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Exploring Stereogenic Phosphorus: The Search for New Chiral Diphosphines

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Abstract: The synthesis of P-stereogenic ligands bearing 2,6-disubstituted phenyl groups at the P atom is a challenging problem. The results reported herein help define the scope and limitations of the existing synthetic protocols, such as Jugé's oxazaphospholidine borane method and the enantioselective deprotonation of $P(BH_3)(CH_3)_2(R)$ developed by Evans and Imamoto. Jugé's new approach based on chlorophosphine boranes was exploited for the preparation of a C_1-symmetric MiniPhos-like ligand. Preliminary results concerning the application of the new ligands in the rhodium and ruthenium hydrogenation of olefins are also reported.

Keywords: Asymmetric hydrogenation · Chiral diphosphines · Rhodium · Ruthenium · Stereogenic phosphorus.

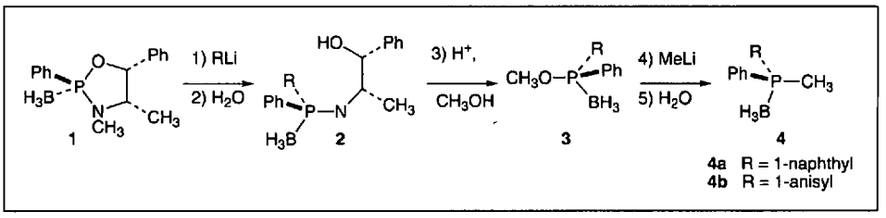
1. Introduction

Chiral diphosphines have become an important class of ligands for asymmetric catalysis. The question is: 'Do we need other chiral ligands?' The answer is yes, and for a number of reasons. The first one is that asymmetric catalysis is developing at such an explosive rate that no class of ligands can be considered as 'universal' anymore [1]. This refers both to the 'scope' of a given reaction with a certain M(P–P*)-catalyst (substrate **A** forms product **B** with high enantioselectivity, but substrate **C** gives product **D** with only a low one), and to the class of reaction (ligand **X** is good for the rhodium-catalyzed asymmetric hydrogenation of olefins, but not for the ruthenium-catalyzed reduction of ketones). A second important consideration (for people working in – or in contact with – industry) is that the successful ligand classes are already protected by patents. In this sense, chemical innovation is equal to the production of wealth.

These two considerations are the rationale for collaboration between industry and academia. However, such a collaboration implies that academia keeps an eye on the needs of industry, and that industry accepts the risks of innovative projects, which are (or could be) productive only in the long term. The story told herein is paradigmatic.

2. A Short History

Years ago, one of us became involved in the chemistry of stereogenic phosphorus. The general idea was that, in a reaction involving more than one molecule around a metal center acting as the catalyst, it is difficult to control the stereochemistry of the resulting complex, *unless the ligands bear bulky substituents that stretch out toward the coordinated reactants*. This idea originated from Luigi M. Venanzi [2], and he wanted to test it in a new reaction, the ruthenium-catalyzed asymmetric acetalization [3]. For a number of reasons, the original project remained on paper only. However, digging deeper into the topic of P-stereogenic phosphines, it became soon clear that in 1994 the state of knowledge about this class of ligands was much like nearly twenty years before, when Knowles [4] actually 'invented' this field of research [5]. This was mainly owing to the lack of a general procedure for the stereoselective synthesis of the P-stereocenter. However, new protocols have become available since the mid 1990s. The first improvement was Imamoto's use of borane as protecting group, which stabilizes the phosphine with respect to oxidation. It also allows easy handling by turning intractable oils into crystalline compounds that can be chromatographed and crystallized [6]. Then, Jugé's invention of the oxazaphospholidine boranes **1** afforded a powerful stereoselective synthetic method of P-stereogenic phosphines (Scheme 1) [7]. As we shall see below, **2**, **3**, and **4** are also useful synthons.



