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Jérémy Stemper, Kevin Isaac, Véronique Duret, Pascal Retailleau, Arnaud Voituriez, et al.. [3,3]Paracyclophanes as planar chiral scaffolds for the synthesis of new phosphoric acids.. Chemical Communications, 2013, 49 (54), pp.6084-6086. 10.1039/c3cc41496e . hal-00852762

HAL Id: hal-00852762

<https://hal.science/hal-00852762>

Submitted on 2 Sep 2022

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[3,3]Paracyclophanes as Planar Chiral Scaffolds for the Synthesis of New Phosphoric Acids.

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Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX
DOI: 10.1039/b000000x

Cyclic phosphoric acids displaying C₂-symmetric planar chiral paracyclophane structures which include a 1,1'-ferrocendiyl unit, have been designed as a new class of chiral organocatalysts. Their synthesis, optical resolution, structural characterization as well as preliminary catalytic tests are reported.

Optically active BINOLs have demonstrated to be privileged chiral scaffolds for the development of chiral phosphorus auxiliaries including Br  nsted acids¹ and chiral anions,² as well as of phosphoramidites,³ phosphonites⁴ and phosphite⁵ ligands for organo- and/or organometallic processes. The use of BINOLs has been complemented recently by the development of alternative chiral diols including VAPOL,⁶ H₈-BINOL,⁷ SPINOL,⁸ TADDOL⁹ and others¹⁰ for the same applications.

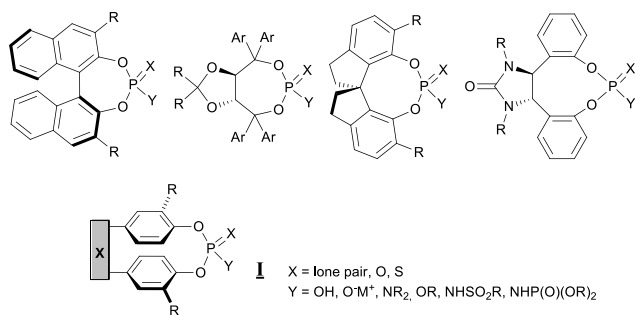
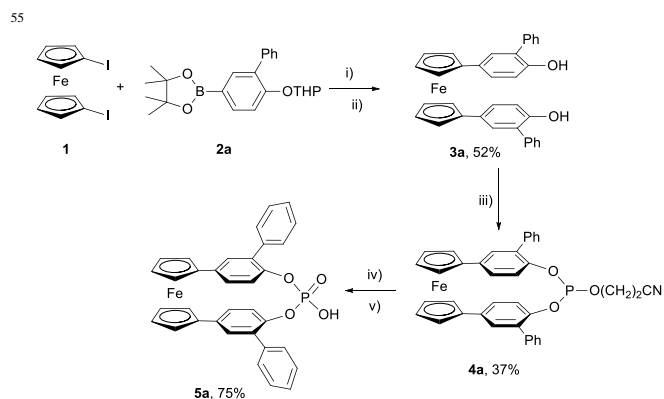


Figure 1. Phosphorus catalysts and ligands embedding chiral diol units and the targeted paracyclophanes (**I**).

All these diols are C₂-symmetrical species displaying either axial or central chirality, while diols with planar chirality have been barely investigated so far for analogous purposes.¹¹ We intend to disclose here the design of an alternative, structurally distinct diol framework allowing the synthesis of the first phosphoric acids based on C₂-symmetric planar chiral paracyclophane scaffolds.¹²

Aim of this study is to investigate the availability of [3,3]paracyclophanes in which one of the chains tethering the aromatic rings is a three atom O-P-O sequence, as sketched in Figure 1 above (**I**).¹³ Planar chirality would be generated by adding *pseudo-meta*¹⁴ substituents, R, on the aryl rings which constitute the paracyclophane scaffold. The first challenge of this work was to identify a suitable tethering chain, X, that would minimize ring strain while ensuring configurational stability to the planar chiral paracyclophane structure.¹⁵ As the tethering chains, we have considered at first the three-atom chains CH₂-

N(Ts)-CH₂, 1,8-naphthalendiyl and CH₂-S-CH₂, that are currently used in the synthesis of [3,3]- or [2,3]-paracyclophanes.¹⁶ None of these linkers allowed the desired phosphorus macrocycles to be isolated from the corresponding bis-phenols. Later on, based on theoretical evaluations of ring strain in paracyclophanes of this class,¹⁷ we envisioned bridging the aromatic rings of **I** by a 1,1'-ferrocendiyl unit, a slightly bigger and more flexible three atom scaffold.¹⁸ This design proved appropriate, since the desired phosphoric acid **5a** could be accessed easily by the reaction sequence in Scheme 1.



Scheme 1. Reagents and conditions: i) PdCl₂(SPhos)₂ (5 mol%), Ba(OH)₂·8H₂O (4 equiv.), dioxane, 100  C, 24h; ii) MeOH, PTSA (cat); iii) (Prⁱ₂N)₂PO(CH₂)₂CN, 1H-tetrazole (4 equiv.), CH₂Cl₂, rt, 4h; iv) tBuOOH, 3 equiv. CH₂Cl₂, 0  C to rt, 30 min; v) DBU (2 equiv.), CH₂Cl₂, rt, 30 min.

