramidites, and ferrocenic phosphonites and phosphates, respectively. None of these compounds have been prepared in enantiomerically enriched form, neither have they been investigated for catalytic purposes.

As mentioned in our preliminary communication,[11] phosphoric acids of the general formula **B** can be accessed when the tethering chain "X" is a 1,1′-ferrocenediyl unit. This chain has been designed initially, following on from calculations of the ring strain and configurational stability for a range of phosphoric acids of this class. Results of these calculations are reported hereafter in Scheme 1.

Two factors have been initially identified as crucial for the choice of the tethering chain. First, the strain energy associated with the macrocyclic structure: the longer the tethering chain "X" is, the easier the cyclization process would be. Secondly, the configurational stability of the planar chiral scaffold: a long linker "X" might induce loss of the configurational stability, by allowing easy rotation of the phenylene rings of the paracyclophane moiety around the $X–C_{aryl}–O$ axis. The nature of the tethering chain must therefore be finely adjusted. DFT calculations have been run to estimate ring strain energies for paracyclophanic acids, relative to the BINOL-derived phosphoric acid (ΔE_{RSE}), according to the isodesmic reaction depicted in Scheme 1. The computed data, obtained at the M06/6-31G(d,p) level are shown.

A 2-atom chain (**IIa**) induces the larger ring strain energy, whereas 3-atom (**IId**) and, to a larger extent,



Scheme 1. Isodesmic reaction used to compute the relative ring strain energy of **IIa–f** relative to the BINOL-derived phosphoric acid.

4-atom chains (**IIf**) significantly reduce strain. The 1,1′-ferrocenediyl unit (**IIe**) decreases significantly the ring strain with respect to the 3-atom chains of **IIb–d**. This comparatively low ring strain likely relates to the high flexibility of the ferrocene unit, a unique structural feature that has allowed previously the synthesis of ferrocenophanes of various ring sizes, including the highly constrained phospha[1]- and phospha[2]ferrocenophanes.[15]

Geometrical parameters of the macrocyclic structures **IIa–f** also correlate well with the computed ring strain energies: smaller and less flexible linkers increase the deformation angles of the benzene ring of the paracyclophane unit (see sum of deformation angles, $\Sigma_{\alpha+\beta}$ in Table 3),[16] as well as the strain of the O–P–O bridge, as shown by the increased O···O distance (Table 3).

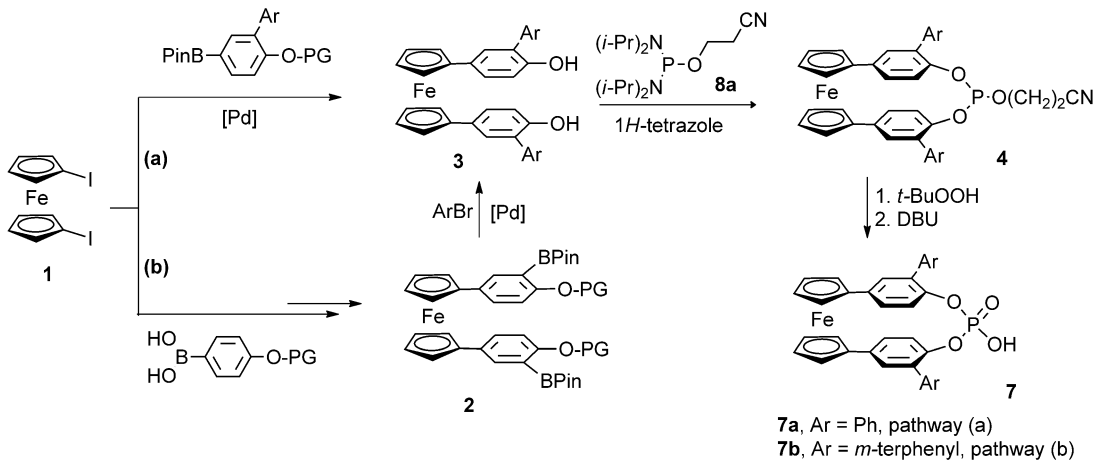
Concerning the configurational stability of paracyclophanes, it has been computed recently that the barrier for rotation of the *p*-phenylene ring in [3.3]- and [4.4]paracyclophanes are of about 300 and 80 kJ·mol^{-1}, respectively,[17] indicating that this barrier could be overcome only for the larger macrocycles and at high temperature. A similar trend is expected to be found in the targeted macrocyclic phosphoric acids. For the ferrocenic derivative **IIe** and the naphthalene-derived macrocycle **IIc**, the energy barriers for the rotation of the *p*-phenylene units around the X–C_{aryl}–O axis have been calculated at about 216 and 387 kJ·mol^{-1}, respectively [at the M06/6-31G(d,p) level] in accordance with the chain size and flexibility of these structures.

The theoretical studies above have oriented our choice toward 1,1′-ferrocenediyl units as the key components of phosphoric acids **B**, due to their low ring strain energy and high racemization barrier. Initial experiments have demonstrated that ferrocene-based paracyclophanes of the general formula **B** can indeed be accessed and display acceptable chemical and configurational stability. As described in our previous communication, the ferrocene-tethered phosphoric acids **7** could be obtained according to two general strategies shown in Scheme 2.[11]

For both pathways, the key step is the macrocyclization reaction of a 1,1′-bis(*para*-hydroxyphenyl)ferrocene, **3**, with bis(diisopropylamino)cyanoethoxyphosphine **8a**. The two pathways differ from each other by the reaction sequence leading to the ferrocenic diol **3**. Pathway (a) involves the reaction of 1,1′-diiodoferrocene with a preformed biarylboronate [BPin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane] in the presence of a palladium catalyst, under Suzuki conditions. Path (b) entails the synthesis of the bis-boronate **2** as a common platform allowing introduction of various aryl substituents (Ar) at a later step of the reaction sequence. The aryl substituents are introduced here by a palladium-catalyzed Suzuki coupling on **2**. In the final step of the reaction sequence, diols **3** have been reacted with bis(diisopropylamino)cyanoethoxyphosphine in the presence of four equivalents of 1*H*-tetrazole to afford the desired *d,l*-phosphites **4**.[18] Phosphites **4** have been oxidized into the corresponding phosphates with *tert*-butyl hydroperoxide, then removal of the cyanoethyl chain by elimination of acrylonitrile under basic conditions (DBU) afforded the racemic acids **7**. Pathway (a) has been applied to the synthesis of the phenyl-substituted phosphoric acid **7a** (Ar = Ph), while path (b) allowed the synthesis of the *meta*-terphenyl-substituted acid **7b**.

The racemic mixtures of **7a** and **7b** have been separated initially into enantiomerically pure acids by semipreparative HPLC on a CHIRALPAK® ID column.

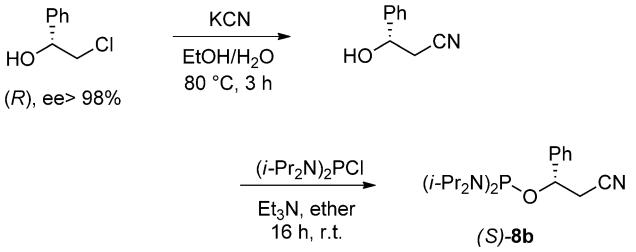
However, the use of semi-preparative chiral HPLC as the resolution method is a potential drawback of the synthetic approach above, as far as it might prevent suitable scale-up of the acids **7**. On the other hand, the strategy of resolving the diol precursors



Scheme 2. Synthetic approaches to the 1,1′-ferrocenediyl-tethered paracyclophanes **7**.

commonly applied to the synthesis of chiral phosphoric acids,[19] cannot be applied here because of the peculiar structural features of this series. Acids **7** differ indeed from the BINOL- or SPINOL-derived analogues in that chirality is generated at the phosphination step, while the diol precursors are achiral. This means that resolution must be performed at a later step of the synthetic sequence.