Scheme 1. Jugé's method for the synthesis of P-stereogenic phosphine boranes

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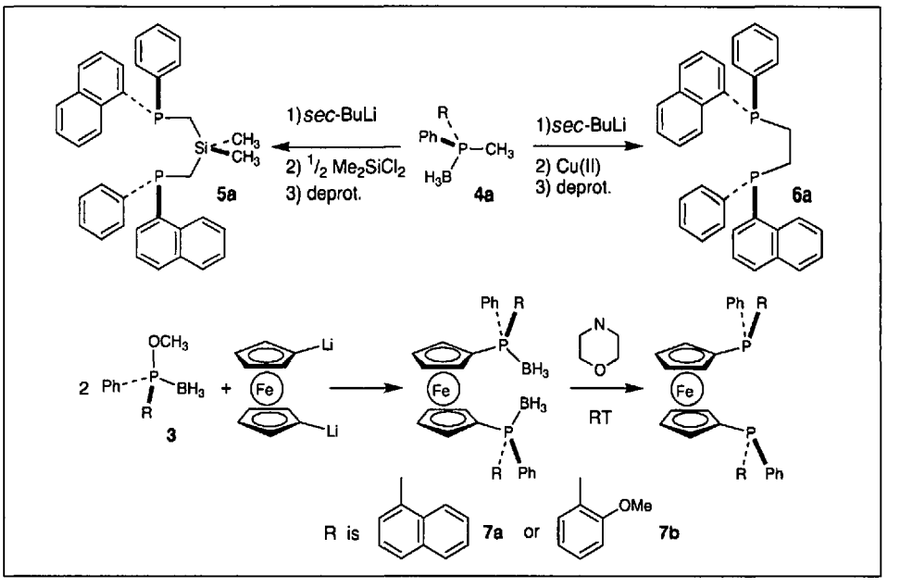
Further developments were to follow shortly, as we shall see below. However, the new synthetic methodologies mentioned above had opened the door to (what seemed to be) a whole class of new ligands. Apparently, nobody was systematically investigating the field at that time. It was in 1995 that we set sail to investigate it.

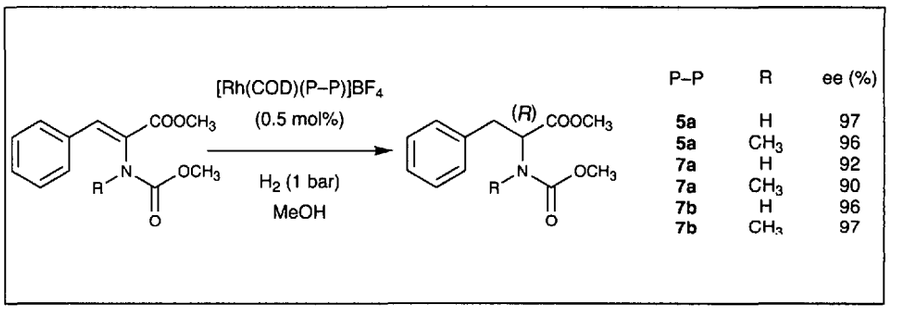
3. The Intellectual Challenge as the Starting Point

We extended Jugé's method and prepared the diphosphines **5a** [8], **6a** [9], **7a**, and **7b** [10] (Scheme 2). These are excellent ligands for the asymmetric hydrogenation of acetamido cinnamates (Scheme 3). In particular, **5a** and **7a,b** are highly effective also with N-substituted dehydroamino acids, a class of substrates that react sluggishly and with low enantioselectivity with most catalytic systems [11].

However, the screening of different substrates confronted us quickly with the usual question as to why P-stereogenic phosphines only work well (or very well) with a single class of substrates, namely the dehydroamino acids. In fact, all of the ligands **5a**, **6a**, and **7a,b** gave disappointing results in the hydrogenation of non-functionalized olefins and in the reduction of carbonyl compounds to alcohols. Both with ruthenium and with rhodium, only low or moderate enantioselectivity was achieved in the asymmetric hydrogenation of functionalized ketones, such as acetylacetone (56% ee) [8], ketopanto lactone (29% ee), and methyl pyruvate (34% ee) [10]. As a working hypothesis, we assumed that this could be related to the possible formation of rotamers. This was suggested by the structural data exposed below.



