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Stereoselective Synthesis of P-Stereogenic Aminophosphines: Ring Opening of Bulky Oxazaphospholidines

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Supporting Information

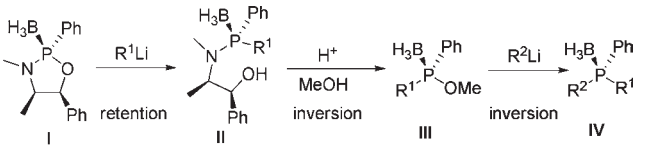
ABSTRACT: A highly diastereoselective and efficient synthesis of P-stereogenic bulky alkyl and aryl aminophosphines that relies on ring opening of *tert*-butyl-oxazaphospholidine **2** is described. Ring opening with several organometallic reagents takes place with inversion of configuration at the phosphorus center as it has been demonstrated by X-ray analysis of two ring-opened intermediates. The unprecedented reactivity observed is attributed to the presence of a free NH functionality that facilitates the attack of the organometallic reagent in an S_N2@P-type process.

Efficient and readily available chiral ligands remain a principal target in catalysis. Bulky P-stereogenic phosphines (P*) have demonstrated efficiency in myriad catalytic processes.[1] However, their synthesis in an enantiomerically pure form is often tedious.[2] The work of Evans and co-workers in 1995 represented a breakthrough in this field.[3] These authors unveiled that alkyl(dimethyl)phosphine borane complexes could be selectively deprotonated at one of their methyl groups in the presence of (−)-sparteine. This strategy was later utilized by Imamoto and others for the synthesis of C_2 symmetric bulky diphosphine ligands.[4] Its chief drawbacks are that it requires very low temperatures and that only the naturally occurring enantiomer of sparteine is available. For stereoselective synthesis of P*-compounds, the main alternative to enantioselective deprotonation is ring opening of oxazaphospholidines (Scheme 1). The pioneering work of Jugé[5a−c] showed that both the condensation of a bis(dialkylamino) phenylphosphine with (−)-ephedrine and the ring opening of the resulting oxazaphospholidine (**I**) with alkyllithium reagents to give **II** are highly diastereoselective.[5] This elegant work has been used to prepare several P-stereogenic ligands.[5] However, it is not amenable to the synthesis of bulky P*-building blocks, due to the lack of reactivity of intermediate **II** when a bulky group is attached to the phosphorus.[6]

We recently described the synthesis of bulky aminophosphines of type **V** as valuable P*-building blocks for ligand synthesis.[7] We showed that these compounds can be readily and efficiently converted into useful PnP ligands of type **VI** such as MaxPHOS (Figure 1).[8]

Compounds of type **V** were obtained via dynamic kinetic resolution (DKR) of racemic chlorophosphines with chiral amines as resolving agents, followed by reductive cleavage of the benzylic amine. Although this strategy afforded aminophosphines **V** in optically pure form (>99% ee), the synthesis was hindered by the low diastereoselectivity of the DKR step. At this point, in the search for a more efficient synthesis of P*-aminophosphine building blocks, we turned our attention to oxazaphospholidine chemistry. Herein we report the synthesis of new, bulky *tert*-butyl-oxazaphospholidines and their diastereoselective ring opening and subsequent reductive cleavage. This methodology constitutes a novel, practical, and efficient route to P*-aminophosphines and their PnP derivatives.

Scheme 1. Jugé's Strategy for Synthesizing P-Stereogenic Tertiary Phosphines



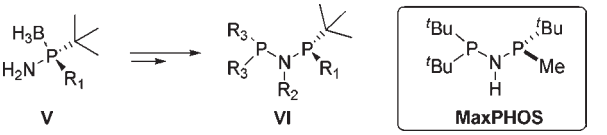


Figure 1. Bulky P-stereogenic aminophosphines and their corresponding PnP ligands.

