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A crystalline chiral phosphide for the synthesis of the first P-stereogenic P(III) fluoride: a stable ligand for the Rh-catalyzed asymmetric arylation of isatins

Laila Al Baridi, Giorgio Parla, Alberto Herrera,* Frank W. Heinemann and Romano Dorta *

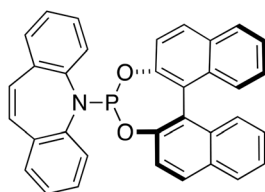
Stable P-stereogenic P(III) fluorides of the type $*PR^1R^2F$ have long resisted isolation, despite their great potential as ligands in asymmetric catalysis. We report the synthesis of a crystalline, chiral lithium alkene-phosphide that undergoes rapid, enantiospecific fluorination with *N*-fluorobenzenesulfonimide with retention of configuration to yield the corresponding fluorophosphinamide-alkene hybrid ligand in >99% ee. The ligand is configurationally stable up to 100 °C and forms a Rh(I) complex that catalyzes the base- and water-free asymmetric arylation of isatins to biologically important 3-hydroxyoxindoles with up to 99.5% ee.

Introduction

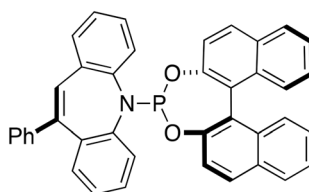
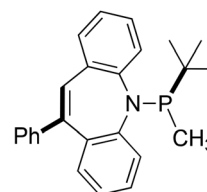
Despite the fact that Burg and Brendel 66 years ago reported the synthesis of the first organo-fluorophosphine, namely $(CF_3)_2PF$,¹ the use of P(III) fluorides as ligands in coordination chemistry is, apart from PF_3 ,² scarcely described.³ Applications in catalysis are even rarer,⁴ and asymmetric versions have not yet been reported, due to the lack of effective synthetic methods towards optically pure fluorophosphines. Chiral phosphines are the ligands of choice for many transition-metal-catalyzed asymmetric reactions in industry and academia.⁵ Of special interest are P-stereogenic phosphines, which place chirality in proximity of the metal center. This concept gained industrial maturity with Monsanto's L-Dopa process in the late 1970's, for which Knowles was awarded the Nobel prize.⁶ However, the synthesis of enantiopure P-stereogenic compounds is notoriously difficult⁷ and a topic of high relevance to asymmetric catalysis.⁸ In particular, the stereoselective installation of a P-F bond in

P-stereogenic phosphine ligands has remained elusive so far and is of prime interest because it would allow to introduce strong steric and electronic differentiation on the P-donor and considerably widen the diversity of chiral ligand design.⁹ Even though the P-F bond is polar and possesses a significant strength of 545 kJ mol⁻¹,¹⁰ applications of fluorophosphines in catalysis have been hampered by their high propensity towards redox disproportionation.⁴

In a recent evolution of the 'privileged ligand' **1**¹¹ we found the planar chirality in the diastereomers (p*S*,*R*)-**2** and (p*R*,*R*)-**2** to completely overwhelm the axial chirality of the potent binol auxiliary in the enantioselective Hayashi-Miyaura reaction.¹² Some years ago, we explored the possibility to introduce the promising P-chiral *tert*-butylmethylphosphine function¹³ to such systems by isolating the stereochemically stable ligand *rac*-**3**.¹⁴ Having taken inspiration from the seminal reports on P-stereogenic P(III)-fluorides by Wild,¹⁵ Pringle,^{4b} Puckette,^{4e} and others,¹⁶ we dis-