Scheme 2. Use of $P(BH_3)(CH_3)(Ph)(R)$ and $P(BH_3)(OCH_3)(Ph)(R)$ as synthons



P–P	R	ee (%)
5a	H	97
5a	CH_3	96
7a	H	92
7a	CH_3	90
7b	H	96
7b	CH_3	97

Scheme 3. Asymmetric hydrogenation of an N-substituted dehydroamino acid with [Rh(COD)(P–P*)]BF_4 (P–P = **5a**, **7a**, or **7b**)

The X-ray structure of [$PtCl_2$(**7b**)] shows that the unit cell contains two crystallographically independent molecules of the complex with completely different geometric features (Fig. 1) [10]. Molecule **I** is approximately C_2-symmetric, with both OMe groups 'looking' toward the metal, and the Fe atom lying on the PtP_2 plane. Molecule **II**, instead, is C_1-symmetric, as one OMe groups is *rotated away* from the metal, and the ferrocenyl is tilted out of the PtP_2 plane. Additional evidence of the formation of 'rotamers' came from the behavior of the rhodium diolefin complexes $[Rh(COD)(P–P)]^+$ (P–P is **5a**, **7a**, or **7b**). Indeed, the ^{31}P

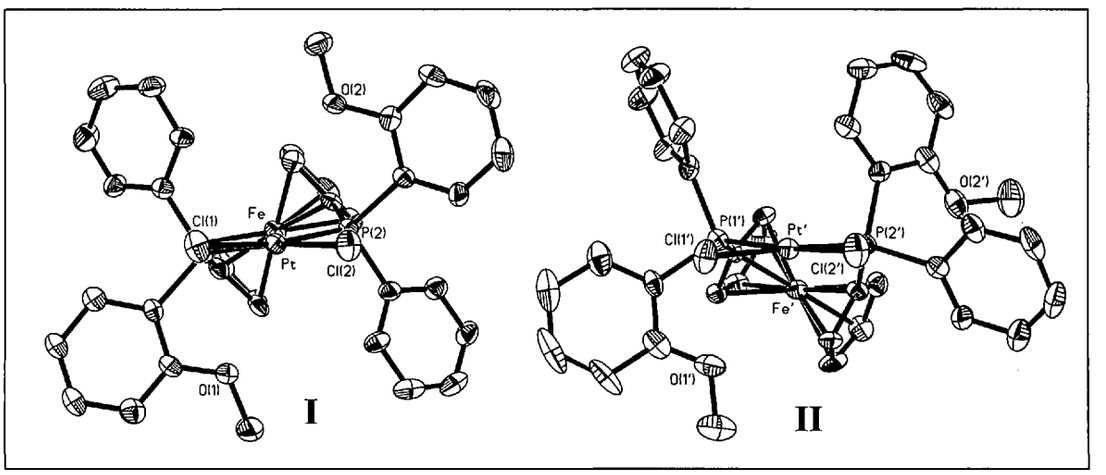


Fig. 1. ORTEP view of the two crystallographically independent molecules of [$PtCl_2$(**7b**)]

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NMR spectra of latter complexes are broad at room temperature. The broad signal resolves into two AB spin systems with different relative intensity (one for each rotamer) at low temperature in CD_2Cl_2 [10]. Molecular modeling (with the Cerius[2] program) suggests that two conformers are possible, depending on the orientation of the anisyl or 1-naphthyl group, as observed for [$PtCl_2$(**7b**)].

Could the conformational flexibility of the P–P ligand be the cause of the low enantioselectivity with most substrates? *The intellectual challenge was there.* Our answer was: Let's introduce substituents at the P atom that are C_2-symmetric with respect to rotation about the P–C bond! In addition, the crystal structures of the six-coordinate complexes [$RuCl_2$(**6a**)$_2$] indicate that, owing to the conformational freedom, aryl substituents such as phenyl and 1-naphthyl are very similar from a steric viewpoint [9]. The latter point lent further support to the idea of using (bulkier) 2,6-disubsituted aryls.

4. The Symmetry of Asymmetry

The first approach that we tried is sketched in Scheme 4. However, we did not get far. Indeed, in contrast with the *o*-substituted aryl groups (such as 1-anisyl, 1-naphthyl, *etc.*), the oxazaphospholidine borane **1** does not react with mesityl lithium, 9-anthryl lithium, or 2,4,6-trimethoxyphenyl lithium. Only *tert*-butyl lithium reacted and gave the phosphinoamino alcohol **2**. However, the resulting ligand, buppe (**6c**), has already been prepared by Imamoto by a different method (see below) [12].