Among the commercially available β-amino alcohols, we choose for our study the *cis*-1-amino-2-indanol **1**, which has been utilized to prepare chiral sulfoxides and sulfinamides.[9] Compound **1** contains a benzylic amine, and both of its enantiomers are equally available in bulk, characteristics essential to our strategy.[10] A possible inconvenience of amino alcohol **1** was that, to the best of our knowledge, there were no oxazaphospholidines with the free NH functionality described in the literature.[11] With this in mind, we began to screen the condensation of **1** with different *tert*-butylphosphine reagents (Table 1). Dichloro-*tert*-butylphosphine and *tert*-butyl-bis(diethylamino)-phosphine reagents provided the desired product with good selectivity but in low yields (Table 1, entries 1 and 2). The best reagent was the racemic chloro-*tert*-butyl(diethylamino)-phosphine, which provided the corresponding condensation product in an excellent yield of 78% and with diastereomeric ratios of up to 18:1 (Table 1, entry 4). Most conveniently, the major diastereomer was separated by crystallization to afford **2** in diastereomerically pure form. As confirmed by X-ray analysis, the bulky *tert*-butyl group in **2** was positioned *trans* to the Indane fragment, thereby avoiding steric

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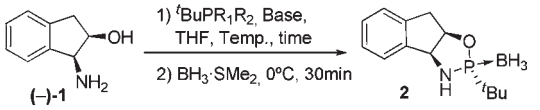
Table 1. Condensation of (1*S*,2*R*)-*cis*-1-Amino-2-indanol (−)-1 with Different *tert*-Butylphosphine Derivatives



Entry	R_1	R_2	Base	Temp (°C)	Time (h)	Yield (%)[a]	dr[b] (R_P/S_P)
1	Cl	Cl	NEt_3	rt	5	22	10:1
2	NEt_2	NEt_2	–	60	4	18	11:1
3	Cl[c]	NEt_2	–	rt	7	0	n.a.
4	Cl[c]	NEt_2	–	reflux	8	78	18:1

[a] Yields correspond to the mixture of diastereomers. [b] Diastereomeric ratios were determined by ^{31}P NMR. [c] Racemic.

Table 2. Nucleophilic Ring Opening of 2

Entry	R[MX][a]	Temp (°C)	Yield (%)[b]	dr[c]	Product
1	MeLi[d]	−78	0	n.a.	**3a**
2	MeLi[e]	40	47	>96:4[f]	**3a**
3	MeLi	40	76	>96:4[f]	**3a**
4	MeMgBr	100	91	>99:1[g]	**3a**
5	EtMgBr	100	91	>96:4[f]	**3b**
6	BuMgCl	100	77	>96:4[f]	**3c**
7	*i*-PrMgCl	100	85	>96:4[f]	**3d**
8	$H_3CCCMgBr$	100	96	>96:4[f]	**3e**
9	PhMgBr	100	96	96:4	**3f**
10	2-MeOPhMgBr	100	94	>96:4[f]	**3g**
11	Me_3Al	80	90	93:7	**3a**
12	Et_3Al	100	88	90:10	**3b**

[a] Between 2.2 and 4.5 equiv of organometallic reagent were used. [b] Yield corresponds to the mixture of diastereomers. [c] Determined by ^1H NMR. [d] Et_2O was used as solvent. [e] THF was used as solvent. [f] A single isomer was observed by ^1H NMR. [g] The minor isomer was not detected by HPLC analysis.

encumbrance. When the (1*S*,2*R*) isomer ((−)-**1**) was used as starting material, the phosphorus center in **2** had the *R* configuration.[12]

We then turned our attention to the ring opening of oxazaphospholidine **2** with different organometallic reagents (Table 2). The standard reaction conditions for the ring opening of *N*-methyloxazaphospholidines employ an alkyllithium reagent at low temperature (−78 °C).[5] Attempts at the ring opening of **2** using 2 equiv of MeLi under these conditions failed to produce the desired product (Table 2, entry 1). However, increasing the reaction temperature to 40 °C and using toluene as solvent enabled the preparation of **3a**, isolated in 76% yield and with complete stereoselectivity, as determined by ^1H NMR (Table 2, entry 3). Ring opening was further improved using MeMgBr

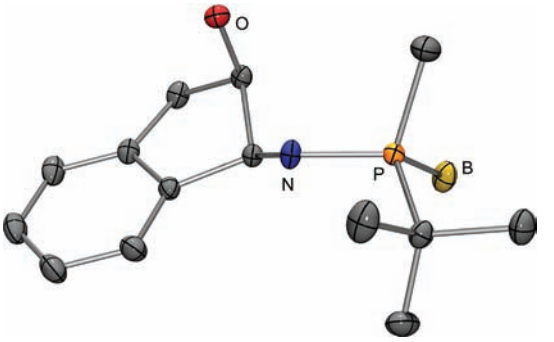
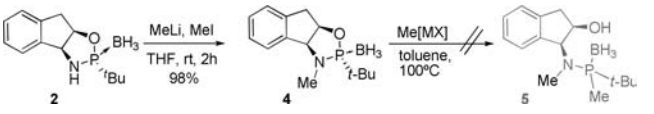


Figure 2. X-ray structure of compound **3a** (ORTEP drawing showing 50% probability ellipsoids).