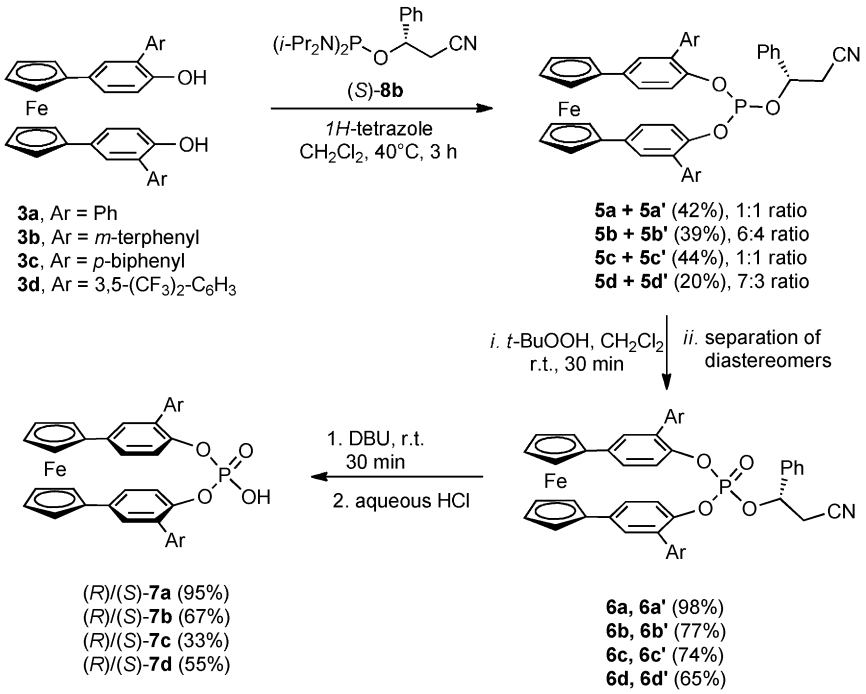
Thus, in order to avoid chiral HPLC separation, we have envisioned an original approach, that is, the use of a chiral auxiliary as the phosphinating agent and subsequent separation of diastereomeric pairs. We have developed (*S*)-**8b** as a chiral variant of the classical cyanoethoxy-substituted phosphinating agent **8a**. The new phosphorodiamidite (*S*)-**8b** contains a cyanoethoxy moiety as a precursor for the acidic P–OH function, but, unlike **8a**, it displays a stereogenic carbon in close proximity to the phosphorus center. It is easily available in two steps, starting from the commercially available (*R*)-(−)-2-chloro-1-phenylethanol, as shown in Scheme 3. After a Cl/CN substitution step, the resulting (*S*)-3-hydroxy-3-phenylpropanenitrile[20] has been reacted with $[(i\text{-Pr})_2N]_2PCl$ at room temperature in the presence of Et_3N. The desired phosphorodiamidite (*S*)-**8b** has been isolated as a white solid after filtration on a silica gel column.



Scheme 3. Synthesis of the chiral phosphorodiamidite (*S*)-**8b**.

Phosphorodiamidite (*S*)-**8b** has been used as the phosphinating agent for the previously reported diols **3a** (Ar = Ph) and **3b** (Ar = *meta*-terphenyl), but also for the newly synthesized ferrocenic diols **3c**, **d** [Ar = *para*-biphenyl and 3,5-$(CF_3)_2C_6H_3$], as shown in Scheme 4. Diol **3c** has been prepared *via* palladium-catalyzed coupling of 1,1′-diiodoferrocene, **1**, with the corresponding biarylboronate [path (a) in Scheme 2]. Diol **3d** has been obtained *via* path (b) in Scheme 2, that is, coupling of 1-bromo-3,5-bis(trifluoromethyl)-benzene with the ferrocenic bisboronate **2** [PG = methoxymethyl, catalyst = $Pd(PPh_3)_4$]. The experimental procedures for these reactions are given in the Supporting Information.

Diols **3a–d** have been reacted with the chiral phosphorodiamidite (*S*)-**8b** in the presence of 1*H*-tetrazole to afford the desired macrocyclic, paracyclophane-type phosphites **5a–d** (Scheme 4). In principle, the cyclization step might afford both the *meso*- and *d,l*-isomers of **5**, but, gratifyingly, these reactions occurred with high stereoselectivity leading to the desired *d,l*-isomers as the only isolated products. We can assume that steric effects are responsible for the observed selectivity, as far as the steric hindrance of the Ar substituents is expected to favor their positioning on opposite faces of the paracyclophane ring. From



Scheme 4. Use of the chiral phosphorodiamidite (*S*)-**8b** in the synthesis of phosphoric acids **7**.

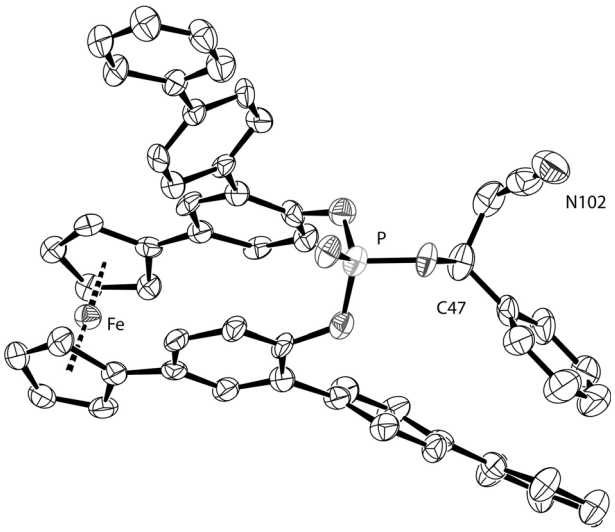


Figure 2. X-Ray crystal structure of (−)-(S_p,*S*)-**6c′**.

these reactions, phosphites **5a–d** have been isolated as mixtures of two diastereomers in 1:1 to 7:3 ratios. The mixtures have been oxidized with *t*-BuOOH to obtain the corresponding phosphates **6a–d**. The four phosphates could be separated easily into pure diastereomers by either column chromatography (for **6b–d**) or HPLC (for **6a**). Thus, for instance, phosphates **6c**, **c′** (Ar = 4-biphenyl) have been separated by flash chromatography on silica gel (Combiflash) with a toluene/heptane/THF gradient (from 60:30:0 to 60:30:2) as the eluent {**6c**: $R_f = 0.39$, $[\alpha]_D^{20}$: +1151 ($c = 0.5$, $CHCl_3$); **6c′**: $R_f = 0.34$, $[\alpha]_D^{20}$: −1138 ($c = 0.5$, $CHCl_3$)}.

An X-ray crystal study on **6c′** demonstrated an (*S*)-configuration of its planar chiral scaffold (Figure 2). Since **6c′** displays a negative rotatory power, we tentatively assume that, in the whole series, negative *alpha* values are associated to phosphates and phosphoric acids with (*S*)-configurations.

The phosphates **6** are chemically and configurationally stable: neither decomposition nor interconversion of isomeric derivatives has been observed after either prolonged storage in air at room temperature or heating overnight at 80 °C.

The last step of the reaction sequence in Scheme 4 is the removal of the chiral auxiliary. The 1-phenyl-2-cyanoethyl chain could be removed under the conditions usually applied for removal of the analogous achiral cyanoethyl chain: DBU easily induces deprotonation and subsequent elimination of 3-phenylacrylonitrile, with concomitant generation of the desired phosphoric acid salt. Starting from single diastereomers of phosphates **6**, the enantiomerically enriched acids **7a–d** have been obtained as yellow-orange solids after filtration on silica gel with a DCM/MeOH gradient (0 to 10% MeOH) and work-up with aqueous HCl (6 N). The enantiomeric excesses of the acids have been measured by HPLC.