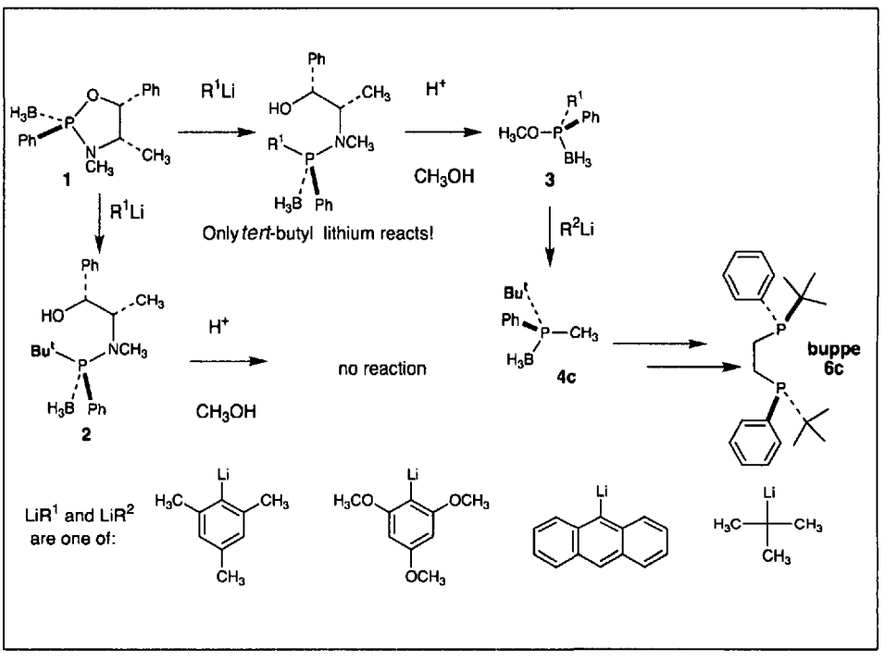
The second approach was the introduction of a 2,6-disubstituted aryl at the oxazaphospholidine stage. The diastereomerically pure mesityl derivative **1d** was obtained in 50% yield as shown in Scheme 5 (the configuration is arbitrarily drawn). However, the ring-opening reaction with alkyl lithium reagents gives low yields of derivatives **3**, and is not useful synthetically.

The next approach that we devised was based on Evans' enantioselective deprotonation of the prostereogenic $P(BH_3)(CH_3)_2(R)$ [13], which has been successfully applied by Imamoto [12] (Scheme 6). We adapted this approach to our idea of using C_2-symmetric aryl substituents, and the results are shown in Scheme 7. Unfortunately, the enantioselectivity of the deprotonation with *sec*-BuLi in the presence of sparteine is low when the aryl group of $P(Ar)(BH_3)(CH_3)_2$ is mesityl (37% ee) or 9-anthryl (18% ee). Thus, the method is not useful for synthetic purposes.

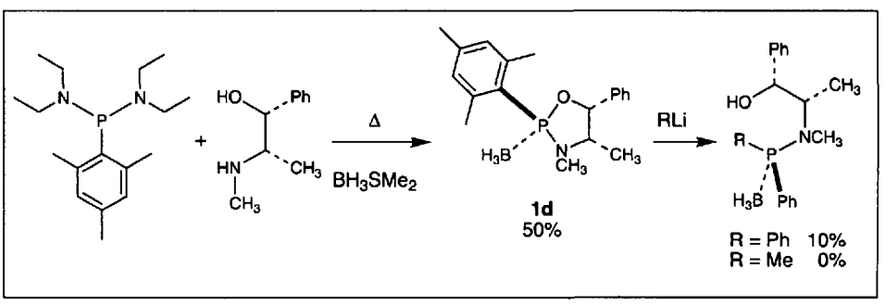
5. C_1-MiniPhos

At this point, help came from a method recently developed by Jugé, which affords the highly reactive chlorophosphine boranes $P(BH_3)Cl(CH_3)Ph$ with high ee [14]. We found that this chiral synthon reacts with the monolithiated $P(Ar)(BH_3)(CH_3)_2$ (Ar = mesityl) (2 equi-