Scheme 2. Synthesis and Failed Attempt at Ring Opening of *N*-Methyl-2-*tert*-butyl-1,3,2-oxazaphospholidine 4



instead of MeLi (Table 2, entry 4). Although the Grignard reagent was less reactive than methyl lithium, it provided a cleaner reaction. This enabled increasing the reaction temperature up to 100 °C in toluene to afford **3a** in an excellent yield (91%) and with total selectivity.[13]

We next explored the scope of this ring-opening process using different alkyl and aryl Grignard reagents. We were pleased to find that primary and even secondary alkylmagnesium reagents provided excellent yields and total selectivity as determined by ^1H NMR (Table 2, entries 5, 6, and 7). Furthermore, a reaction with both alkynyl- and arylmagnesium reagents took place with near to perfect yields and selectivity (Table 2, entries 8, 9, and 10). Finally, we tested two aluminum reagents. Although they were also effective in this process, they provided compounds **3a** and **3b** with lower selectivity than did the organomagnesium reagents (Table 2, entries 11 and 12).

Most unexpectedly, X-ray analysis of compound **3a** (Figure 2) showed that the phosphorus atom had the *S* configuration.[14] Consequently, the ring opening of **2** gave an inversion of configuration at the phosphorus center. Moreover, X-ray analysis of **3f** revealed that both alkyl- and aryl-magnesium reagents proceed with the same stereochemical pathway.[15] To our knowledge, this behavior is unprecedented, since the ring opening of oxazaphospholidines type **I** (Scheme 1) usually occurs with retention of configuration.[5] Jugé et al. has suggested that metal coordination of the Li−R reagent to the ring-oxygen atom facilitates the alkyl attack to phosphorus, leading to a pentacoordinate phosphorus center that ultimately forces out the oxygen leaving group.[16] In the case of **2**, we sought to clarify whether the free NH group was accountable for the distinct stereochemical behavior that we had observed. To check this hypothesis, we prepared *N*-methyl oxazaphospholidine **4** and then submitted it to ring opening with MeLi, MeMgBr, and $AlMe_3$ (Scheme 2). Remarkably, under the same reaction conditions used for **2**, compound **4** did not undergo ring opening, and the starting material was recovered. The lack of reactivity of **4** confirmed that the free NH group is crucial for opening the bulky oxazaphospholidine **2**. Moreover, the requirement of >2 equiv of the alkylating reagent for ring opening indicates that the

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Scheme 3. Mechanistic Hypothesis for the Ring Opening of 2 with Lithium, Magnesium, and Aluminum Reagents

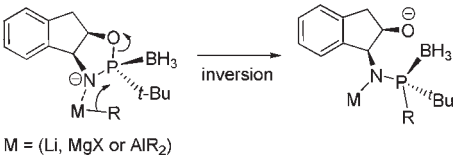
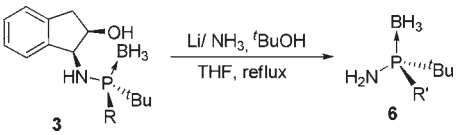


Table 3. Reductive Cleavage of Ring-Opened Compounds 3



Entry	S.M.	R	Product	R′	Yield (%)
1	**3a**	Me	**6a**	Me	71[a]
2	**3b**	Et	**6b**	Et	78
3	**3c**	Bu	**6c**	Bu	71
4	**3d**	*i*-Pr	**6d**	*i*-Pr	71
5	**3e**	H_3CCC	**6e**	*n*-C_3H_7	81
6	**3f**	Ph	**6f**	Ph	—[b]

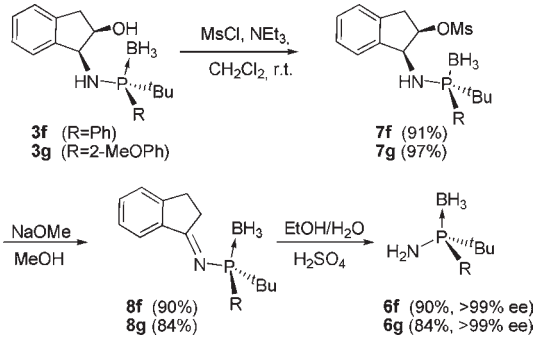
[a] GC analysis on a chiral stationary phase revealed >99% ee. [b] Birch-type reduction at the phenyl group attached to phosphorus was obtained as described in refs 7 and 19.