Unlike the corresponding phosphates **6**, acids **7** displayed moderate thermal stability giving non-identified decomposition products after heating at 60 °C in toluene for several hours. For instance, **7a** undergoes an estimated 10% decomposition after heating for 18 h at 60 °C. Therefore, to ensure the integrity of their molecular scaffold, these acids are stored routinely at −20 °C and used then in catalytic experiments at room temperature.

In summary, we have demonstrated here that the use of the chiral phosphorodiamidite (*S*)-**8b** as the phosphinating agent provides an easier access to the phosphoric acids **7**, the first family of planar chiral acids based on paracyclophane structures.

With suitable synthetic methods in hand, we have then started a systematic investigation of the behavior of acids **7** as Brønsted acid catalysts.

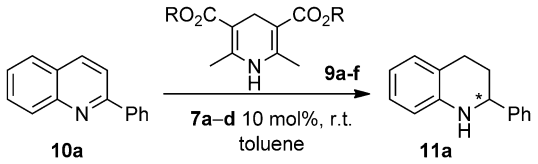
Our investigations have been focused on the transfer hydrogenation of 2-substituted quinolines with the Hantzsch ester as a benchmark reaction (Table 1).[21] We have compared the catalytic properties of the four acids **7a–d** which display aryl groups with various steric bulk and long-arm effects. The shape and bulk of these aryl substituents are expected to play a major role in enantioselective catalysis, as impressively demonstrated with the analogous BINOL-derived phosphoric acids.[22]

At first, the behavior of **7a–d** has been surveyed in the reduction of 2-phenylquinoline with the Hantzsch ester **9a** (R = Et, entries 1–4). All catalytic experiments have been run in toluene on a 0.05-mmol scale. Standard conditions involve toluene as the solvent, room temperature, 10 mol% of chiral catalyst.

Acids **7a–d** displayed excellent catalytic activity at room temperature, as they give total conversion in less than 2 h. As anticipated, the nature of the aryl substituents of the acids strongly modulates the enantioselectivity levels, with enantiomeric excesses going from 26%, for Ar = phenyl, to 60% for the bulky, *meta*-terphenyl-substituted acid **7b**.

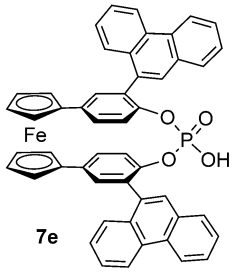
In addition to catalysts **7a–d**, we have tested also the 9-phenanthryl-substituted acid **7e**[24] (entry 5) since 9-phenanthryl substituents are known to give the most efficient acid in the binaphthyl series.[21a] Acid **7e** afforded, however, a very low enantiomeric excess. Generally speaking, we have observed that the substituent effects do not follow the same trends in the binaphthyl-derived and paracyclophane-type phosphoric acids. Such divergent substituent effects can be easily understood as far as the two series display totally different structural features and, especially, different arrangements of the aryl groups around the phosphorus functions. Comparative views of the molecular structures of a BINOL-derived phosphoric acid and the corresponding paracyclophanic acid **7a**, obtained from DFT calculations, are given in Figure 3.

Table 1. Survey of phosphoric acids and Hantzsch esters for the H-transfer hydrogenation of 2-phenylquinoline.[a]



	Catalyst	Hantzsch ester	R	Time [h][b]	*ee* [%][c] (*config.*)
1	(+)-**7a**	**9a**	Et	2	27 (*S*)[d]
2	(+)-**7b**	**9a**	Et	2	60 (*S*)
3	(+)-**7c**	**9a**	Et	2	55 (*S*)[e]
4	(+)-**7d**	**9a**	Et	2	56 (*S*)
5	(−)-**7e**	**9a**	Et	2	26 (*R*)[g]
6	(−)-**7b**	**9b**	Me	16	50 (*R*)
7	(−)-**7b**	**9c**	*t*-Bu	20[f]	70 (*R*)
8	(−)-**7b**	**9d**	CH_2Ph	3	74 (*R*)
9	(+)-**7b**	**9e**	$CH_2(4\text{-}MeOC_6H_4)$	2	85 (*S*)
10	(−)-**7b**	**9 f**	$CH_2(4\text{-}BnOC_6H_4)$	2	87 (*R*)[d]

[a] Reactions were run at a substrate concentration of 0.05 to 0.01 M, depending on the solubility of the Hantzsch ester in toluene.
[b] Reaction times giving total conversion rates (NMR monitoring of the crude mixtures).
[c] The *ee*s were determined by HPLC on CHIRALPACK® IB (*i*-PrOH/heptane 5:95). Configuration assigned from $[\alpha]_D$ values.[23]
[d] The same conversion rate and *ee* were observed at a catalyst loading of 5 mol%.
[e] CH_2Cl_2 and THF were also used as solvents in this reaction, they afforded however lower reaction rates and enantioselectivity levels (*ee* = 30%).
[f] 80% conversion rate.
[g] 5 mol% catalyst.



Most particularly, in **7a** the eclipsed conformation of the ferrocene unit and the parallel arrangement of the *para*-phenylene groups cause a bent arrangement of the O–P–-O function and subsequent loss of the C_2 symmetry of the molecule. Therefore, while in the C_2-symmetrical BINOL-derived acid the phenyl groups are distributed symmetrically on opposite sides of the phosphorus function, in **7a** one of the phenyl substituents becomes closer to the phosphorus function and the second one is kept away considerably. Based on these significant structural differences, we cannot expect similar trends in the structure-activity relationships in the two series. This obviously prevents us from making predictive hypotheses, but, on the other hand, the peculiar structural features of acids **7** might hopefully give complementary applications, with respect to BINOL-derived acids and analogues.

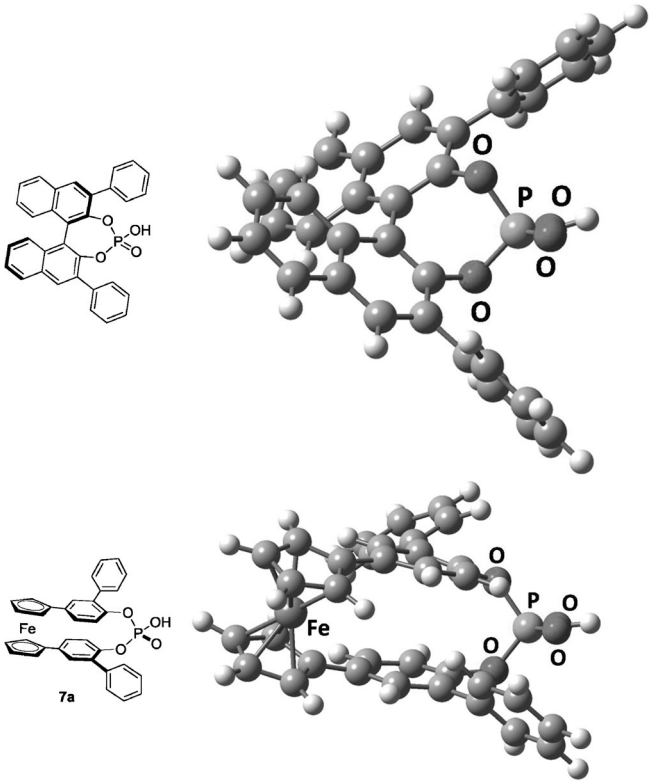


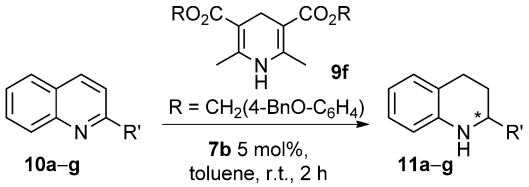
Figure 3. DFT computed molecular structures of a BINOL-derived phosphoric acid and the corresponding paracyclophanic acid **7a**.

