**Concave P-Stereogenic Phosphorodiamidite Ligands for Enantioselective Rh(I)-Catalysis**

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ABSTRACT: The development of a new class of concave P-stereogenic phosphorodiamidite ligands, derived from Tröger Bases (TBs), is explored. These ligands, characterized by their remarkable stability and unique structural geometry around the P-atom, are used in asymmetric Rh(I)-catalyzed additions of boronic acids to NH-isatins resulting in excellent reactivities and reasonable enantioselectivity (*e.r.* up to 92:8).

Since the pioneering studies by Horner1 and Mislow2 on enantiopure phosphines, and their application in asymmetric catalysis,3 P-chiral trivalent phosphorus compounds have become prevalent ligand families in stereoselective chemistry.4 Among these compounds, phosphorodiamidites (diamidophosphites), which present two P–N and one P–O bonds around the stereogenic P(III) atom, have received a limited attention overall.5 Synthesized by direct condensation of enantiopure aminoalcohols or diamines with simple PX3 precursors, these derivatives yield often a mixture of diastereomers scrambled at the phosphorus atom (P-epimers). Achieving high stereoselectivity during preparation remains thus a synthetic challenge – underscoring the importance of developing novel chiral rigid backbones to control effectively the configuration at phosphorus, improve structural properties and subsequent reactivity.

Tröger Bases (TBs), unique [3.3.1] bicyclic structures with configurationally stable nitrogen atoms,6 are broadly used as chiral analytes or molecular building blocks6-7 but are seldom employed as organocatalysts or ligands in asymmetric catalysis,8 due to a configurational lability in the presence of *Brønsted* or *Lewis* acids.6, 9 There are several means to address this limitation,10 including the *in-situ* reactivity of carbenes with TBs to generate, after [1,2]-Stevens rearrangement, configurationally-stable ethano-bridged [3.3.2] moieties. In this context,



**Figure 1.** **A**: One-pot synthesis of rigid concave diamine scaffolds; Xray structure (CCDC 1832810, H and p-Tol omitted). **B**: Stereoselective synthesis of concave phosphorodiamidites (d.r. > 49:1, es > 99%).

condensations under Rh(II)-catalysis of TB **1** with -imino carbenes derived from *N*-sulfonyl-1,2,3-triazoles **2** were developed and generate, after a reaction cascade, polycyclic indoline-benzodiazepines **3** in good yield (75%) and high diastereoselectivity.11 Compounds **3** possess an original chalice-like geometry (Figure 1A, X-ray) and are easily resolved into single enantiomers by chiral stationary phase HPLC.11b Of importance, removal of the aminal functional group of **3** is possible and afford rigid sterically-constraint diamine backbones of type **4** (Figure 1B).12 Herein, based on this favorable diamine geometry and with the addition of a phenolic arm, new convave P-stereogenic phosphorodiamidites are afforded in three steps only (Figure 1B, yields up to 84%). Products **6** resulting from the final ring closure are obtained as single epimers (*d.r.* > 49:1, 31P NMR) and present a unique -conformation for the P-stereogenic atom (X-ray, *vide infra*). Application of phosphorodiamidites **6** to Rh(I)-catalyzed additions of boronic acids to unhindered NH-isatins result in good to excellent yields (50-95%) and satisfactory levels of *enantiomeric ratios* (*e.r.* 85:15 on average, up to 92:8).

With (*R*,*R*)-**4a** in hand,12 treatment with Na/Naphthalene in THF provided the corresponding diamine **4b** by deprotection of the tosyl group (Scheme 1); subsequent reductive amination with salicylaldehydes in the presence of NaBH4 forming enantiopure hydroxyldiamine precursors **5a** to **5d** in excellent yields (85-99%). Then, addition of PBr3 to solutions of (*R*,*R*)-**5a** to **5d** in CH2Cl2 containing an excess of Et3N, afforded the targeted phosphorodiamidites. 31P-NMR analysis of crude mixtures presented single peaks around  122 ppm indicative of unique diastereomers in solution. Confirmation of complete stereoselectivity at phosphorus (single P-epimers) was afforded by 1H, 13C and 31P-NMR spectroscopy of isolated products **6a** to **6d**, which were obtained in moderate to good yields after chromatography (Scheme 1, 58-84%). Of note, **6a** to **6d** exhibit chemical and configurational stability both in solution and solid states.

