

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 Juge^{5a–c} showed that both the condensation of a bis(dialkylamino) phenylphosphine with (–)-ephedrine and the ring opening of the resulting oxazaphospholidine (**1**) with alkyl-lithium 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

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

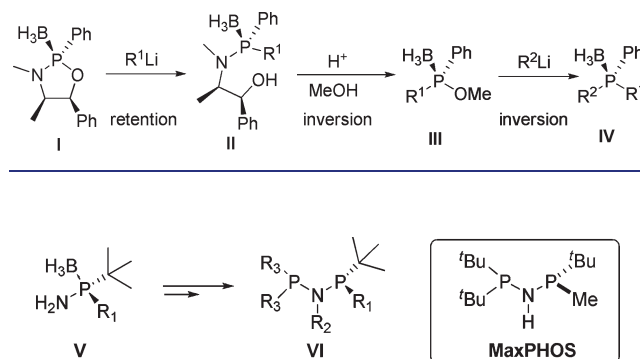


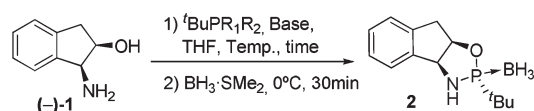
Figure 1. Bulky P-stereogenic aminophosphines and their corresponding PnP ligands.

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.

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 sulfonamides.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

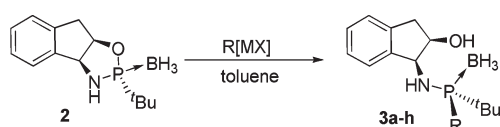
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Table 1. Condensation of (1*S*,2*R*)-*cis*-1-Amino-2-indanol (–)-1 with Different *tert*-Butylphosphine Derivatives

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

^aYields correspond to the mixture of diastereomers. ^bDiastereomeric ratios were determined by ³¹P NMR. ^cRacemic.

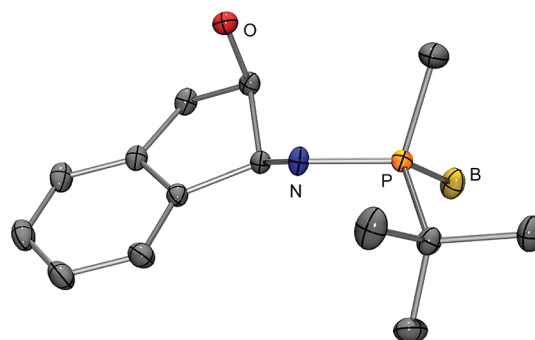
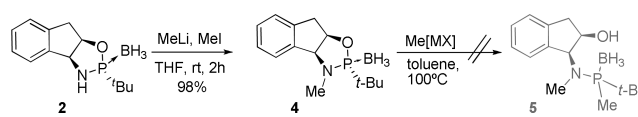
Table 2. Nucleophilic Ring Opening of 2

Entry	R[MX] ^a	Temp (°C)	Yield (%) ^b	dr ^c	Product
1	MeLi ^d	–78	0	n.a.	3a
2	MeLi ^c	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>i</i> -PrMgCl	100	85	>96:4 ^f	3d
8	H ₃ CCCMgBr	100	96	>96:4 ^f	3e
9	PhMgBr	100	96	96:4	3f
10	2-MeOPhMgBr	100	94	>96:4 ^f	3g
11	Me ₃ Al	80	90	93:7	3a
12	Et ₃ Al	100	88	90:10	3b

^aBetween 2.2 and 4.5 equiv of organometallic reagent were used. ^bYield corresponds to the mixture of diastereomers. ^cDetermined by ¹H NMR. ^dEt₂O was used as solvent. ^eTHF was used as solvent. ^fA single isomer was observed by ¹H NMR. ^gThe 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

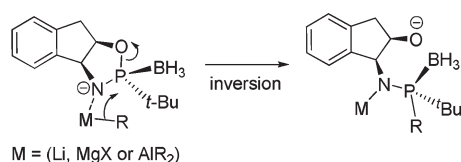
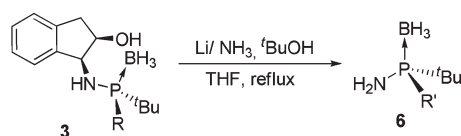
We then turned our attention to the ring opening of oxazaphospholidine 2 with different organometallic reagents (Table 2). The standard reaction conditions for the ring opening of *N*-methyloxazaphospholidines employ an alkyllithium reagent at low temperature (–78 °C).⁵ Attempts at the ring opening of 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 AlMe₃ (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

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**

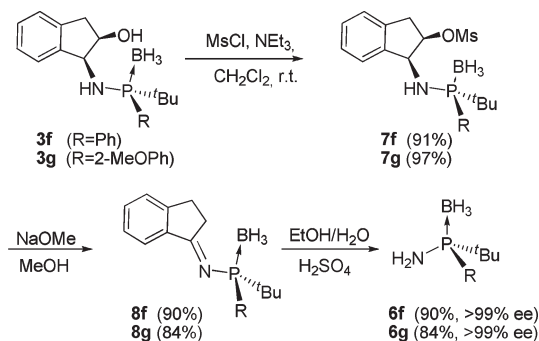
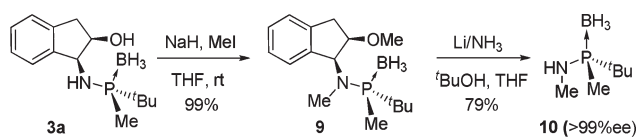
Entry	S.M.	R	Product	R'	Yield (%)
1	3a	Me	6a	Me	71 ^a
2	3b	Et	6b	Et	78
3	3c	Bu	6c	Bu	71
4	3d	<i>i</i> -Pr	6d	<i>i</i> -Pr	71
5	3e	H ₃ CCC	6e	<i>n</i> -C ₃ H ₇	81
6	3f	Ph	6f	Ph	— ^b

^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/H₂O 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,

Scheme 4. Hydrolytic Cleavage of Aryl Aminophosphines**Scheme 5. Synthesis of Secondary Aminophosphine from 3a**

enabled the synthesis of the *ortho*-methoxyphenylaminophosphine 6g, again in excellent yields and in optically pure form.

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/NH₃ 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 oxazaphospholidine 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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- (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.
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