From the initial screening of chiral acids in Table 1, entries 1–5, we retained **7b** (Ar = terphenyl) as the most promising catalyst for the H-transfer reduction of **10a** and we investigated then the role of the dihydropyridine partner (entries 2, 6–10 in Table 1). According to recent theoretical studies on the reduction of imines with Hantzsch esters, the esters are assumed to give H-bonds with the catalyst in the stereodetermining H-transfer step.[25] Consequently, the nature of the ester should have effects on the reaction outcome in terms of stereochemical control. Although so far the literature shows that the Hantzsch ester plays a minor role in analogous reactions,[21f,26] in our study an extensive screening of esters has allowed a significant improvement of the enantioselectivity levels. Several known and new Hantzsch esters [e.g., R = *t*-Bu, CH_2Ph, $CH_2(4\text{-}MeOC_6H_4)$, $CH_2(4\text{-}BnO\text{-}C_6H_4)$] have been prepared from formaldehyde, ammonium acetate and the desired acetoacetate, following a usual procedure.[27]

As shown in Table 1, in the reduction of 2-phenylquinoline catalyzed by acid **7b**, the enantiomeric excess increased with the steric hindrance of the Hantzsch esters (R = Me < Et < *t*-Bu). Finally, benzyl esters afforded the highest enantioselectivity levels, with an 87% *ee* obtained with ester **9f**, R = CH_2(4-BnO-C_6H_4). In these reactions, the catalyst loading could be decreased to 5 mol% without decreasing the conversion rate and enantioselectivity.

With these improved conditions in hand (**7b** as the catalyst and **9f** as the reducing agent) we have investigated the scope of the H-transfer reaction by varying the quinoline substrates. The main results are summarized in Table 2.

Table 2. Survey of 2-substituted quinolines **10** in H-transfer reductions promoted by **7b**.



	Substrate	R′	Acid	Product[a]	ee [%][b] (*config.*)
1	**10a**	Ph	(−)-**7b**	**11a**	87 (*R*)
2	**10b**	4-MeO-C_6H_4	(+)-**7b**	**11b**	83 (*S*)
3	**10c**	2-naphthyl	(+)-**7b**	**11c**	92 (*S*)
4	**10d**	*para*-biphenyl	(−)-**7b**	**1d**	82 (*R*)
5	**10e**	3,5$(CF_3)_2C_6H_3$	(−)-**7b**	**11e**[c]	87 (+)
6	**10f**	1-naphthyl	(−)-**7b**	**11f**[c]	40 (*R*)
7	**10g**	C_6H_{11}	(−)-**7b**	**11g**[c]	40 (*R*)

[a] Conversion rates are quantitative.
[b] Configuration assigned from $[\alpha]_D$ values of known compounds: **11a,b,c**,[23] **11d**,[21a] **11f**,[28] **11g**.[29]
[c] Conversion rate 50%.

These experiments show that the new catalyst **7b** affords high levels of enantioselectivity (*ee* 82–92%) in the reduction of various α-aryl-substituted quinolines (entries 1–5). Under the same conditions, alkyl-substituted quinolines are reduced with lower conversion rates and enantiomeric excess (entry 7: R′ = cyclohexyl, 40% *ee*). Even so, the potential of planar chiral paracyclophanic acids as an enantioselective organocatalyst is demonstrated here.

Conclusions

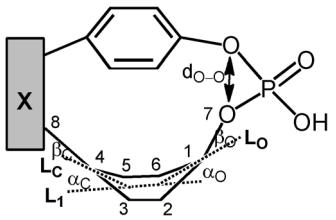
This work has disclosed phosphoric acids **7** as the first series of enantiomerically enriched phosphoric acids with paracyclophane structures. Their unprecedented scaffolds display an O–P–O chain and a 1,1′-ferrocenediyl unit tethering the aromatic rings of the paracyclophane, while suitably positioned aromatic substituents generate planar chirality. We have demonstrated that the planar chiral phosphoric acids **7** display high catalytic activity and promising enantioselectivity levels in model H-transfer reductions (*ee*s up to 92%). Their behavior as Brønsted acid organocatalysts will be further investigated. Given their peculiar structural features, including the lack of C_2-symmetry, it can be anticipated that these acids will have complementary application fields with respect to other known chiral phosphoric acids. Further studies of their catalytic properties are ongoing in our group.

Experimental Section

Computational Method

Calculations have been carried out with the *Gaussian09* package of programs.[30] Full geometry optimizations for all compounds were carried out with the use of the M06[31] density functional level of theory and the 6-31G(d,p) basis set for all atoms. This level of calculation is known to produce reasonable geometries and energies for molecules in which non-covalent interactions, like π-π interactions in paracyclophane-type systems, play a noticeable role. To get accurate geometries and energies, the SCF convergence criterion has been systematically tightened to 10^{-8} a.u., and the force minimizations were carried out until the rms force becomes smaller than (at least) 1×10^{-5} a.u. Frequency analyses were

Table 3. Computed relative ring strain energy and geometric parameters for **IIa–f**.[a]



	ΔE_{RSE}[b]	α_O[c]	α_C[c]	β_O[c]	β_C[c]	$\Sigma_{\alpha+\beta}$	d_{O-O}[d]
IIa	87	11.1	10.0	2.6	11.8	35.5	2.611
IIb	43	7.8	6.2	2.1	6.3	22.4	2.596
IIc	40	9.5	8.2	2.5	0.9	21.1	2.601
IId	35	7.5	6.7	2.2	5.7	22.1	2.596
IIe	17	6.0	4.4	2.1	2.8	15.3	2.582
IIf	13	4.2	3.0	2.3	4.7	14.2	2.573

[a] Angle α_O (α_C) is defined by lines L_1 and L_O (L_C). Angle β_O (β_C) is defined by line L_O (L_C) and the C1–O7 (C4–C8) bond. L_1 goes through the midpoints of C2–C6 and C3–C5. L_O (L_C) goes through the midpoints of C2–C6 (C3–C5) and C1 (C4).
[b] Ring strain energy relative to the BINOL-derived phosphoric acid in kJ mol^{-1}.
[c] Phenylene ring deformation angles in degrees.
[d] O···O distance in Å. d_{O-O} = 2.536 Å for the BINOL-derived phosphoric acid.

carried out to confirm that the reported structures are minima or transition states on the M06/6-31G(d,p) potential energy surface (Table 3).

General Methods

Semipreparative HPLC was carried out on an SiO_2 column (250×10 mm, 5 mic). ^{31}P NMR have been recorded at 202 MHz. Phosphoric acid (−)-**7e** (Ar=9-phenanthryl) has been prepared according to Scheme 2b. Quinolines **10b–f**[32] and **10g**[33] have been prepared according to reported methods.

Synthesis of (*S*)-(2-Cyano-1-phenylethyl) *N,N,N′,N′*-Tetraisopropylphosphorodiamidite (*S*)-8b

(*S*)-2-Cyano-1-phenylethanol[34] (3.90 g, 26.5 mmol) was dissolved in dry diethyl ether (50 mL), treated with anhydrous triethylamine (4.06 mL, 29.2 mmol) and cooled to 0 °C. A solution of bis(diisopropylamino)chlorophosphine (7.50 g, 26.5 mmol) in dry ether (30 mL) was added dropwise, the mixture was allowed to warm to room temperature and stirred overnight. The white solid was filtered off, the solution was evaporated under reduced pressure. The final product was purified by filtration on a short silica gel column with heptane/ethyl acetate/Et_3N 70:29:1 as the eluent to furnish (*S*)-**8b** as a white solid. ^{31}P NMR ($CDCl_3$): $\delta=114$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.41$ (d, $J=7.8$ Hz, 2H), 7.36 (t, $J=7.8$ Hz, 2H), 7.31 (t, $J=7.8$ Hz, 1H), 4.85 (dt, $J=11.4$, 6 Hz, 1H), 3.6 (m, 2H), 3.5 (m, 2H), 2.85 (ddd, $J=16.3$, 6.2 Hz, 1H), 2.78 (dd, $J=16.3$, 5.0 Hz, 1H), 1.27 (d, $J=6.8$ Hz, 6H), 1.19 (d, $J=6.8$ Hz, 6H), 1.14 (d, $J=6.8$ Hz, 6H), 1.03 (d, $J=6.8$ Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=141.1$ (C), 128.5 (CH), 128.3 (CH), 126.2 (CH), 117.3 (CN), 71.3 (d, $J=18.6$ Hz, CH), 45.2 (d, $J=13.1$ Hz, CH), 44.8 (d, $J=13.1$ Hz, CH), 28.6 (d, $J=4.4$ Hz, CH_2), 24.7 (CH_3), 24.6 (CH_3), 24.5 (CH_3), 24.4 (CH_3), 24.3 (CH_3); HR-MS (ESI): $m/z=396.2809$, calcd. for $C_{21}H_{36}N_3OP$ $[M+H_2O+H]^+$: 396.2780; $[\alpha]_D^{20}$: +60 ($c=1$, $CHCl_3$).