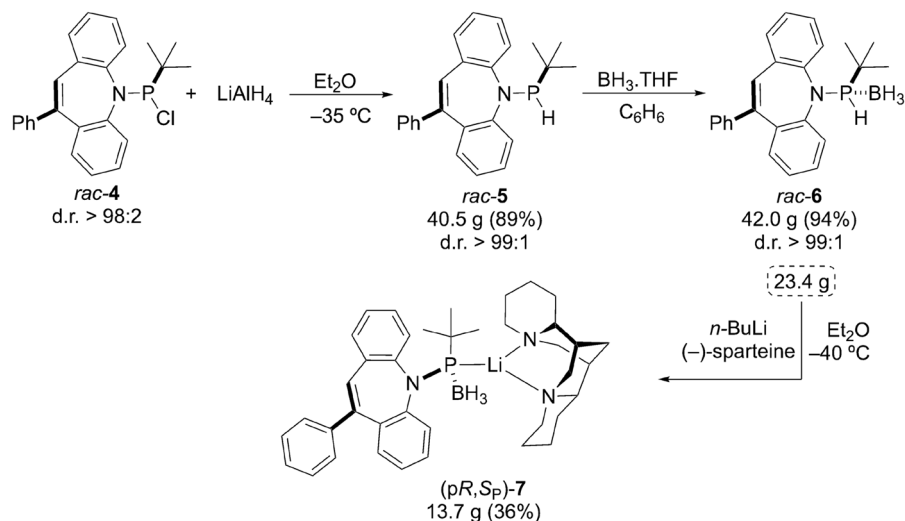
(R)-1

(p*S*,*R*)-2*rac*-3

Department Chemie und Pharmazie, Anorganische und Allgemeine Chemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Egerlandstraße 1, 91058 Erlangen, Germany. E-mail: romano.dorta@fau.de

close here a perfectly stereoselective P-F bond forming protocol that allowed us to isolate the first enantiopure P-stereogenic P(III) fluoride, its Rh(I) complex, and use in catalytic asymmetric C-C bond formation.





Scheme 1 Synthetic route to the enantiopure crystalline phosphide $(pR,S_P)\text{-7}$.

Results and discussion

We opted for Livinghouse's protocol for the synthesis of optically pure P-stereogenic phosphines *via* chiral phosphide intermediates obtained by enantioselective deprotonation of secondary phosphine-boranes, which then are quenched with organic electrophiles.¹⁷ In our case, the diastereomerically pure, BH_3 -protected, secondary phosphinamide *rac-6* (Scheme 1) is prepared by reducing diastereomerically enriched (d.r. > 98:2) chlorophosphine *rac-4* with LiAlH_4 to almost diastereopure *rac-5* followed by protection with $\text{BH}_3\cdot\text{THF}$. Deprotonation of 23.4 g of *rac-6* with the $n\text{-BuLi}/(-)\text{-sparteine}$ mixture in Et_2O at -40°C , yields 13.7 g of phosphide $(pR,S_P)\text{-7}$. Non-decoupled NMR spectra of the ^{31}P , ^{11}B , and ^7Li nuclei display multiplets centered at 96.5, 31.6, and 0.8 ppm, respectively. The molecular mass for 7, estimated by DOSY-NMR (585 g mol^{-1}) corresponds to a monomer (MW = 612 g mol^{-1}). Single crystals of 7 grow from 1,2-difluorobenzene/ Et_2O and XRD analysis confirms its absolute configuration and monomeric structure featuring a P–Li bond (see Fig. 1) contrasting Livinghouse's chiral phosphide, in which the borane moiety bridges the Li-sparteine complex.¹⁸ Unlike Livinghouse's dynamically resolving system, we think that in our case the $\text{BuLi}/\text{sparteine}$ deprotonation enables resolution of the lithium phosphide sparteine complex by diastereoselective crystallization¹⁹ from cold Et_2O solutions, which might explain the modest yields of $(pR,S_P)\text{-7}$. The $(pS,R_P)\text{-antipode}$ is accessible by using $(+)\text{-sparteine}$ (see the SI for details).