Diiodoferrocene **1** was subjected to a Suzuki coupling with the 1,1'-biphenyl-2-ol derived boronate **2a**, under palladium catalysis. Optimized conditions for the coupling reaction involve PdCl₂(SPhos)₂ as the catalyst (SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) and Ba(OH)₂·8H₂O as the base. After deprotection of the hydroxyl functions, the ferrocenic bisphenol **3a** was isolated in 52% yield over two steps. For the conversion of diol **3a** into the corresponding phosphoric acid **5a**, the most efficient procedure is a three step sequence based on the use of (Prⁱ₂N)₂PO(CH₂)₂CN as the phosphinating agent,¹⁹ oxidation of the phosphite **4a** into the corresponding phosphate and removal of the cyanoethyl substituent in basic conditions (DBU).

The macrocyclization reaction converting diol **3a** into phosphite **4a** is the crucial step, as far as the stereochemical control in favor of the *dl*-isomer is a key issue here. This step occurs actually with high diastereoselectivity, *dl*-**4a** being the only well-defined product observed in the mixture (37% isolated yield). The main side-products of the macrocyclization are oligomeric species derived from intermolecular reactions of the bifunctional reactants.

The molecular structure of the final acid **5a** has been confirmed by X-ray diffraction studies on its calcium salt (**5a**)₂.Ca.²⁰ The ORTEP diagram is given as Supporting Information. In the solid state this salt combines two phosphate units and four methanol molecules surrounding the Ca²⁺ atom. The views of the molecular structure of (**5a**)₂.Ca in Figure 2(a) show that the cyclopentadienyl rings and the aryl units have eclipsed conformations, which forces the phosphorus center to lie out of the C₂-axis of the paracyclophane scaffold. The molecule therefore lacks C₂-symmetry and displays two non-equivalent oxygen atoms. These solid state structural features strongly differentiate the paracyclophane based acid **5a** from the known chiral phosphoric acids displayed in Figure 1.

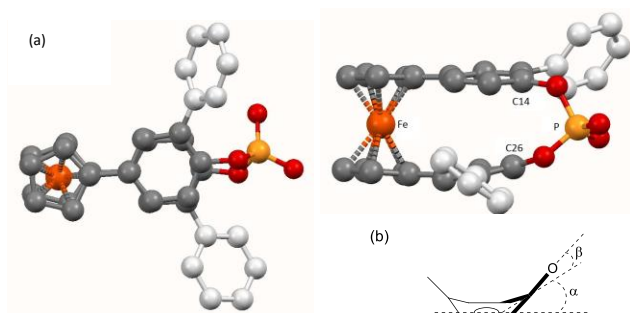
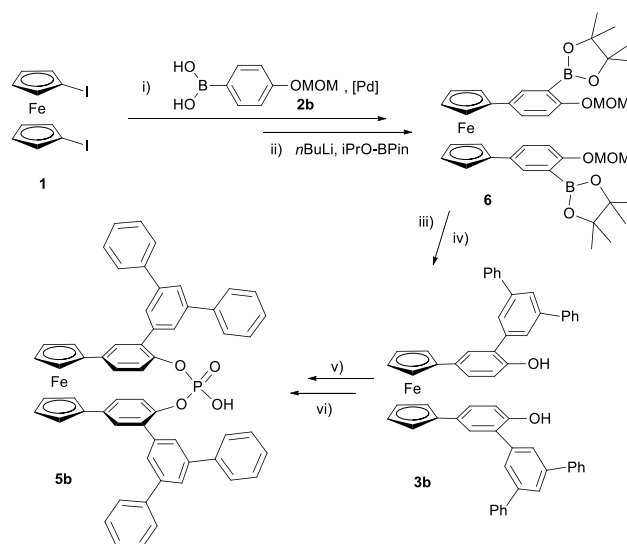


Figure 2. The paracyclophane moiety of the (**5a**)₂.Ca salt, from X-ray data (a); α and β angles used to define the deformation of the aryl ring (b).

X-ray data also show an almost parallel arrangement of the cyclopentadiene rings and a moderate curvature degree of the aryl units. The α and β angles which define the out-of-plane deformation of the aryl rings (Figure 2b)²¹ measure 7.5 and 7.8 degrees respectively (average values for α and β angles involving the C14 and C26 carbons). These values rank between those of carbon tethered [2.2]- and [3.3]-paracyclophanes,²² suggesting a non-negligible ring strain in the paracyclophane unit.

The successful synthesis of **5a** (Scheme 1) validates our design of ferrocene based, chiral phosphoric acids with paracyclophane type structures. In designing these acids we have targeted specifically paracyclophanes with aromatic substituents next to the phosphorus function, since the presence and tuning of these aryl groups are expected to play a key role in enantioselective catalytic reactions.

In order to modulate easily these aromatic substituents, we have envisioned an alternative synthetic approach by which the aromatic groups are introduced at a later step of the synthetic sequence. The method is typified in Scheme 2 by the synthesis of the terphenyl-substituted acid **5b**.