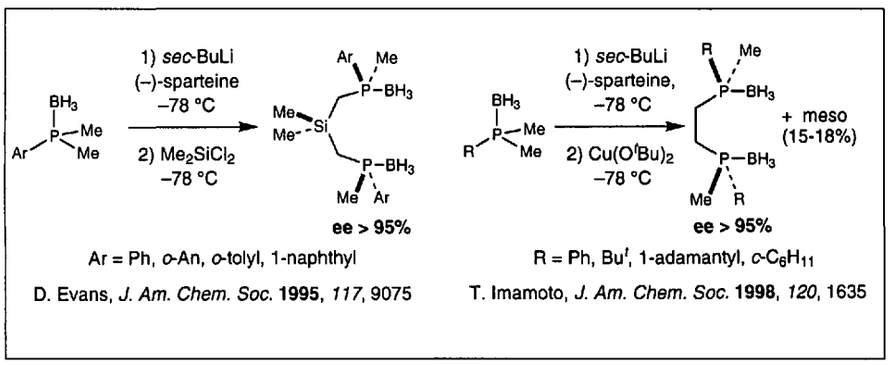
Scheme 4. Attempted synthesis of 2,6-disubstituted phosphines



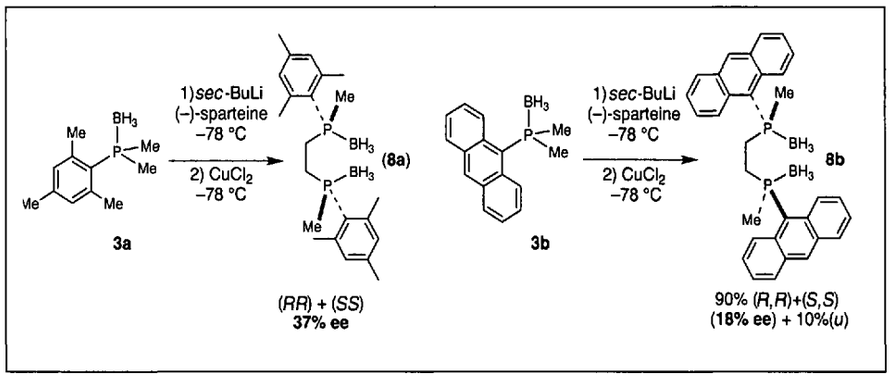
Scheme 5. Synthesis of an oxazaphospholidine borane containing a 2,6-disubstituted phenyl group



Scheme 6. Enantioselective deprotonation of $P(BH_3)(CH_3)_2(R)$



Scheme 7. Enantioselective deprotonation of $P(9\text{-anthryl})(BH_3)(CH_3)_2$

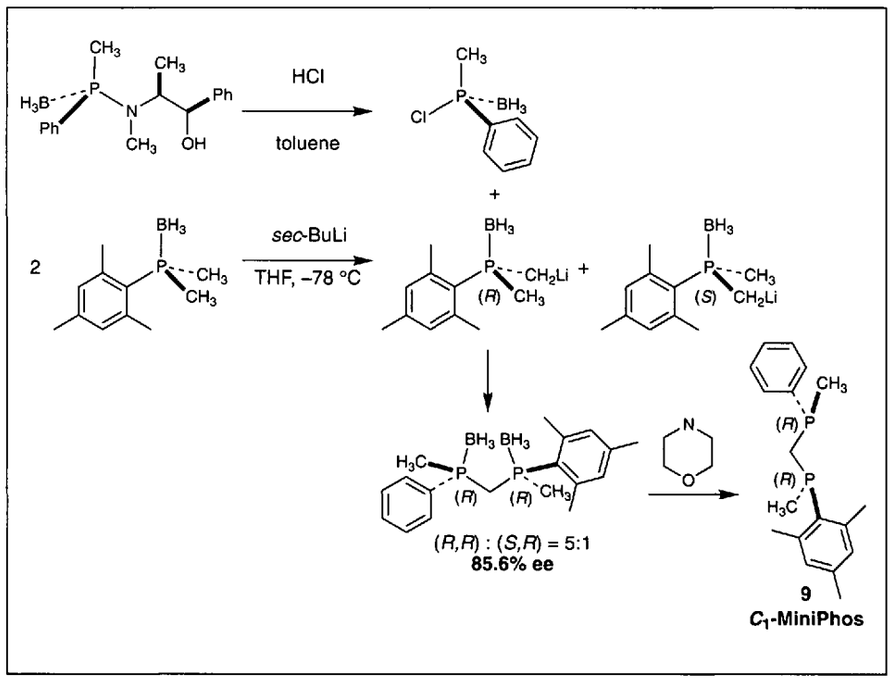


valents) to give the methylene-bridged C_1-MiniPhos (**9**), an analogue of Imamoto's MiniPhos (Scheme 8) [12]. The reaction is diastereoselective and affords predominantly the (*l*)-diastereomer of the borane protected, C_1-MiniPhos ligand with >85% ee, as determined by HPLC on chiral column. Deprotection with morpholine at room temperature yields the free diphosphine **9**.