With optically pure phosphide $(pR,S_P)\text{-7}$ in hand we first validated its utility as a stereospecific nucleophile for the synthesis of our well-understood P-alkene *rac-3* since earlier attempts of stereospecific C–N bond formation between lithium phenyldibenzoazepinate²⁰ and enantiopure $(R)\text{-(Me)(}t\text{Bu)PBr(BH}_3\text{)}$ (Imamoto's method)²¹ only afforded *rac-3* albeit in diastereomerically pure form. Gratifyingly, methyl iodide reacts smoothly with $(pR,S_P)\text{-7}$ to produce the protected phosphinamide $(pR,R_P)\text{-8}$ in 99% ee (Scheme 2), which is deprotected to $(pR,R_P)\text{-3}$ by

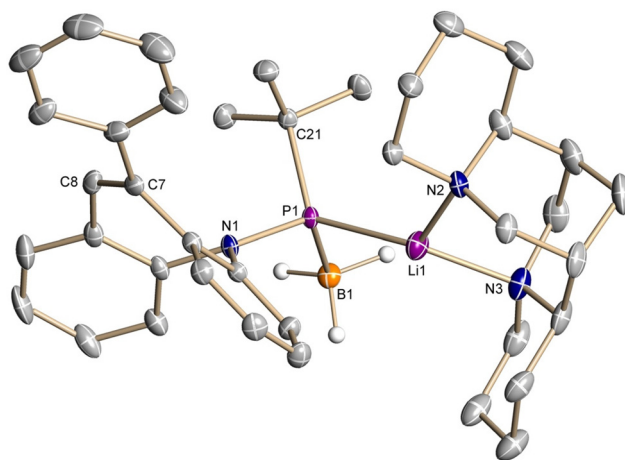
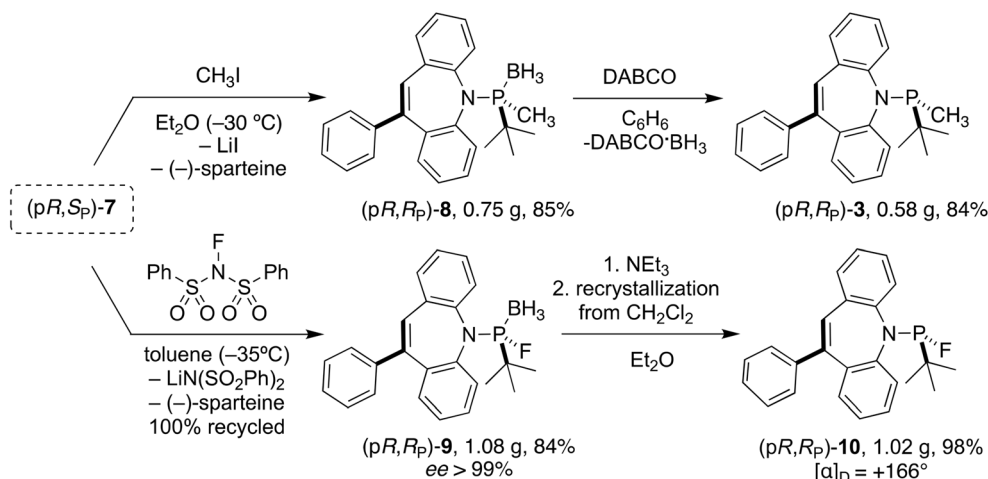


Fig. 1 Crystal structure of $(pR,S_P)\text{-7}$ (50% displacement ellipsoids, most H atoms are omitted). Selected distances (Å) and angles (deg): Li1–P1 2.488(3), Li1–N2 1.995(4), Li1–N3 2.024(4), P1–B1 1.956(2), P1–N1 1.7469(15), P1–C21 1.8790(17), C7–C8 1.355(3), N1–P1–Li1 106.06(10), C21–P1–Li1 121.50(10), N1–P1–C21 112.88(9), N1–P1–C21 103.46(7).

DABCO. Its precise stereochemistry is established by the crystal structure of the Rh(I) complex **11** (see below and Fig. S1).

