ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

[3,3]Paracyclophanes as planar chiral scaffolds for the synthesis of new phosphoric acids†

Cite this: *Chem. Commun.*, 2013, **49**, 6084

Received 27th February 2013,
Accepted 8th May 2013

DOI: 10.1039/c3cc41496e

www.rsc.org/chemcomm

Jérémy Stemper, Kevin Isaac, Véronique Duret, Pascal Retailleau, Arnaud Voituriez, Jean-François Betzer* and Angela Marinetti*

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

Optically active BINOLs have been demonstrated to be privileged chiral scaffolds for the development of chiral phosphorus auxiliaries including Brønsted acids[1] and chiral anions,[2] as well as of phosphoramidite,[3] phosphonite[4] and phosphite[5] 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] H_8-BINOL,[7] SPINOL,[8] TADDOL[9] and others[10] for the same applications. All these diols are C_2-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 C_2-symmetric planar chiral paracyclophane scaffolds.[12]

The 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 Fig. 1 (**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, **Z**, that would minimize ring strain while ensuring configurational stability of the planar chiral paracyclophane structure.[15] As the tethering chains, we have considered at first the three-atom chains CH_2–N(Ts)–CH_2, 1,8-naphthalenediyl and CH_2–S–CH_2, which 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 evaluation of ring strain in paracyclophanes of this class,[17] we envisioned bridging of the aromatic rings of **I** by a 1,1′-ferrocenediyl 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.

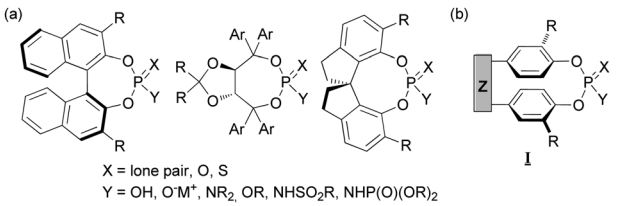
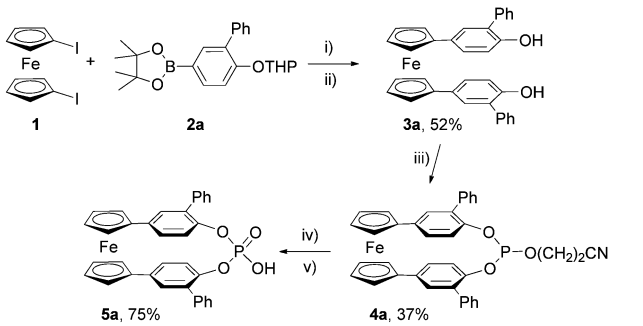


Fig. 1 (a) Phosphorus catalysts and ligands embedding chiral diol units and (b) the targeted paracyclophane derivatives **I**.

Diiodoferrocene **1** was subjected to a Suzuki coupling with the 1,1′-biphenyl-2-ol derived boronate **2a**. Optimized conditions for the coupling reaction involve $PdCl_2(SPhos)_2$ as the catalyst (SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) and $Ba(OH)_2{\cdot}8H_2O$ as the base. After deprotection of the hydroxyl functions, the ferrocenic bisphenol **3a** was isolated in 52% yield



Scheme 1 *Reagents and conditions*: (i) $PdCl_2(SPhos)_2$ (5 mol%), $Ba(OH)_2{\cdot}8H_2O$ (4 equiv.), dioxane, 100 °C, 24 h; (ii) MeOH, PTSA (cat), rt, 2 h; (iii) $(iPr_2N)_2PO(CH_2)_2CN$, 1*H*-tetrazole (4 equiv.), CH_2Cl_2, rt, 4 h; (iv) *t*BuOOH (3 equiv.), CH_2Cl_2, 0 °C to rt, 30 min, then HCl 6M; (v) DBU (2 equiv.), CH_2Cl_2, rt, 30 min.

Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Centre de Recherche de Gif, 1 av. de la Terrasse, 91198 Gif-sur-Yvette, France.
E-mail: angela.marinetti@icsn.cnrs-gif.fr, jean-françois.betzer@icsn.cnrs-gif.fr

† Electronic supplementary information (ESI) available: Experimental procedures and NMR spectra for the new compounds. X-ray data for $(\mathbf{5a})_2Ca$. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc41496e

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 $(Pr^i_2N)_2PO(CH_2)_2CN$ as the phosphinating agent,[19] oxidation of the phosphite **4a** into the corresponding phosphate and removal of the cyanoethyl substituent under basic conditions (DBU).