Representative Procedures for the Synthesis of the Phosphoric Acids 7: Phosphoric Acid 7a (Ar=Ph)

(a) Phosphites 5a,a′: To a solution of 1,1′-bis-(4-hydroxy-3-phenyl-1-phenyl)ferrocene **3a**[11] (261 mg, 0.50 mmol) and 1*H*-tetrazole (147 mg, 2.00 mmol, 4 equiv.) in anhydrous DCM (25 mL) was added dropwise *via* cannula a solution of [(*S*)-2-cyanoethyl-1-phenyl] *N,N,N′,N′*-tetraisopropylphosphorodiamidite (*S*)-**8b** (226 mg, 0.60 mmol, 1.2 equiv.) in anhydrous DCM (5 mL). The flask was then equipped with a reflux condenser and the mixture was heated at 40 °C for 3 h. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (20 mL) and extracted twice with DCM (2×20 mL). The organic phase was dried over $MgSO_4$ and the solvents were removed under reduced pressure. Purification by flash chromatography on silica gel (eluent: heptane/EtOAc 9:1) gave the desired macrocyclic phosphites **5a,a′** in a 1:1 ratio, as an orange solid; yield: 146 mg (42%). $R_f=0.6$ (heptane/EtOAc 7:3). ^{31}P NMR ($CDCl_3$): $\delta=131.2$ and 130.9; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.60$–7.25 (m, 14H), 7.14–7.08 (m, 1H), 6.92–6.80 (m, 2H), 6.61–6.53 (m, 1H), 6.44–6.15 (m, 3H), 5.46–5.32 (m, 1H), 4.54 (bs, 1H), 4.50 (bs, 3H), 4.39 (bs, 2H), 4.35 (bs, 2H), 2.81–2.60 (m, 2H); HR-MS (ESI): $m/z=698.1486$, calcd. for $C_{43}H_{32}FeNO_3P$ $[M+H]^+$: 698.1547.

(b) Phosphates 6a, 6a′: A mixture of phosphites **5a,a′** (140 mg, 0.20 mmol) was dissolved in DCM (6 mL). TBHP (5.5 M in decane, 110 μL, 0.60 mmol) was added to the solution at 0 °C. Then the reaction mixture was allowed to warm to room temperature and stirred for 45 min. The reaction was treated with saturated aqueous $Na_2S_2O_3$. The layers were separated, the organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel (heptane/EtOAc 7:3, $R_f=0.2$) to afford a mixture of **6a,a′** as an orange solid; yield: 140 mg (98%). The mixture was separated by semipreparative HPLC, with heptane./toluene/THF 35:70:5. Retention times: **6a**, 21 min; **6a′**, 24 min.

6a: ^{31}P NMR ($CDCl_3$): $\delta=-15$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.54$ (m, 2H), 7.5–7.4 (m, 7H), 7.40 (t, $J=7.3$ Hz, 1H), 7.3 (m, 3H), 7.14 (m, 2H), 6.98 (bs, 2H), 6.86 (d, $J=8.6$ Hz, 1H), 6.34 (dd, $J=8.6$, 2.3 Hz, 1H), 6.27 (dd, $J=8.3$, 2.3 Hz, 1H), 6.17 (d, $J=8.3$ Hz, 1H), 5.32 (dt, $J_{H,P}=6.9$, $J=6.2$ Hz, 1H), 4.62 (s, 1H), 4.59 (s, 1H), 4.53 (s, 1H), 4.48 (s, 1H), 4.40 (s, 2H), 4.37 (s, 2H), 2.83 (d, $J=6.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=146.8$ (d, $J=6.4$ Hz, C), 145.9 (d, $J=8.6$ Hz, C), 137.2 (C), 136.5 (C), 133.9 (C), 132.4 (d, $J=7.5$ Hz, C), 131.3 (C), 130.5 (C), 129.6 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.2 (CH), 126.2 (CH), 125.6 (CH), 122.4 (CH), 120.1 (CH), 115.5 (CN), 85.8 (C), 76.6 (d, $J=6.6$ Hz, CH), 69.9 (CH), 69.8 (CH), 69.3 (CH), 66.6 (CH), 66.5 (CH), 65.6 (CH), 65.4 (CH), 27.6 (d, $J=8.8$ Hz, CH_2). IR: $\nu_{max}=3031$, 3057, 2961, 2925, 1732, 1599, 1574, 1512, 1495, 1457, 1412, 1303, 1261, 1211, 1055, 1036, 1022, 930 cm^{-1}; HR-MS (ESI): $m/z=714.1487$, calcd. for $C_{43}H_{33}FeNO_4P$ $[M+H]^+$: 714.1497; $[\alpha]_D^{20}$: +877 ($c=1$, $CHCl_3$).

6a′: ^{31}P NMR ($CDCl_3$): $\delta=-15$; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.6$–7.3 (m, 13H), 7.3–7.2 (m, 3H), 6.99 (bs, 2H), 6.62 (d, $J=8.5$ Hz, 1H), 6.34 (d, $J=8.5$ Hz, 1H), 6.26 (dd, $J=8.5$, 1.5 Hz, 1H), 6.22 (dd, $J=8.5$, 1.7 Hz, 1H), 5.50 (m, 1H), 4.61 (bs, 2H), 4.50 (bs, 2H), 4.40 (bs, 2H), 4.38 (bs, 2H), 2.67 (dd, $J=16.5$, 4.8 Hz, 1H), 2.46 (dd, $J=16.5$, 7.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=146.6$ (C), 146.5 (C), 137.5 (C), 136.9 (C), 136.4 (C), 133.1 (C), 132.6 (C), 131.1 (C), 130.8 (C), 129.8 (CH), 129.5 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.0 (CH), 127.7 (CH), 126.4 (CH), 125.9 (CH), 125.4 (CH), 122.0 (CH), 120.5 (CH), 115.6 (CN), 85.8 (C), 76.2 (d, $J=5.4$ Hz, CH), 69.9 (CH), 69.3 (CH), 66.7 (CH), 66.6 (CH), 65.6 (CH), 65.5 (CH), 26.7 (d, $J=6.5$ Hz, CH_2). IR: $\nu_{max}=3056$, 3031, 2926, 2854, 1732, 1600, 1574, 1512, 1495, 1457, 1412, 1294, 1262, 1211, 1129, 1037, 1014, 973, 936, 822 cm^{-1}; HR-MS (ESI): $m/z=714.1498$, calcd. for $C_{43}H_{33}FeNO_4P$ $[M+H]^+$: 714.1497. $[\alpha]_D^{20}$: −871 ($c=1$, $CHCl_3$).

