BOM-phosphinite as an electrophilic P-stereogenic transfer reagent for the synthesis of bulky phosphines. Synthesis of *tert*-butyl(3,5-di-*tert*-butylphenyl)BisP*.

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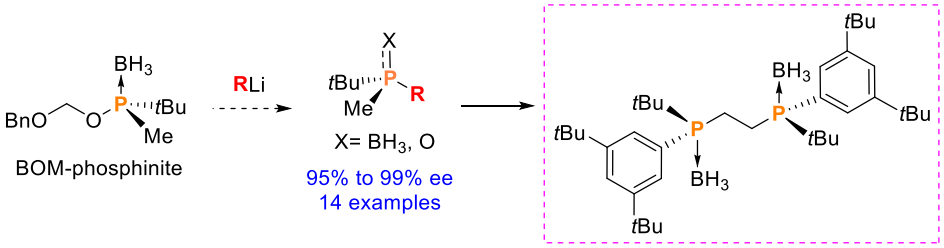
Supporting Information Placeholder

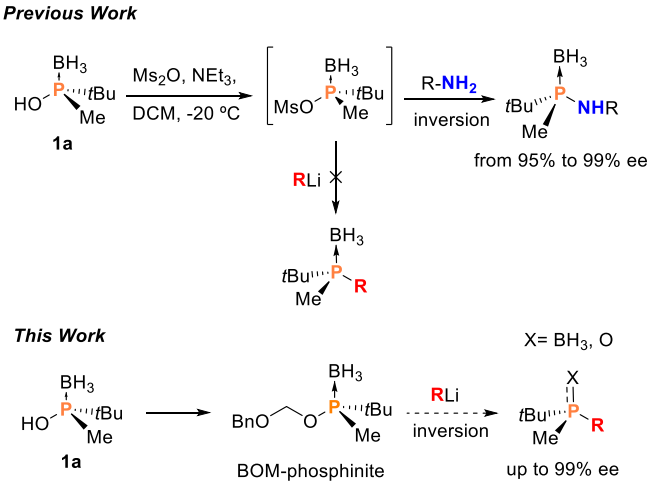


ABSTRACT: BOM-*tert*-butylmethylphosphinite borane is an efficient electrophilic P-stereogenic transfer reagent for the synthesis of bulky tertiary phosphines. The novel methodology relies on a one-pot deprotection/substitution on the trivalent phosphinite that takes place with very high stereospecificity. The potential of this strategy is demonstrated with the synthesis of a wide scope of tertiary phosphines in excellent enantiomeric excess. The methodology was applied to the synthesis of a bulky P-stereogenic BisP* ligand analog.

Chiral phosphines are essential ligands for asymmetric catalytic transformations.[1] Among them, P-stereogenic ligands bearing bulky substituents have emerged as one of the most efficient class of ligands, particularly for asymmetric hydrogenation reactions.[2,3] In the last decade, our group has developed the synthesis of P-stereogenic synthons and ligands bearing *tert*-butyl and methyl substituents.[4] The large steric bias between these two groups confers excellent enantioselectivity. In 2015, we reported that phosphinous acid **1a** could act as an efficient P-stereogenic transfer reagent (Scheme 1).[5] Activation of **1a** with Ms_2O allowed swift coupling with amines, with inversion of configuration at the phosphorus. This enabled a convenient access to P-stereogenic aminophosphine ligands that have shown excellent results in catalysis.[6] However, reaction of activated **1a** with alkyllithium or aryllithium reagents was unproductive.[7]

To address this shortcoming, here we report on the efficiency of benzyloxymethyl phosphinite (BOM-phosphinite) as a P-stereogenic transfer reagent for organolithium nucleophiles, thus opening access to P-stereogenic tertiary phosphines with the useful *tert*-butylmethyl core.[8] Moreover, we demonstrate the utility of this strategy with the synthesis of the bulky 1,2-bis(*tert*-butyl(3,5-di-*tert*-butylphenyl)phosphino)ethane ligand.

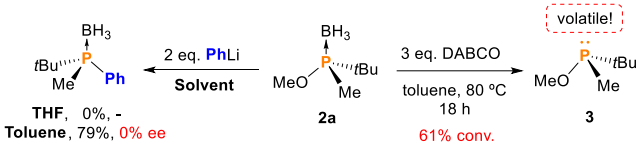
Scheme 1. Use of **1a** and BOM-phosphinite as a P-stereogenic transfer reagents.