The macrocyclization reaction converting diol **3a** into phosphite **4a** is a crucial step, as far as stereochemical control in favor of the dl-isomer is required. 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 $(\mathbf{5a})_2{\cdot}Ca$.[20] The ORTEP diagram is given as ESI (CCDC 916122).† In the solid state this salt combines two phosphate units and four methanol molecules surrounding the Ca^{2+} atom. The views of the molecular structure of $(\mathbf{5a})_2{\cdot}Ca$ in Fig. 2a show that the cyclopentadienyl rings and the aryl units have eclipsed conformations, which force the phosphorus center to lie out of the C_2-axis of the paracyclophane scaffold. The molecule therefore lacks C_2-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 Fig. 1.

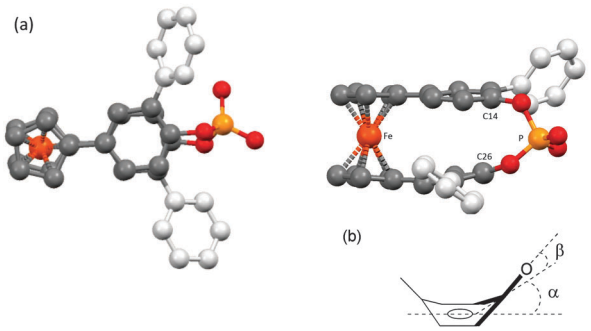
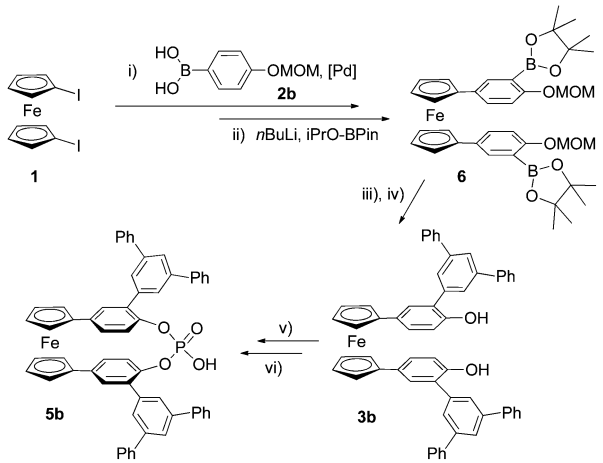


Fig. 2 The paracyclophane moiety of the $(\mathbf{5a})_2{\cdot}Ca$ salt from X-ray data (a); α and β angles used to define the deformation of the aryl ring (b).

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 (Fig. 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



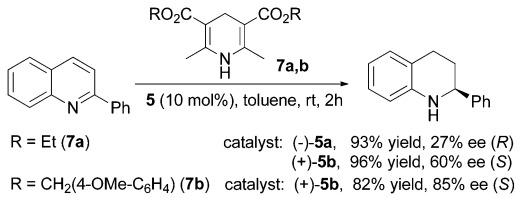
Scheme 2 *Reagents and conditions*: (i) **2b** (3 equiv.), $PdCl_2$(dppf) (5 mol%), NaOH (4 equiv.), DME/H_2O 4 : 1, 85 °C, 18 h, 80% yield; (ii) *n*BuLi, THF, −78 °C to rt, 4 h; 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 equiv.), rt, 15 h, 89% yield (**6**); (iii) 1-bromo-3,5-diphenylbenzene (2.5 equiv.), $Pd(PPh_3)_4$ (10 mol%), $Ba(OH)_2{\cdot}8H_2O$ (4 equiv.), 1,4-dioxane/H_2O 5 : 1, 100 °C, 18 h, 86%; (iv) PTSA, NaI, THF/H_2O 8 : 2, 60 °C, 18 h, quantitative yield (**3b**); (v) $(iPr_2N)_2PO(CH_2)_2CN$, 1*H*-tetrazole (4 equiv.), CH_2Cl_2, rt, 3 h, 42% yield; (vi) *t*BuOOH (3 equiv.), CH_2Cl_2, 0 °C to rt, 30 min; DBU (2 equiv.), CH_2Cl_2, rt, 30 min, then HCl 6N, 84% yield (**5b**).