(c) Phosphoric acid (*R*)-7a: Phosphate (*R*)-**6a** (45 mg, 0.06 mmol) was dissolved in DCM (2 mL) and DBU (19 μL, 0.12 mmol) was added at room temperature. After 30 min, the mixture was purified by column chromatography with a DCM/MeOH gradient (100:0 to 90:10; $R_f=0.2$). The crude **6a**·DBU salt was diluted in DCM (10 mL) and treated with HCl 6N (3×10 mL). The layers were separated and the organic layer was concentrated under vacuum to afford the chiral phosphoric acid (*R*)-**7a**;[11] yield: 35 mg (95%). $[\alpha]_D^{20}$:

+931 ($c=1$, $CHCl_3$). The enantiomeric excess of the acids was measured by HPLC on an ID column.

Phosphoric acid 7b (Ar = (5′-*meta*-Terphenyl)

(a) Phosphites 5b,b′: Obtained from **3b**[11] as a 6:4 mixture of isomers; yield: 39% yield; $R_f=0.7$ in heptane/EtOAc 7:3. ^{31}P NMR ($CDCl_3$): $\delta=133$ and 131; HR-MS (ESI): $m/z=$ 1002.2784, calcd. for $C_{67}H_{49}FeNO_3P$ $[M+H]^+$: 1002.2799.

(b) Phosphates 6b, 6b′: Separated on a CombiFlash® system using a silica gel column. Eluents: toluene/heptane/THF gradient from 65:35:0 to 65:35:1.5. $R_f=0.41$ for **6b** (major) and 0.38/for **6b′** (toluene/heptane/THF = 6:3.5:1).

6b: ^{31}P NMR ($CDCl_3$): $\delta=-15$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.93$ (bs, 1H), 7.8–7.6 (m, 13H), 7.6–7.3 (m, 12H), 7.2–7.0 (m, 8H), 6.39 (d, $J=8.5$ Hz, 1H), 6.33 (bs, 2H), 5.35 (m, 1H), 4.63 (s, 1H), 4.60 (s, 1H), 4.54 (s, 1H), 4.51 (s, 1H), 4.39 (s, 2H), 4.36 (s, 2H), 2.64 (dd, $J=16.0$, 6.0 Hz, 1H), 2.53 (dd, $J=16.0$, 6.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=147.0$ (d, $J=6.9$ Hz, C), 145.9 (d, $J=$ 9.5 Hz, C), 142.5 (C), 142.1 (C), 141.4 (C), 140.7 (C), 138.3 (C), 138.1 (C), 136.3 (C), 133.5 (C), 132.1 (d, $J=6.5$ Hz, C), 131.5 (C), 130.9 (C), 129.5 (CH), 129.3 (CH), 129.0 (CH),128.9 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 126.2 (CH), 126.1 (CH), 125.9 (CH), 122.5 (CH), 120.5 (CH), 115.3 (CN), 85.9 (C), 85.8 (C), 76.8 (CH), 70.0 (CH), 69.3 (CH), 67.0 (CH), 66.8 (CH), 65.7 (CH), 65.5 (CH), 27.2 (d, $J_{P,C}=$ 7.2 Hz, CH_2); IR : $\nu_{max}=3058$, 2955, 2924, 2854, 1716, 1684, 1595, 1512, 1498, 1455, 1414, 1302, 1267, 1231, 1205, 1183, 1136, 1078, 1035, 934, 877 cm^{-1}; HR-MS (ESI): $m/z=$ 1018.2766, calcd. for $C_{67}H_{49}FeNO_4P$ $[M+H]^+$: 1018.2749; $[\alpha]_D^{20}$: +918 ($c=1$, $CHCl_3$).

6b′: ^{31}P NMR ($CDCl_3$): $\delta=-15$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.08$ (bs, 1H), 7.9–7.7 (m, 13H), 7.7–7.4 (m, 12H), 7.3–7.2 (m, 7H), 6.88 (d, $J=8.5$ Hz, 1H), 6.46 (d, $J=$ 8.5 Hz, 1H), 6.42 (d, $J=8.5$ Hz, 1H), 6.34 (d, $J=8.5$ Hz, 1H), 5.69 (m, 1H), 4.73 (s, 1H), 4.71 (s, 1H), 4.61 (s, 1H), 4.59 (s, 1H), 4.50 (s, 2H), 4.48 (s, 2H), 2.80 (dd, $J=16.5$, 4.7 Hz, 1H), 2.52 (dd, $J=16.5$, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=146.8$ (d, $J=9.9$ Hz, C), 146.6 (d, $J=$ 9.7 Hz, C), 142.6 (C), 142.4 (C), 141.3 (C), 140.7 (C), 138.5 (C), 137.8 (C), 136.0 (d, $J=4.8$ Hz, C), 132.7 (d, $J=6.7$ Hz, C), 132.4 (d, $J=4.6$ Hz, C), 131.5 (C), 131.0 (C), 129.8 (CH), 129.4 (CH), 129.1 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 126.5 (CH), 126.2 (CH), 126.1 (CH), 125.7 (CH), 122.3 (CH), 120.4 (CH), 115.2 (CN), 85.7 (C), 85.6 (C), 76.2 (d, $J=4.9$ Hz, CH), 70.0 (CH), 69.4 (CH), 66.9 (CH), 66.7 (CH), 65.6 (CH), 26.3 (d, $J=$ 5.6 Hz, CH_2); IR: $\nu_{max}=3035$, 2926, 2855, 1595, 1513, 1456, 1414, 1297, 1232, 1206, 1036, 1009, 966, 937, 877 cm^{-1}; HR-MS (ESI): $m/z=1018.2745$, calcd. for $C_{67}H_{49}FeNO_4P$ $[M+H]^+$: 1018.2749; $[\alpha]_D^{20}$: −710 ($c=1$, $CHCl_3$).

(c) Phosphoric acid (*R*)-7b: Obtained from (*R*)-**6b** (81 mg); yield: 53 mg (67%). ^{31}P (DMSO-d_6): δ −12; $[\alpha]_D$: +775 ($c=1$, CH_2Cl_2); HPLC: ID column, THF/heptane/TFA/Et_3N 60:40:0.5:0.3.

Phosphoric Acid 7c (Ar = *para*-Biphenyl)

(a) Phosphites 5c,c′: Obtained from **3c**[11] as a 1:1 mixture of isomers; yield: 44%; $R_f=0.5$ in heptane/EtOAc 7:3. ^{31}P NMR ($CDCl_3$): $\delta=132$ and 131; HRMS (ESI): $m/z=$ 850.2173, calcd. for $C_{55}H_{40}FeNO_3P$ $[M+H]^+$: found: 850.2178. The starting diol **3c** has been prepared according to path (a) in Scheme 2 (see the Supporting Information).

(b) Phosphates 6c, 6c′: Separated on a CombiFlash® system using a silica gel column. Eluents: toluene/heptane/THF gradient from 60:30:0 to 60:30:2; $R_f=0.39$ for **6c** and 0.34 for **6c′** (toluene/heptane/THF = 6:3:1).

6c: ^{31}P NMR ($CDCl_3$): $\delta=-15$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.8$–7.6 (m, 8H), 7.6–7.3 (m, 13H), 7.1 (m, 2H), 7.04 (bs, 2H), 6.89 (d, $J=8.4$ Hz, 1H), 6.34 (d, $J=8.4$ Hz, 1H), 6.27 (bs, 2H), 5.47 (m, 1H), 4.66 (bs, 2H), 4.58 (bs, 1H), 4.54 (bs, 1H), 4.44 (bs, 2H), 4.42 (bs, 2H), 2.87 (d, $J=$ 5.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=147.0$ (d, $J=$ 7.3 Hz, C), 146.2 (d, $J=10.5$ Hz, C), 141.0 (C), 140.9 (C), 140.7 (C), 140.6 (C), 136.6 (C), 136.3 (C), 136.2 (C), 133.4 (C), 131.9 (d, $J=7.9$ Hz, C), 132.0 (C), 131.9 (C), 130.1 (CH), 129.7 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 126.2 (CH), 125.9 (CH), 122.3 (CH), 120.4 (CH), 115.6 (CN), 86.5 (C), 86.4 (C), 76.7 (C), 70.1 (CH), 69.5 (CH), 66.9 (CH), 66.7 (CH), 65.8 (CH), 65.7 (CH), 27.6 (d, $J=7.3$ Hz, CH_2). IR: $\nu_{max}=3032$, 2967, 2926, 2855, 1601, 1508, 1488, 1458, 1399, 1367, 1304, 1258, 1212, 1185, 1128, 1055, 1034, 1022, 978, 934, 842, 768 cm^{-1}; HR-MS (ESI): $m/z=866.2188$, calcd. for $C_{55}H_{40}FeNO_4P$ $[M+H]^+$: 866.2123; $[\alpha]_D^{20}$: +1151 ($c=0.5$, $CHCl_3$).