Likewise, phosphide $(pR,S_P)\text{-7}$ reacts with *N*-fluorobenzene-sulfonamide²² with retention of configuration at phosphorous to the BH_3 -protected diastereo- and enantiopure amido-*t*-butyl fluorophosphine $(pR,R_P)\text{-9}$ (Scheme 2).²³ P–F bond formation is evident in $^{31}\text{P}\{^1\text{H}\}$ and non-decoupled ^{19}F NMR spectra, which show a doublet of multiplets and a doublet of quartets centered at 155.9 ($J_{\text{PF}} \approx 1050\text{ Hz}$) and -109.4 ppm ($J_{\text{FP}} \approx 1050\text{ Hz}$, $J_{\text{FH}} = 16.1\text{ Hz}$), respectively (Fig. S26). The ^1H NMR spectrum shows a doublet at 1.09 ppm and broad multiplets between 0.45–0.26 ppm corresponding to the *t*Bu and BH_3 moieties. Enantiopurity was confirmed by chiral HPLC (Fig. S41 in the SI). Fig. 2 shows the crystal structure of $(pR,$





Scheme 2 Syntheses of enantiopure (*pR,Rp*)-**3** and fluorophosphinamide (*pR,Rp*)-**10**.

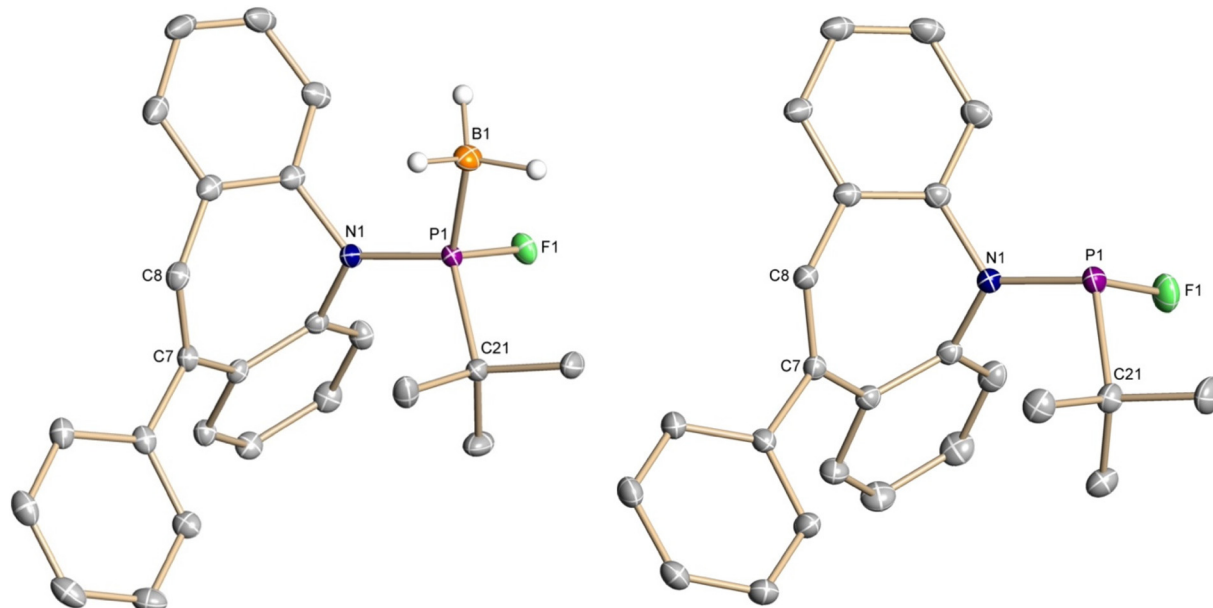


Fig. 2 Crystal structures of (*pR,Rp*)-**9** and (*pR,Rp*)-**10** (50% displacement ellipsoids, most H atoms are omitted). Selected distances (Å) and angles (deg) for (*pR,Rp*)-**9**: P1–F1 1.5851(10), P1–N1 1.6509(14), P1–B1 1.899(2), P1–C21 1.8303(17), C7–C8 1.348(2), F1–P1–N1 106.13(6), F1–P1–B1 109.60(7), F1–P1–C21 100.51(7), N1–P1–B1 112.98(8). For (*pR,Rp*)-**10**: P1–F1 1.6286(10), P1–N1 1.6805(12), P1–C21 1.8579(15), C7–C8 1.3540(18), F1–P1–N1 103.19(6), F1–P1–C21 97.10(6), N1–P1–C21 106.08(6).