aromatic groups are introduced at a later step of the synthetic sequence. The method is typified in Scheme 2 for the synthesis of the terphenyl-substituted acid **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^{-1}. Retention time is 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^{-1})): retention time is 6.4 min for (+)-**5b** and 12.5 min for (−)-**5b**. The acids display very high optical rotation values, with $[\alpha]_D^{2c}$ = +931 (c = 1, $CHCl_3$) for (+)-**5a** and $[\alpha]_D^{2c}$ = +775 (c = 1, CH_2Cl_2) 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** displayed good catalytic activity, giving total conversion after 2 h at r.t. As anticipated, the nature of the aromatic substituent in **5** modulates the enantioselectivity to a large extent, the bulkier and more extended *m*-terphenyl group of **5b** allowing a more efficient stereocontrol (60% ee),



Scheme 3 Asymmetric transfer hydrogenation of 2-phenylquinoline.

with respect to the phenyl substituent in **5a** (27% ee). Gratifyingly, the enantioselectivity level could be improved then to 85% ee using the 4-methoxybenzyl ester **7b** as the reducing agent and **5b** as the catalyst. Thus, these preliminary results clearly demonstrate the potential of these new paracyclophane-based phosphoric acids in Brønsted acid organocatalysis.[24]

In summary, we have found a suitable access to the first series of cyclic phosphoric acids displaying C_2-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 of 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.

Besides 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 (Ph.D. grant to J.S.), the I.C.S.N., the Agence Nationale de la Recherche (ANR Blanc SIMI7 2011, "Chiracid") and the COST ORCA action CM0905.