6c′: ^{31}P NMR ($CDCl_3$): $\delta=-15$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.8$–7.6 (m, 9H), 7.6–7.3 (m, 11H), 7.2 (m, 2H), 7.07 (bs, 2H), 6.68 (d, $J=8.0$ Hz, 1H), 6.43 (d, $J=8.0$ Hz, 1H), 6.31 (dd, $J=8.0$, 2.1 Hz, 1H), 6.27 (dd, $J=8.0$, 2.1 Hz, 1H), 5.56 (m, 1H), 4.67 (s, 2H), 4.55 (s, 2H), 4.45 (s, 2H), 4.43 (s, 2H), 2.70 (dd, $J=16.5$, 4.8 Hz, 1H), 2.51 (dd, $J=$ 16.5, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=147.2$ (d, $J=9.6$ Hz, C), 147.0 (d, $J=10.3$ Hz, C), 141.4 (C), 141.3 (C), 141.2 (C), 140.9 (C), 136.9 (C), 136.3 (C), 133.2 (d, $J=$ 6.9 Hz, C), 132.7 (d, $J=6.0$ Hz, C), 131.7 (C), 131.4 (C), 130.4 (CH), 130.2 (CH), 130.1 (CH), 129.7 (CH), 129.5 (CH), 129.4 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 126.8 (CH), 126.4 (CH), 126.0 (CH), 122.6 (CH), 120.9 (CH), 116.0 (CN), 86.5 (C), 86.4 (C), 76.8 (d, $J=5.5$ Hz, CH), 70.5 (CH), 69.9 (CH), 67.2 (CH), 67.1 (CH), 66.1 (CH), 27.2 (d, $J=7.7$ Hz, CH_2). IR: $\nu_{max}=3030$, 2925, 2853, 1730, 1600, 1508, 1488, 1457, 1294, 1254, 1211, 1184, 1130, 1034, 1007, 971, 934, 840, 820 cm^{-1}; HR-MS (ESI): $m/z=866.2147$, calcd. for $C_{55}H_{40}FeNO_4P$ $[M+H]^+$: 866.2123; $[\alpha]_D^{20}$: −1138 ($c=0.5$, $CHCl_3$).

An *S*-planar configuration has been assigned to compound **6c′** by X-ray diffraction studies: CCDC 951975 contains the corresponding crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

(c) Phosphoric acid (*R*)-7c: Obtained from (*R*)-**6c** (25 mg); yield: 7 mg (33%). ^{31}P NMR (DMSO-d_6): $\delta=-12$; ^{1}H NMR (600 MHz DMSO-d_6): $\delta=7.78$ (d, $J=8.0$ Hz, 4H), 7.77 (d, $J=7.3$ Hz, 4H), 7.69 (d, $J=8.0$ Hz, 4H), 7.51 (t, $J=$ 7.3 Hz, 4H), 7.40 (t, $J=7.3$ Hz, 2H), 7.09 (bs, 2H), 6.62 (d, $J=8.5$ Hz, 2H), 6.50 (d, $J=8.5$ Hz, 2H), 4.86 (s, 2H), 4.74 (s, 2H), 4.45 (s, 2H), 4.41 (s, 2H); ^{13}C NMR (150.7 MHz, DMSO-d_6): $\delta=146.8$ (d, $J_{P,C}=5.6$ Hz, C), 139.9 (C), 138.7 (C), 137.0 (C), 131.6 (d, $J_{P,C}=5.2$ Hz, C), 129.8 (CH), 129.5 (C), 129.0 (CH), 127.5 (CH), 127.1 (CH), 126.7 (CH), 126.5

(CH), 126.0 (CH), 121.2 (CH), 86.0 (C), 69.3 (CH), 68.7 (CH), 66.6 (CH), 65.5 (CH); IR: ν_{max} = 3029, 2923, 2852, 1600, 1507, 1488, 1457, 1398, 1379, 1259, 1216, 1190, 1089, 1017, 1007, 911, 838 cm^{-1}; HR-MS (ESI): *m/z* = 736.1485, calcd. for $C_{46}H_{33}FeO_4P$: 736.1466; $[\alpha]_D^{20}$: +966 (*c* = 0.7, $CHCl_3$).

Phosphoric Acid 7d [Ar = 3,5-Bis(trifluoromethyl)-phenyl]

(a) Phosphites 5d,d′: Obtained from **3d**[11] as a 7:3 mixture of isomers; yield: 20%; R_f = 0.7 in heptane/EtOAc 7:3. ^{31}P NMR ($CDCl_3$): δ = 136 and 133; HR-MS (ESI): *m/z* = 970.1098, calcd. for $C_{47}H_{28}F_{12}FeNO_3P$ $[M+H]^+$: 970.1043. The starting diol **3d** has been prepared according to path (b) in Scheme 2 (see the Supporting Information).

(b) Phosphates 6d, 6d′: Separated on a CombiFlash® system using a silica gel column, eluents: toluene/heptane/THF gradient from 70:30:0 to 70:30:1; R_f = 0.38 for **6d** (major) and 0.34 for **6d′** (toluene/heptane/THF = 7:3:1).

6d: ^{31}P NMR ($CDCl_3$): δ = −12; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −62.5 and −62.6; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.98 (s, 3H), 7.96 (s, 2H), 7.41 (m, 3H), 7.24 (m, 2H), 7.01 (bs, 2H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.46 (d, *J* = 8.7 Hz, 1H), 6.35 (d, *J* = 8.5 Hz, 1H), 6.23 (d, *J* = 8.53 Hz, 1H), 5.56 (q, *J* = 6.5 Hz, 1H), 4.67 (s, 1H), 4.66 (s, 1H), 4.64 (s, 1H), 4.57 (s, 1H), 4.51 (s, 2H), 4.47 (s, 1H), 2.96 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 146.6 (d, $J_{P,C}$ = 5.6 Hz, C), 145.2 (d, $J_{P,C}$ = 8.7 Hz, C), 139.4 (C), 138.8 (C), 136.1 (C), 136.0 (C), 132.3 (q, $J_{F,C}$ = 33.9 Hz, C), 132.7 (C), 132.0 (q, $J_{F,C}$ = 33.6 Hz, C), 131.6 (C), 131.2 (C), 129.9 (CH), 129.3 (CH), 129.2 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 127.0 (CH), 125.7 (CH), 123.6 (q, $J_{F,C}$ = 273.0 Hz, CF_3), 123.5 (q, $J_{F,C}$ = 273.0 Hz, CF_3), 123.3 (CH), 121.8 (CH), 120.0 (CH), 115.1 (CN), 85.3 (C), 85.2 (C), 77.0 (d, $J_{P,C}$ = 3.9 Hz, C), 70.4 (CH), 69.7 (CH), 67.4 (CH), 67.1 (CH), 65.7 (CH), 65.5 (CH), 27.5 (d, $J_{P,C}$ = 7.7 Hz, CH_2); IR: ν_{max} = 3089, 2929, 1723, 1621, 1604, 1514, 1457, 1414, 1373, 1277, 1179, 1130, 1052, 1037, 1016, 931, 900 cm^{-1}; HR-MS (ESI): *m/z* = 986.1035, calcd. for $C_{47}H_{28}F_{12}FeNO_4P$ $[M+H]^+$: 986.0992. $[\alpha]_D^{20}$: +722 (*c* = 1, $CHCl_3$).