Rp)-**9**, which confirms the formation of the P–F bond ($d_{\text{P-F}} = 1.585(10)$ Å), the absolute configuration of the P-atom, and the planar chirality of the dibenzoazepine ring, which are (*pR,Rp*). Importantly, expensive (–)-sparteine can be recycled quantitatively. The basicity of the P-donor in (*pR,Rp*)-**9** seems lower than in (*pR,Rp*)-**3**,²⁴ because removal of the BH₃ moiety from (*pR,Rp*)-**9** is achieved with NEt₃, instead of DABCO affording diastereo- and enantiopure free fluorophosphinamide (*pR,Rp*)-**10** in excellent yields. To make sure deprotection did not erode enantiopurity, (*pR,Rp*)-**10** was re-protected with BH₃·THF

giving back (*pR,Rp*)-**9** in > 99% optical purity. ³¹P and ¹⁹F NMR spectra show new doublets at 176.7 ppm and –132.3 ppm, respectively, with $J_{\text{PF}} = 970.6$ Hz. In the ¹³C NMR spectrum, the quaternary carbon and the methyl groups of the *t*Bu moiety, appear at 35 ppm as a doublet of doublets at 35.0 ($J_{\text{CP}} = 25.3$ Hz, $J_{\text{CF}} = 12.1$ Hz) and 25.4 ppm ($J_{\text{CP}} = 19.5$ Hz, $J_{\text{CF}} = 1.7$ Hz), respectively. The crystal structure confirms the unaltered configuration in (*pR,Rp*)-**10** and shows significant elongation of both the P–F (to 1.6286(10) Å) and P–N bonds compared with (*pR,Rp*)-**9** (Fig. 2). Deprotected (*pR,Rp*)-**9** is surpris-



ingly robust: It is air-stable in the solid state and withstands boiling chloroform and toluene solutions without showing signs of decomposition or epimerization.

(*pR,R_p*)-**3** and (*pR,R_p*)-**10** both react with $[\text{RhCl}(\text{COE})_2]_2$ (COE = cyclooctene) to form the respective P-alkene ligated dinuclear complexes (*pR,R_p*)-**11** (see Fig. S1 in the SI for its crystal structure) and (*pR,R_p*)-**12**²⁵ according to eqn (1). The $^{31}\text{P}\{\text{H}\}$ spectrum of (*pR,R_p*)-**12** shows the formation of a single isomer with a doublet of doublets centered at 231.5 ppm ($J_{\text{PF}} = 1066$ Hz, $J_{\text{PRh}} = 249.6$ Hz), and the non-decoupled ^{19}F spectrum exhibits a doublet of doublets at -104.8 ppm ($J_{\text{F-P}} = 1065$ Hz, $J_{\text{F-Rh}} = 16.4$ Hz). The alkene-C-H resonates at relatively low frequency as a singlet at

5.70 ppm, indicating alkene coordination. (*pR,R_p*)-**12** crystallizes as red blocks from benzene solution, and its crystal structure in Fig. 3 confirms the bidentate coordination of the ligands in an *anti*-fashion to the Rh_2Cl_4 butterfly core, which spans an angle of 99° between the square coordination planes around the Rh atoms. The P-F bond is shorter than in the free ligand and is comparable to the P-F bond in borane complex **8**. The P-F bond in complex (*pR,R_p*)-**12** is significantly shorter than the P-Me bond in complex (*pR,R_p*)-**11**, measuring 1.58 vs. 1.82 Å, respectively (1.63 vs. 1.82 Å in the respective free ligands). Including the H-atoms of the methyl substituent an even larger difference in the respective van-der-Waals volumes is expected. Fluorine substitution at the P-donor also shortens