**Scheme 1. Synthesis of P-Stereogenic Phosphorodiamidites and Au(I) Complex**



i) Na/Naphthalene, THF, -78 °C, 16 h, 25 °C; ii) a) Salicylaldehydes, MeOH, AcOH (1 mol%), 3 h; b) NaBH4, MeOH/THF, 0 °C to 25 °C, 16 h; iii) Et3N, PBr3, CH2Cl2, 0 °C to 25 °C, 16 h; iv) (tht)AuCl, CH2Cl2, 25 °C. X-Ray structure: Stick (H atoms and apical phenyl group omitted) and space filling models.

Searching for clues to the full stereocontrol at the P-atom by the chiral diamine and to determine the configuration of the stereogenic phosphorus, care was taken to obtain structural information about adducts **6a** to **6d** by X-ray diffraction. Direct analysis was not be possible by lack of crystallinity, but treatment of compounds **6** with chloro(tetrahydrothiophene)gold(I) or (tht)AuCl, afforded the targeted complexes (31P NMR  ~106 ppm) of which (**6d**)AuCl was obtained as a mono-crystal by diffusion of pentane into a CH2Cl2 solution. The crystallographic analysis (CCDC 2327334) revealed a conservation of the concave structure of the ligand and, to our surprise, an inward orientation of the phosphorus lone pair (-form, inside the cavity) rather than outward. The Au(I) atom is then completely embedded into the chalice-like geometry as shown by the representations of (**6d**)AuCl in Scheme 1. A (*R*,*R*,*S*P)-configuration can be assigned to ligand **6d** and, as evidence for a configurational lability at phosphorus could not be found spectroscopically, the complexation with gold is assumed to be fully stereoretentive.13 The polycyclic and sterically-constraint diamino backbone of the chiral ligand plays clearly a major role in the resulting geometry of adducts **6** and in the stereoselective formation from precursors **5** (*d.r.* > 49:1). Furthermore, with the structural information in hand, calculations using the SambVca 2.1 14 provided the steric mapping and buried volume (*V*bur) of ligand **6d**. As illustrated in Figure S3, the topographic steric map revealed a significant *V*bur of 45%. This observation, coupled with the original orientation of the phosphorus atoms in their β-form, led us to explore their potential in enantioselective catalysis.

**Table 1. Optimization of the Reactivity of Ligands**



|  |  |  |  |
| --- | --- | --- | --- |
| Entry | Ligand | Conversion | *e.r.* |
| 1 | **6a** | 100% | 70:30 |
| 2 | **6b** | 100% | 52:48 |
| 3 | **6c** | 100% | 77:23 |
| 4 | **6d** | 100% | 65:35 |
| 5 | **6e** | 100% | 80:20 |
| 6 | **6f** | 100% | 87:13 |
| 7 | **6g** | 100% | 82:18 |
| 8 | **6h** | 100% | 84:16 |
| 10 | **6e’** | 100% | 49:51 |

As proof of concept, the Rh(I)-catalyzed asymmetric addition of boronic acids to NH-isatins was selected. For instance, this reaction was previously explored by Feringa and Minnaard with phosphoramidite ligands resulting in excellent yields (99%) and moderate levels of enantiomeric excess (*ee* 55%).15 Improvement in asymmetric induction was observed by Hayashi with MOP ligands (*ee* 87%, 47% yield).16 While most studies were performed with N-protected isatins,17 interesting results could be obtained with NH analogs.18 Using 3 mol% of Rh(acac)(C2H4)2 and 6 mol% of ligands **6** in the presence of isatin **7a** and boronic acid **8a**, crude NMR analyses were performed. Full conversion and quantitative formation of product **9aa** were achieved (Table **1**). While a lack of selectivity was noticed with **6b** (*e.r.* 52:48), moderate levels of asymmetric induction were observed for **6a,** **6c** and **6d**, 70:30, 77:23, and 65:35% respectively.