6d′: ^{31}P NMR ($CDCl_3$): δ = −12.2; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −62.57 and −62.53; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (s, 2H), 7.98 (s, 1H), 7.88 (s, 1H), 7.80 (s, 2H), 7.43–7.38 (m, 3H), 7.35–7.30 (m, 2H), 7.02 (s, 1H), 6.96 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.43 (d, *J* = 8.7 Hz, 1H), 6.29 (d, *J* = 8.8 Hz, 1H), 6.21 (d, *J* = 8.8 Hz, 1H), 5.67 (q, *J* = 6.6 Hz, 1H), 4.65 (s, 1H), 4.61 (s, 2H), 4.52 (s, 1H), 4.47 (s, 2H), 4.44 (s, 2H), 2.94 (dd, *J* = 16.7, 6.2 Hz, 1H), 2.84 (dd, *J* = 16.7, 6.2 Hz, 1H): ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 146.6 (d, $J_{P,C}$ = 5.6 Hz, C), 145.4 (d, $J_{P,C}$ = 8.7 Hz, C), 139.3 (C), 138.8 (C), 136.1 (C), 136.0 (C), 132.7 (C), 132.3 (q, $J_{F,C}$ = 33.3 Hz, C), 132.0 (q, $J_{F,C}$ = 33.3 Hz, C), 131.7 (C), 131.2 (C), 131.1 (C), 130.1 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 127.7 (CH), 127.2 (CH), 127.0 (CH), 126.1 (CH), 125.3 (C), 123.1 (CH), 121.8 (CH), 121.7 (CH), 120.2 (CH), 115.1 (CN), 85.3 (C), 85.2 (C), 76.7 (d, $J_{P,C}$ = 3.3 Hz, C), 70.5 (CH), 70.4 (CH), 69.8 (CH), 67.3 (CH), 67.1 (CH), 65.7 (CH), 65.6 (CH), 27.0 (d, $J_{P,C}$ = 6.3 Hz, CH_2); IR: ν_{max} = 3089, 2931, 1719, 1620, 1604, 1514, 1457, 1413, 1373, 1277, 1180, 1130, 1051, 1037, 1015, 934, 900 cm^{-1}; $[\alpha]_D^{20}$: −737 (*c* = 1, $CHCl_3$).

General Procedure for the Synthesis of the Hantzsch Esters 9d–f[27]

Paraformaldehyde (1 equiv.), ammonium acetate (2 equiv.), and the desired acetoacetate $MeCOCH_2CO_2R$ (2 equiv.) were refluxed under argon for 2 h under strong agitation. After cooling, the product was recrystallized from ethanol. **9d** is a known product.[27]

Bis-(4-methoxybenzyl) 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (9e): ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.37 (bs, 1H), 7.27 (d, *J* = 8.5 Hz, 4H), 6.90 (d, *J* = 8.5 Hz, 4H), 5.01 (s, 4H), 3.75 (s, 6H), 3.16 (s, 2H), 2.11 (s, 6H).

Bis-(4-benzyloxybenzyl) 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (9f): ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.38 (bs, 1H), 7.44–7.29 (m, 14H), 6.98 (d, *J* = 8.4 Hz, 4H), 5.09 (s, 4H), 5.01 (s, 4H), 3.75 (s, 6H), 3.16 (s, 2H), 2.11 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.9 (CO), 158.0 (C), 147.0 (C), 137.0 (C), 129.4 (CH), 129.1 (C), 128.4 (CH), 127.8 (CH), 127.6 (CH) 114.6 (CH), 96.9 (C), 69.2 (CH_2), 64.4 (CH_2), 24.7 (CH_2), 18.0 (CH_3); HR-MS (ESI): *m/z* = 590.2524, calcd. for $C_{37}H_{36}NO_6$ $[M+H]^+$: 590.2543.

Representative Procedure for the Catalytic Reduction of α-Arylquinolines

A solution of 2-phenylquinoline **10a** (11 mg, 0.05 mmol), Hantzsch dihydropyridine **9a** (0.12 mmol) and the acid catalyst **7a** (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 (11a): Obtained as a colorless oil. The *ee*s were determined by HPLC using a CHIRALPAK® IB column, eluent: *i*-PrOH/*n*-heptane 5:95, at a flow rate of 1 mL min^{-1} [detection at 275 nm]: retention times of 6.7 min for (−)-(*S*)-**11a** and 8.2 min (+)-(*R*)-**11a**; {Lit.[23] (*S*)-**11a:** $[\alpha]_D^{20}$: −35.7 (*c* = 0.8, $CHCl_3$)}.

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (11b): CHIRALPAK® IB, eluent: *i*-PrOH/*n*-heptane, 5:95 at a flow rate of 1 mL min^{-1} [detection at 250 nm]: retention times of 7.7 min [(−)-(*S*)-**11b**] and 17.9 min [(+)-(*R*)-**11b**]; {Lit.[23] (*S*)-**11b:** $[\alpha]_D^{20}$: −26.1 (*c* = 1, $CHCl_3$), 86% *ee*}.

2-(2-Naphthyl)-1,2,3,4-tetrahydroquinoline (11c): CHIRALPAK® IB, eluent: *i*-PrOH/*n*-heptane, 5:95 at a flow rate of 1 mL min^{-1} [detection at 250 nm]: retention times of 9.6 min [(−)-(*S*)-**11c**] and 15.5 min [(+)-(*R*)-**11c**]; {Lit.[23] (*S*)-**11c:** $[\alpha]_D^{20}$: −27.5 (*c* = 1, $CHCl_3$), 91% *ee*].

2-(*para*-Biphenyl)-1,2,3,4-tetrahydroquinoline (11d): CHIRALPAK® IB, eluent: *i*-PrOH/*n*-heptane, 5:95 at a flow rate of 1 mL min^{-1} [detection at 250 nm]: retention times of 9.4 min [(−)-(*S*)-**11d**] and 17.9 min [(+)-(*R*)-**11d**]; {Lit.[21a] (*S*)-**11d:** $[\alpha]_D^{20}$: −13.8 (*c* = 1, $CHCl_3$), >99% *ee*}.

2-[3,5-Bis(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroquinoline (11e): CHIRALPAK® IB, eluent: *i*-PrOH/*n*-heptane, 5:95 at a flow rate of 1 mL min^{-1} [detection at 250 nm]: retention times of 8.4 min [(−)-**11e**] and 17.2 min [(+)-**11e**].

2-(1-Naphthyl)-1,2,3,4-tetrahydroquinoline (11f): CHIRALPAK® IB, Eluent: *i*-PrOH/*n*-heptane, 5:95 at a flow rate of 1 mL min^{-1} [detection at 250 nm]: retention times of 10.7 min [(−)-(*S*)-**11f**] and 18.1 min [(+)-(*R*)-**11f**]; {Lit.[28] (*R*)-**11c:** $[\alpha]_D^{20}$: +117 (*c* = 1, $CHCl_3$), 88% *ee*}.

2-(1-Cyclohexyl)-1,2,3,4-tetrahydroquinoline (11g):[21b] CHIRALPAK® IC, eluent: *i*-PrOH/*n*-heptane, 2:98 at

a flow rate of 1 mL min^{-1} [detection at 250 nm]: retention times of 4.4 min [(+)-(*S*)-**11g**] and 4.7 min [(−)-(*R*)-**11g**]; {Lit.[29] (*S*)-**11g:** $[\alpha]_D^{20}$: +48.3 (*c* = 0.1, $CHCl_3$), 96% *ee*}.

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