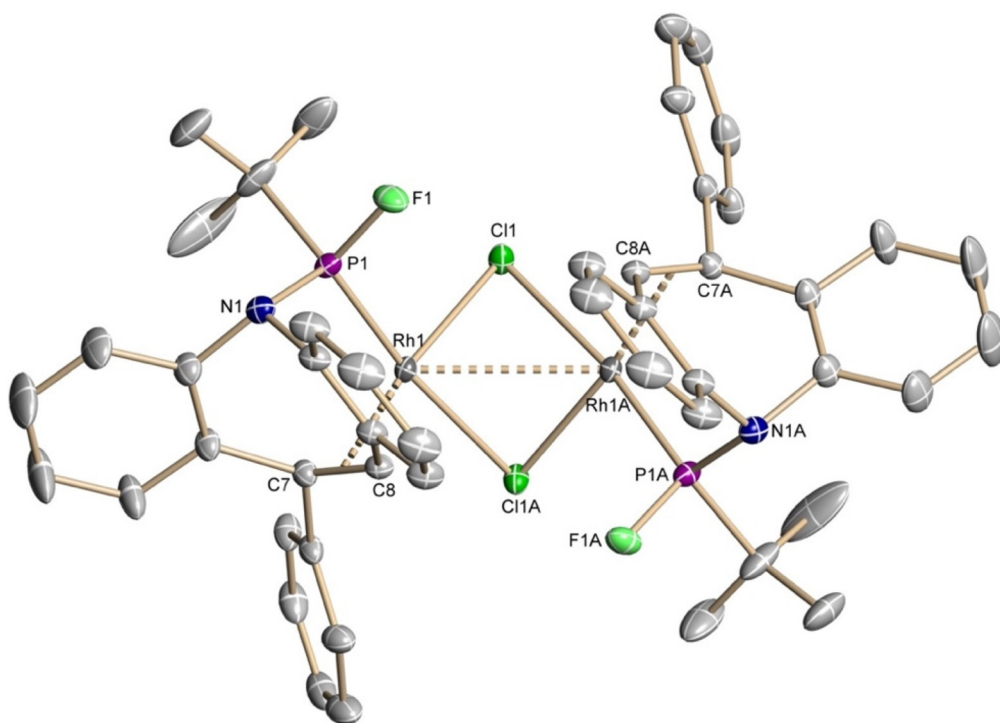
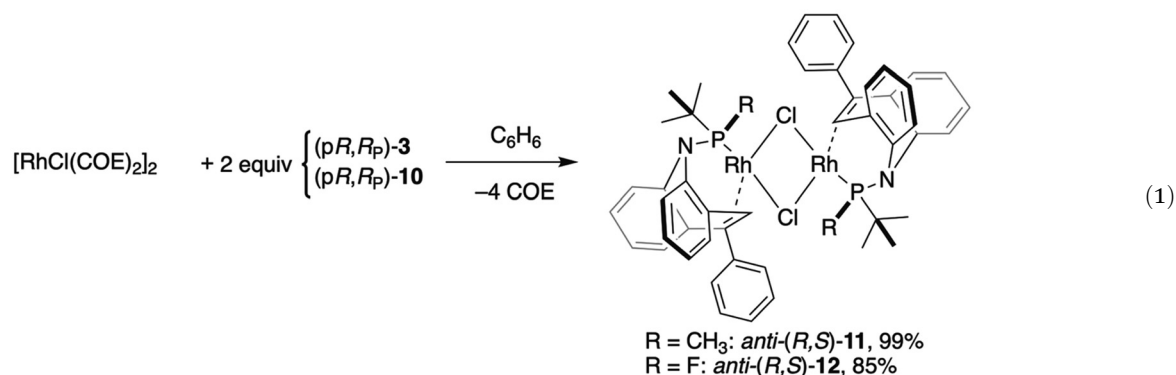


Fig. 3 Crystal structure of (*pR,R_p*)-**12** (50% displacement ellipsoids, H atoms are omitted). Selected distances (Å) and angles (deg): Rh1–Cl1 2.3685 (3), Rh1–Cl1A 2.5010 (3), Rh1–P1 2.132 (4), Rh1–C7 2.1654 (13), Rh1–C8 2.1107 (13), C7–C8 1.4330 (19), P1–F1 1.5845 (10), P1–N1 1.7035 (12), F1–P1–Rh1, 113.35 (4), F1–P1–N1 98.17 (6), F1–P1–C21 100.23 (8)