To enhance the enantioselectivity of the Rh-catalyzed addition, a series of modified ligands was prepared (**6e**-**6h**), looking for a better stereocontrol of the ligand geometry. In practice, care was taken to (i) replace the benzylic phenol by a more rigid hydroxylated indenyl ring and (ii) introduce concomitantly an additional stereogenic center next to a chelating nitrogen. Reductive amination reactions were thus attempted between **4b** and hydroxy dihydroindenone derivatives **10e to 10h** (Scheme 2). While traditional conditions for imine formation were unsuccessful, ball milling conditions operating at 30 Hz frequency for >300 minutes, were solely efficient. Subsequent reductions at 25 °C with NaBH4 led to ~1:1 mixture of diastereomers; the ratio of which being improved by performing the reaction at -78 °C (*d.r.* 2.5:1). The major diastereomers were readily isolated after column chromatography (**5e**-**5h**, 43-56%, Scheme 2). Then, treatment with PBr3 afforded **6e** to **6h** in 55-67% yields. The crude mixtures were monitored by 31P-NMR spectroscopy prior to purification and indicated the occurrence of single P-epimers (unique peaks around  130 ppm). In one instance, for future comparison, minor diastereomer **5e'** was reacted with PBr3 to yield **6e'** in 68% yield (31P-NMR.  140 ppm). Configuration assignment of the novel phosphorodiamidite ligands relied again on X-ray diffraction analysis as complex (**6e’**)AuCl was obtained as a mono-crystal by diffusion of pentane into a CH2Cl2 solution (CCDC 2327333). This Au(I) derivative and (**6d**)AuCl present similar concave geometries with incorporation of the metal ion in its -form. Noticeable differences between the two crystallographic structures can be nevertheless observed, which are detailed in Figure S4. Overall, four stereocenters are observed for this minor diastereomer; two (*R*,*R*) carbons belonging to the TB scaffold, one (*R*)-configurated carbon obtained upon reduction of the imine and finally phosphorus atom presenting a (*S*p)-configuration in its free form. Finally, complex (**6e’**)AuCl presents a solid state dimeric packing with Au-Au interaction (Figure S2). Major diastereomer**6e**, epimer of **6e’**, can then assigned the following (*R*,*R*,*S*,*S*P) configuration.

**Scheme 2. Synthesis of Indenyl-Based P-Stereogenic Phosphorodiamidites and Au(I) Complex**



i) **10e-10h,** MeOH, AcOH, Ball milling, 30 Hz; b) NaBH4, MeOH/THF, -78 °C to 25 °C, 16 h; ii) Et3N, CH2Cl2, PBr3, 0 °C to 25 °C 16 h; iv) (tht)AuCl, CH2Cl2, 25 °C. X-Ray structure.

With ligands **6e** to **6h** in hand, their impact on the Rh(I)-catalyzed asymmetric addition was assessed (Table 1). A small enhancement in enantioselectivity is observed from **6c** to **6e** (entry 5). Of note, upon addition of aryl groups as *para* substituents to the indenyl ring, substantial improvement is then achieved with 87:13 *e.r.* values with ligand **6f**, while maintaining an excellent overall reactivity (entry 6). However, further modifications with bulky (*t*Bu, **6g**) or electron-withdrawing (CF3, **6h**) groups, in place of the 3,5-dimethyl substituents (**6f**), provokes a decrease in selectivity with 82:18 and 84:16 *e.r.* values, respectively (entries 7 and 8). Of importance to demonstrate the structural role of the indenyl ring, and of the added stereocenter, product **9aa** was obtained in high yield with ligand **6e’** albeit in essentially racemic form (entry 9).19

With ligand **6f** in hand, the reaction scope was explored using a variety of NH-isatins and aryl boronic acids (Table **2**). Substitution at C-5 and C-7 positions of the isatin heterocycle led to minimal changes in reactivity and resulted in good to excellent yields (67–95%, most > 83%). Enantioselectivity was slightly influenced with *e.r.* being rather constant and values up to 87:13. Changing aryl boronic acid reactants impacted the outcome. While preserving excellent reactivity, enantioselectivity was improved overall and reached 92:8 *e.r.* value. With a few substrates (in grey), a complete lack of conversion was nevertheless observed.

In conclusion, a novel class of P-stereogenic phosphorodiamidite ligands have been synthesized using, to its advantage, the rigid sterically-constraint framework of a chiral diamine derived from Tröger Base. Structural insights, afforded for the most part by X-ray diffraction analysis of Au(I)-complexes, confirmed full stereocontrol for the P-atom and revealed unique β-form geometry. These chemically-stable moieties were further used as chiral ligands in Rh(I)-catalyzed addition of boronic acids to NH-isatins, achieving excellent reactivity and reasonable enantioselectivity levels. Further studies looking at niche applications for these concave-shaped ligands are currently investigated.

**Table 2. Substrate Scope**



**ASSOCIATED CONTENT**

Data Availability Statement

The data underlying this study are openly available yareta.unige.ch at DOI: 10.26037/yareta:c2rz2xbxancklnkqgvqkqbxl3a. It will be preserved for 10 years.

**Supporting Information**

The Supporting Information is available free of charge at ACS Publications website.

Synthetic protocols and spectroscopic characterizations; 1H NMR and 13C NMR of new compounds (PDF)

**Accession codes**

CCDC 2327333 and 2327334 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/structures](http://www.ccdc.cam.ac.uk/structures) or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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(19) The difference between **6e** and **6e’** can be traced back to the geometry as shown in the SI (Fig. S4 and related information).