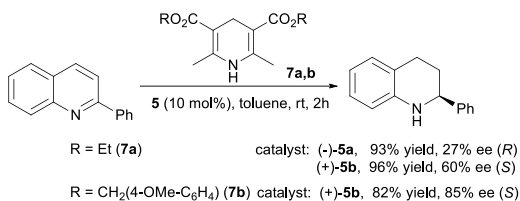
Scheme 2. Reagents and conditions: i) **2b** (3 equiv.), PdCl₂(dppf) (5 mol%), NaOH (4 equiv., DME/H₂O 4:1, 85°C, 18h, 80% yield); ii) *n*BuLi, THF, -78°C to rt, 4h; 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 equiv), rt, 15h, 89% yield (**6**); iii) 1-bromo-3,5-diphenylbenzene (2.5 equiv.), Pd(PPh₃)₄ (10%), Ba(OH)₂·8H₂O, 1,4-dioxane/H₂O 5:1, 100°C, 18h, 86%; iv) PTSA, NaI, THF/H₂O 8:2, 60°C, 18h, quantitative yield (**3b**); v) (PrⁱN)₂PO(CH₂)₂CN, 1*H*-tetrazole (4 equiv.), CH₂Cl₂, rt, 3h, 42% yield; vi) *t*BuOOH (3 equiv.), CH₂Cl₂, 0°C to rt, 30 min; DBU (2 equiv.), CH₂Cl₂, rt, 30 min, 84% yield (**5b**).

The key intermediate is the bis-pinacolborate functionalized ferrocene **6** which is obtained from diiodoferrocene by Suzuki arylation and subsequent metalation/boronation. This core platform will allow introducing various aryl substituents by Suzuki type reactions, shortly before the macrocyclization step. The Suzuki reaction has been applied here to the synthesis of the terphenyl substituted diol **3b** (86% yield) which has been converted then into the corresponding phosphoric acid *dl*-**5b** by following the same procedure as for **5a**.

The enantiomeric resolution of the new phosphoric acids *dl*-**5a,b** has been undertaken on a semi-preparative scale by chiral HPLC. Resolution of **5a** has been made very efficiently on a CHIRALPAK® ID column 60% THF/40% *n*-heptane/0.3% TEA/0.5% TFA, 4.7 mL/min. Retention times 6.4 min, for (+)-**5a** and 14.3 min for (-)-**5a**. Acid **5b** has been obtained in enantiomerically pure form under analogous conditions (CHIRALPAK® ID column with a 36% THF / 64% *n*-heptane / 0.3% TEA / 0.5% TFA mixture (4.7 mL/min): retention times 6.4 min for (+)-**5b** and 12.5 min for (-)-**5b**. The acids display very high optical rotation values, with [α]_D²⁰ = +931 (*c* = 1, CHCl₃) for (+)-**5a** and [α]_D²⁰ = +775 (*c* = 1, CH₂Cl₂) for (+)-**5b**.

To test the potential application of **5a,b** as Brønsted acid organocatalysts, we have investigated a model reaction, the asymmetric transfer hydrogenation of 2-phenylquinoline by the Hantzsch dihydropyridines **7** (Scheme 3).²³ In the reduction with **7a** (R=Et), both **5a** and **5b** display good catalytic activity, giving total conversion after 2h at r.t. in toluene, and significant enantioselectivity levels. As anticipated, the nature of the aromatic substituent in **5** modulates the enantioselectivity to a large extent, the bulkier and more extended terphenyl group of **5b**

allowing a more efficient stereocontrol (60% ee), with respect to the phenyl substituent in **5a** (27% ee). Gratifyingly, the enantioselectivity level could be improved then to an 85% ee by using the 4-methoxybenzyl ester **7b** as the reducing agent and **5b** as the catalyst.



Scheme 3. Asymmetric transfer hydrogenation of 2-phenylquinoline.

Thus, these preliminary results clearly demonstrate the potential of these new paracyclophane-based phosphoric acids in Brønsted acid organocatalysis.

Conclusions

In summary, we have found a suitable access to the first series of cyclic phosphoric acids displaying C₂-symmetric planar chiral paracyclophane scaffolds including phosphorus. The presence of ferrocene as a constitutive element of the paracyclophane core is a key structural feature ensuring satisfying chemical and configurational stability to these compounds. We have demonstrated the efficiency of the new acids as catalysts in model organocatalytic H-transfer reductions. The highly versatile synthetic approach should allow modulation and optimization of the catalytic behavior of these acids, on a case by case basis.

Beside the potential use of the new phosphoric acids as organocatalysts, this work also opens new perspectives for the synthesis of unique ligands based on the same paracyclophane scaffolds, namely chiral phosphoramidites, phosphites and others, which will be available by analogous synthetic strategies.

This work was supported by the Paris Sud University, the I.C.S.N., the Agence Nationale de la Recherche (ANR Blanc, “Chiracids”) and the COST ORCA action CM0905.

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† Electronic Supplementary Information (ESI) available: Experimental procedures and NMR spectra for the new compounds. X-ray data for (**5a**)₂Ca. See DOI: 10.1039/b000000x/

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