N—H group is deprotonated. These facts suggest that the resulting N^- group coordinates the organometallic reagent and guides its attack at phosphorus (Scheme 3). In this scenario, the alkyl transfer occurs from the opposite side of the leaving group enabling an S_N2@P-type process.[17,18]

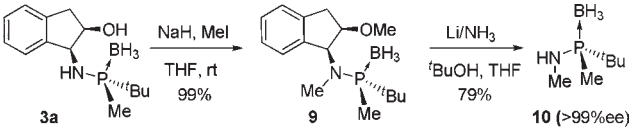
With the open-chain products **3a**—**f** in hand, we assayed reductive cleavage at the benzylic position to attain the desired borane-protected P*-aminophosphines (Table 3). Reduction of recrystallized **3a** with lithium in ammonia in the presence of *tert*-BuOH afforded the desired compound **6a** in 71% yield and 99% ee as determined by chiral GC. This indicated that the reaction is stereospecific. It is worth noting that **6a** is the key intermediate in the synthesis of the ligand MaxPHOS. Following the same procedure, compounds **3b**, **3c**, and **3d** were successfully reduced to provide the corresponding novel P*-aminophosphines (Table 3, entries 2, 3, and 4, respectively). Dissolved metal reduction of **3e**, which bears a 1-propynyl group, afforded the fully reduced *tert*-butyl-*n*-propyl-aminophosphine **6e** in 81% yield (Table 3, entry 5). Finally, reduction of the phenyl-containing intermediate **3f** did not produce the desired aryl-*tert*-butylaminophosphine but instead gave the corresponding Birch-reduction product, as we and others have recently described (Table 3, entry 6).[7,19]

To overcome this limitation, we developed an alternative hydrolytic route to the desired arylaminophosphines (Scheme 4). Starting from **3f**, mesylate formation and elimination using a MeONa/MeOH mixture gave the corresponding iminophosphine **8f** in excellent yields. Finally, acidic hydrolysis of **8f** in EtOH/H_2O afforded the desired arylaminophosphine **6f** in excellent yield. Chiral HPLC analysis revealed that no racemization at the P center had occurred during the hydrolytic cleavage, since **6f** was isolated in >99% ee as determined by chiral HPLC. The same procedure, starting from **3g**, enabled the synthesis of the *ortho*-methoxyphenylaminophosphine **6g**, again in excellent yields and in optically pure form.

Scheme 4. Hydrolytic Cleavage of Aryl Aminophosphines



Scheme 5. Synthesis of Secondary Aminophosphine from 3a



Compounds **3a**—**f** can also be used as intermediates in the synthesis of P-stereogenic secondary aminophosphines (Scheme 5). To demonstrate this, we methylated compound **3a** at both its oxygen and nitrogen atoms to give **9** in quantitative yield. Treatment of **9** with Li/NH_3 afforded the secondary aminophosphine **10** in 79% yield and an optically pure form. As we have previously reported, secondary aminophosphines are also valuable building blocks for P-stereogenic aminodiphosphines.[7]

In summary, we have described a highly diastereoselective and efficient synthesis of P-stereogenic bulky alkyl and aryl aminophosphines that relies on the ring opening of *tert*-butyl-oxazaphospholidine **2**. Attack of the organometallic reagent occurs with inversion of configuration at the phosphorus center. This unprecedented reactivity of the bulky oxaphospholidine **2** is due to the presence of a free NH functionality that facilitates the attack of the organometallic reagent. These findings greatly expand the potential of oxazaphospholidine chemistry in the field of P* synthesis and provide a practical, stereoselective and high-yielding route to chiral aminophosphines, key intermediates to useful PnP ligands. Further experimental and theoretical studies to elucidate the mechanism of the ring opening are underway in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data and spectra for all new compounds, and CIF files for compounds **2**, **3a**, and **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Bulk price for both enantiomers is $800/kg.

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(12) The absolute configuration has been reliably determined by the anomalous dispersion method, Flack = −0.03(5). See Supporting Information for crystallographic data of compound **2**.

(13) The minor diastereomer was not detected when analyzing the reaction crude by HPLC.

(14) The absolute configuration has been reliably determined by the anomalous dispersion method, Flack = −0.02(5). See Supporting Information for crystallographic data of compound **3a**.

(15) The absolute configuration has been reliably determined by the anomalous dispersion method, Flack = −0.03(5). See Supporting Information for crystallographic data of compound **3f**.

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