We prepared $[Rh(COD)(\mathbf{9})]BF_4$ as catalyst precursor. A preliminary screening in the hydrogenation of methyl acetamido cinnamate with the latter complex suggested that **9** coordinates weakly to rhodium [15]. Indeed, inspection of the reaction solution showed that a black precipitate was formed, and the hydrogenation product was racemic. This contrast sharply with the successful application of Imamotos' MiniPhos ($=Bu^t(Me)PCH_2P(Me)Bu^t$) in the same reaction. Indeed, $[Rh(MiniPhos)_2]BF_4$ gives methyl phenylalanine with 99.9% ee. [12]. Again, we obtained negative results with $Bu^t(Ph)PCH_2CH_2P(Ph)Bu^t$ (buppe, **6c**), whereas the related Imamoto's ligand $Bu^t(Me)PCH_2CH_2P(Me)Bu^t$ (= bisP*) gave again excellent enantioselectivity with methyl acetamido cinnamate [12]. The only apparent difference between Miniphos and bisP* on one side and C_1-MiniPhos and buppe on the other side consists of the change from a tris(alkyl) phosphine (as in Imamoto's systems) to a bis(alkyl)aryl one. Apparently, rhodium is not the metal of choice for the latter substitution pattern. Thus, we turned to ruthenium with our ligands.

6. Ruthenium and P-Stereogenic Ligands

Chiral ruthenium catalysts that exploit P-stereogenic ligands are very rare [16]. Thus, we decided to prepare some



Scheme 8. Synthesis of C_1-MiniPhos

ruthenium complexes containing the ligands **5–9**, and test them in the asymmetric hydrogenation of C=C and C=O double bonds. This exploration is still underway. Preliminary results with [RuCl(PPh_3)(**7a**)] as catalyst are encouraging. The five-coordinate [$RuCl_2(PPh_3)$(**7a**)] hydrogenates ethyl acetoacetate with 52% ee and methyl acetamido cinnamate with 42% ee. Other families of complexes that are being prepared and tested are [Ru(η^1-$O_2CCF_3)_2(CH_3OH)_2$(P–P*)] [17] and [Ru(metallyl)$_2$(P–P*)] [16b] (P–P* = **6a**, **6c**, **7a**, **7b**, **9**).

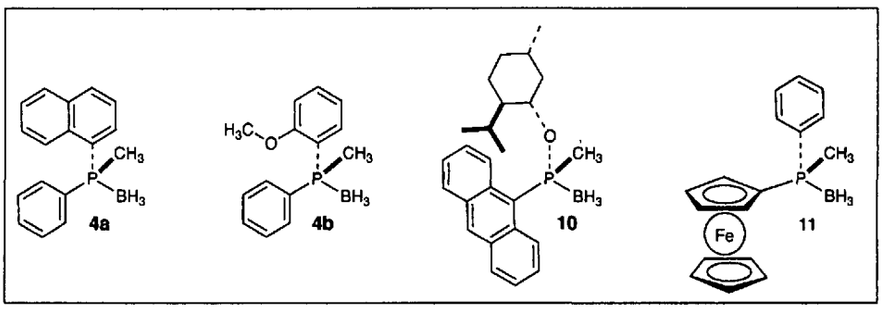


Fig. 2. Some monodentate phosphine (and phosphinite) ligands

7. Conclusion and Outlook

We have prepared a number of new diphosphine ligands that bear stereogenic P atoms. Our investigation contributes to defining the scope and limitations of the existing synthetic methods for this class of ligands. In particular, P-stereogenic diphosphines containing bulky aryl P-substituents are interesting in combination with ruthenium, as the field is virtually unexplored. Finally, the methods developed give access to a set of enantiomerically (or diastereomerically) pure monodentate P-chirogenic ligands **4a**, **4b**, **10** [18], and **11** (Fig. 2) that await application in asymmetric catalysis.

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