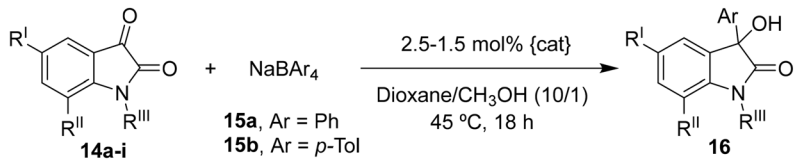
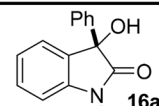
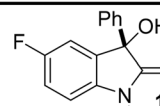
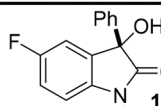
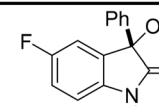
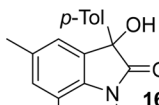
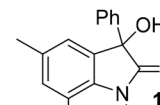
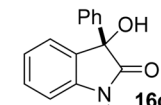
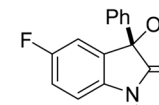
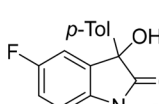
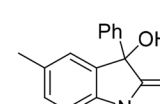
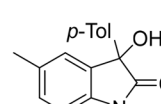
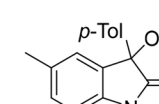
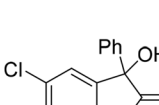
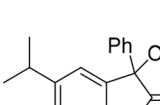
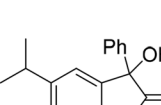
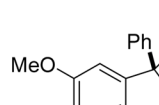


the Rh–P bond in complex (p*R*,*R*_P)-**12** (2.132(4) Å) compared to (p*R*,*R*_P)-**11** (2.1622(9) Å); a small but statistically significant difference.

The P–F ligand (p*R*,*R*_P)-**10** was then benchmarked against ligands (p*R*,*R*_P)-**2** and (p*R*,*R*_P)-**3** of identical planar chirality in the base-free arylation of isatins with sodium tetraarylborates²⁶ to biologically important 3-aryl-3-hydroxyoxindoles (Table 1).²⁷ The arylation of benzyl-protected isatin **14a** with NaBPh₄, is catalyzed by (p*R*,*R*_P)-**12** bearing the P–F ligand affords **16aa** quantitatively in 86% ee, whereas the previously reported cationic complex [Rh((p*R*,*R*)-**2**)₂][BF₄]^{12a} and (p*R*,*R*_P)-**11** bearing ligands (p*R*,*R*_P)-**2** and (p*R*,*R*_P)-**3**, respectively, give conversions of <10%. Only with the electron-poor isatin **14b** do these catalysts

afford relevant quantities of **16ba**. For this product, catalyst (p*R*,*R*_P)-**11** exhibits good enantioselectivity compared with the much more active but less selective (p*R*,*R*_P)-**12**. The sense of induction of the ligands with the Me- and the F-substituted P-donors is identical.²⁸ *In situ* generation of the cationic catalyst [Rh((p*R*,*R*)-**10**)₂][NTf] pushes the ee of the protected dimethyl hydroxyoxindole **16ca** up to 96%. Surprisingly, catalyst (p*R*,*R*_P)-**12** works even better with unprotected NH isatins²⁹ at reduced catalyst loadings. Electron-donating substituents at R^I *para* to the NH function appear to favor enantioselectivity affording hydroxyoxindoles of very high enantiomeric purity (compounds **16fa**, **16ha** and **16ia**), while *N*-protection and the use of tetra-*p*-tolylborate **15b** significantly erode enantioselectivity.