Notes and references

1 (*a*) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566–1568; (*b*) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356–5357; (*c*) M. Terada, *Synthesis*, 2010, 1929–1982; (*d*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744–5758.
2 (*a*) S. Mayer and B. List, *Angew. Chem., Int. Ed.*, 2006, **45**, 4193–4195; (*b*) G. L. Hamilton, E. J. Kang, M. Mba and F. D. Toste, *Science*, 2007, **317**, 496–499; (*c*) M. Mahlau and B. List, *Angew. Chem., Int. Ed.*, 2013, **52**, 518–533; (*d*) K. Brak and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2013, **52**, 534–561.
3 (*a*) A. H. M. de Vries, A. Meetsma and B. L. Feringa, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2374–2376; (*b*) M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *J. Am. Chem. Soc.*, 2000, **122**, 11539–11540; (*c*) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486–2528.
4 (*a*) C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen and P. G. Pringle, *Chem. Commun.*, 2000, 961–962; (*b*) M. T. Reetz and T. Sell, *Tetrahedron Lett.*, 2000, **41**, 6333–6336.
5 M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed.*, 2000, **39**, 3889–3890.
6 (*a*) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang and J. C. Antilla, *J. Am. Chem. Soc.*, 2005, **127**, 15696–15697; (*b*) A. A. Desai and W. D. Wulff, *Synthesis*, 2010, 3670–3680.
7 (*a*) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun and L.-Z. Gong, *J. Am. Chem. Soc.*, 2006, **128**, 14802–14803; (*b*) X. Li, X. Jia, G. Lu, T. T.-L. Au-Yeung, K.-H. Lam, T. W. H. Lo and A. S. C. Chan, *Tetrahedron: Asymmetry*, 2003, **14**, 2687–2691.
8 (*a*) F. Xu, D. Huang, C. Han, W. Shen, X. Lin and Y. Wang, *J. Org. Chem.*, 2010, **75**, 8677–8680; (*b*) I. Čorić, S. Müller and B. List, *J. Am. Chem. Soc.*, 2010, **132**, 17370–17373; (*c*) J.-H. Xie and Q.-L. Zhou, *Acc. Chem. Res.*, 2008, **41**, 581–593; (*d*) A. Z. González, D. Benitez, E. Tkatchouk, W. A. Goddard III and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 5500–5507.
9 (*a*) T. Akiyama, Y. Saitoh, H. Morita and K. Fuchibe, *Adv. Synth. Catal.*, 2005, **347**, 1523–1526; (*b*) A. Voituriez and A. B. Charette, *Adv. Synth. Catal.*, 2006, **348**, 2363–2370; (*c*) H. W. Lam, *Synthesis*, 2011, 2011–2043; (*d*) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel and A. Fürstner, *J. Am. Chem. Soc.*, 2012, **134**, 15331–15342.
10 (*a*) Y. Liu and K. Ding, *J. Am. Chem. Soc.*, 2005, **127**, 10488–10489; (*b*) K. Dong, Z. Wang and K. Ding, *J. Am. Chem. Soc.*, 2012, **134**, 12474–12477.
11 D. Enders, M. Ludwig and G. Raabe, *Chirality*, 2012, **24**, 215–222.
12 For reviews on chiral paracyclophane derivatives and uses in asymmetric catalysis, see: (*a*) S. E. Gibson and J. D. Knight, *Org. Biomol. Chem.*, 2003, **1**, 1256–1269; (*b*) G. J. Rowlands, *Org. Biomol. Chem.*, 2008, **6**, 1527–1534.
13 Achiral paracyclophanes displaying two O–P–O tethering chains have been described by Nifant'ev: (*a*) E. E. Nifant'ev, E. N. Rasadkina and Y. B. Evdokimenkova, *Russ. J. Gen. Chem.*, 2001, **71**, 366–372; (*b*) E. N. Rasadkina, A. V. Petrov and E. E. Nifant'ev, *Russ. J. Gen. Chem.*, 2007, **77**, 241–247.
14 For naming descriptors in cyclophanes, see: N. V. Vorontsova, V. I. Rozenberg, E. V. Sergeeva, E. V. Vorontsov, Z. A. Starikova, K. A. Lyssenko and H. Hopf, *Chem.–Eur. J.*, 2008, **14**, 4600–4617.
15 S. M. Bachrach, *J. Phys. Chem. A*, 2011, **115**, 2396–2401.
16 Representative examples: (*a*) H. Takemura, G. Wen and T. Shinmyozu, *Synthesis*, 2005, 2845–2850; (*b*) Y. Nakamura, M. Matsumoto, Y. Hayashida and J. Nishimua, *Tetrahedron Lett.*, 1997, **38**, 1983–1986; (*c*) T. Hori, Y. Shibata and K. Tanaka, *Tetrahedron: Asymmetry*, 2010, **21**, 1303–1306.
17 Unpublished results.
18 For previous examples of paracyclophanes including ferrocene as a tethering unit, see: (*a*) I. Shimizu, Y. Kamei, T. Tezuka, T. Izumi and A. Kasahara, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 192–198; (*b*) A. Kasahara, T. Izumi, I. Shimizu, T. Oikawa, H. Umezawa, M. Murakami and O. Watanabe, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1560–1569.
19 W. Bannwarth and A. Trzeciak, *Helv. Chim. Acta*, 1987, **70**, 175–186.
20 The calcium salt of **5a** has been isolated after column chromatography of the phosphoric acid on silica gel.
21 S. Grimme, *Chem.–Eur. J.*, 2004, **10**, 3423–3429.
22 The α and β angles display average values of 12.5 and 11.0 degrees for [2.2]paracyclophanes and 5.5 and 4.6 degrees for [3.3]paracyclophanes. See ref. 15 and 21 and references cited therein.
23 (*a*) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 3683–3686; (*b*) M. Rueping, E. Sugiono and F. R. Schoepke, *Synlett*, 2010, 852–865; (*c*) C. Zheng and S.-L. You, *Chem. Soc. Rev.*, 2012, **41**, 2498–2518.
24 The catalytic activity of the new acids **5** is at least as high as that of Binol-derived phosphoric acids. Given that the structural features of **5** differ significantly from those of Binol derivatives, the effects of the substituents on the enantioselectivity levels do not follow the same trends in the two series. Thus, for instance, in the reduction of 2-phenylquinoline with the Hantzsch ester **7a** (Scheme 3), the phenyl-substituted catalyst **5a** performs better than the corresponding phenyl-substituted Binol-derived phosphoric acid (ee = 27% and 5% respectively). In the Binol series the highest enantioselectivity has been obtained with the 9-phenanthryl substituted acid (97% ee, see ref. 23*a*) while the ferrocenic acid **5** with 9-phenanthryl substituents gives a 20% ee (unpublished results).