Table 1 Benchmarking of ligand (p*R*,*R*_P)-**10** in the water- and base-free catalytic arylation of isatins with tetraarylborates

					
 16aa {(p <i>R</i> , <i>R</i> _P)- 12 } 2.5 mol% Conv. 100% ee 86% (<i>S</i>)	 16ba {[Rh((p <i>R</i> , <i>R</i>)- 2) ₂][BF ₄]} 5 mol% Conv. 30% ee 5% (<i>S</i>)	 16ba {(p <i>R</i> , <i>R</i> _P)- 11 } 2.5 mol% Conv. 20% ee 80% (<i>S</i>)	 16ba {(p <i>R</i> , <i>R</i> _P)- 12 } ^a 2.5 mol% Conv. 100% ee 71% (<i>S</i>)		
 16cb {(p <i>R</i> , <i>R</i> _P)- 12 } 2.5 mol% Conv. 100% ee 92%	 16ca {[Rh((p <i>R</i> , <i>R</i>)- 10) ₂][NTf]} ^b 5 mol% Conv. 100% ee 96%	 16da {(p <i>R</i> , <i>R</i> _P)- 12 } 2.5 mol% Conv. 100% ee 91% (<i>S</i>)	 16ea {(p <i>R</i> , <i>R</i> _P)- 12 } 1.5 mol% Conv. 96% ee 93% (<i>S</i>)		
 16eb {(p <i>R</i> , <i>R</i> _P)- 12 } ^c 1.5 mol% Conv. 100% ee 63%	 16fa {(p <i>R</i> , <i>R</i> _P)- 12 } 1.5 mol% Conv. 81% ee 98%	 16fb {(p <i>R</i> , <i>R</i> _P)- 12 } 1.5 mol% Conv. 100% ee 88%	 16fb {(p <i>R</i> , <i>R</i> _P)- 12 } ^c 1.5 mol% Conv. 96% ee 89%		
 16ga {(p <i>R</i> , <i>R</i> _P)- 12 } 1.5 mol% Conv. 94% ee 87%	 16ha {(p <i>R</i> , <i>R</i> _P)- 12 } 1.5 mol% Conv. 80% ee 96%	 16ha {[Rh((p <i>R</i> , <i>R</i>)- 10) ₂][NTf]} ^b 5 mol% Conv. 89% ee 98.5%	 16ia {(p <i>R</i> , <i>R</i> _P)- 12 } 1.5 mol% Conv. 100% ee 99.5% (<i>S</i>)		

^a Reaction performed at 35 °C for 4 d. ^b Catalyst formed *in situ* from (p*R*,*R*_P)-**12** + 2 equiv. (p*R*,*R*_P)-**10** + 2 equiv. AgNTf (for experimental details, see the SI). ^c Reaction performed with 1 equiv. of **15b**.



Conclusions

We report a significant advance in the long-standing synthetic challenge of preparing a stereochemically stable P-stereogenic fluorophosphines of the type PR^1R^2F . This was achieved *via* enantiospecific electrophilic fluorination of the crystalline alkene-phosphide (pR,S_P)-7, yielding the configurationally stable fluorophosphinamide (pR,R_P)-10 in gram quantities. This compound introduces a novel donor motif for chiral ligand design and functions as a bidentate ligand in the Rh(I) complex (pR,R)-12. In rhodium-catalyzed, water- and base-free arylations of isatins using $NaBAR_4$ nucleophiles, (pR,R_P)-10 performs favorably compared to benchmark planar-chiral ligands 2 and 3, particularly in the arylation of unprotected NH-isatins. This transformation marks the first application of a fluorophosphinamide in asymmetric catalysis. Notably in this context, the $P(t-Bu)F$ synthon outperforms the generally effective $P^*(t-Bu)(Me)$ analog.¹³ Furthermore, the crystalline phosphide (pR,S_P)-7 provides a versatile platform for accessing new classes of P-stereogenic P-alkene hybrid ligands, the exploration of which is currently underway.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Synthetic procedures, X-ray crystallographic data, NMR spectra, and HPLC traces for this study are available as Supplementary Information. See DOI: <https://doi.org/10.1039/d5qi01994j>.

CCDC 2390089–2390093 contain the supplementary crystallographic data for this paper.^{30a–e}

Acknowledgements

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