We began this project by testing whether the simple methyl *tert*-butylmethylphosphinite borane **2a** could undergo nucleophilic substitution with phenyllithium (Scheme 2).[9] Jugé and co-workers have

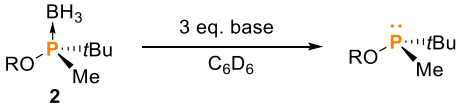
demonstrated that methyl phosphinite boranes provide clean substitution reaction with organolithium reagents.[10] Reaction of **2a** with PhLi was strongly solvent dependent; no reaction was observed with ethereal solvents, while in toluene 79% of the desired product was obtained but with complete loss of the optical purity.[7] The differential behavior compared with the results reported by Jugé, is most likely due to the presence of a bulky *tert*-butyl group attached to phosphorus in **2a**.[11] At this stage, we envisioned that the reaction on a borane-free trivalent phosphorus atom could take place through a stereospecific pathway. Börner and Bayardon have demonstrated that trivalent phosphinites are more reactive when compared to borane-protected ones.[12] To this end, deprotection of **2a** with 1,4-diazabicyclo[2.2.2]octane (DABCO) was examined (Scheme 2). As determined by ^{31}P NMR analysis, low conversion to the desired free phosphinite **3** was observed. In addition to this, due to its volatility any efforts to isolate **3** were unsuccessful. Given these observations, **2a** was deemed an inappropriate substrate for this strategy.

Scheme 2. Initial experiments with methyl phosphinite borane **2a**.



At this point, a phosphinite derivative that could be efficiently deprotected under basic conditions was needed. To this end, ten new phosphinites were prepared from a stable salt of **1a** in excellent yield.[13] See the Supporting Information section for the details of the synthesis and a complete list of phosphinite derivatives. With the new phosphinites in hand, we tested them for deprotection with DABCO in degassed C_6D_6 and analyzed the conversion by ^{31}P NMR. Selected results for phosphinites **2b-e** are shown in Table 1.[14] Using 3 equiv. of DABCO, the benzyl phosphinite was deprotected with only 20% conversion (Table 1, entry 1). The conversion increased slightly when pentafluorobenzyl phosphinite **2c** was used; however, the starting material and product showed decomposition when the temperature was increased to 80 °C (Table 1, entries 2 and 3). Under the same reaction conditions BOM derivative **2d** provided 85% conversion and a cleaner reaction profile (Table 1, entry 4).[15] Finally, switching to quinuclidine which is a stronger base,[16] gave a virtually complete and clean deprotection of **2d** (Table 1, entry 5). Under the same reaction conditions, the related MOM protected **2e**, afforded only 90% conversion (Table 1, entry 6). We hypothesized that the slightly more electron-withdrawing BOM group favored the deprotection process.

Table 1. Highlighted protection assays with different phosphinites.

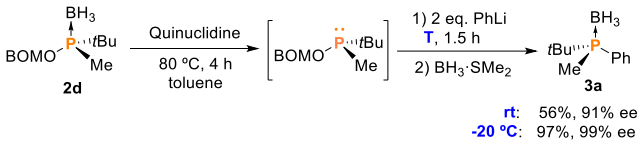


entry	R	substrate[a]	base[a]	conditions	conversion[b]
1	$PhCH_2$	**2b**	DABCO	60 °C, 4 h	20%
2	$C_6F_5CH_2$	**2c**	DABCO	60 °C, 4 h	45%
3	$C_6F_5CH_2$	**2c**	DABCO	80 °C, 4 h	Decomp.
4	$BnOCH_2$	**2d**	DABCO	80 °C, 4 h	85%
5	$BnOCH_2$	**2d**	Quinuclidine	80 °C, 4 h	98%
6	$MeOCH_2$	**2e**	Quinuclidine	80 °C, 4 h	90%

[a] NMR tube experiments, concentration: **2** (0.39 M) and base (1.2 M). [b] Conversion was determined by ^{31}P NMR analysis.

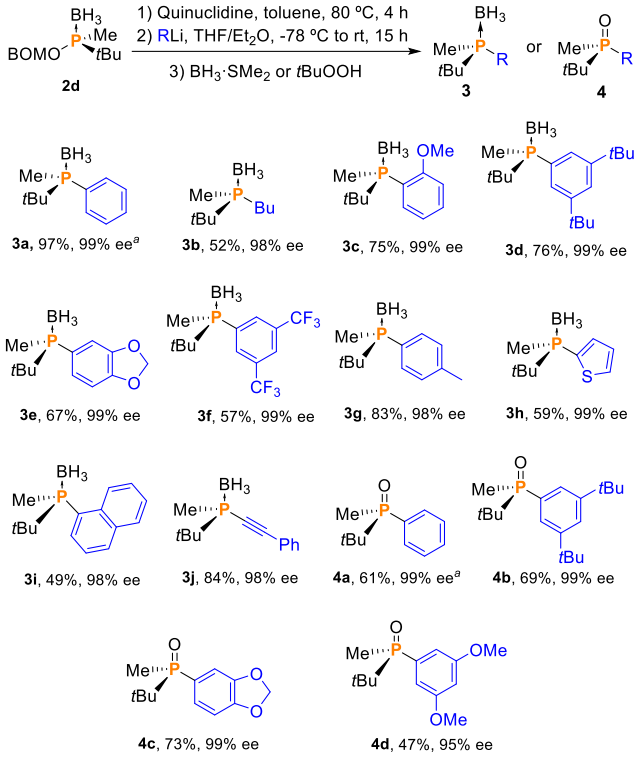
To demonstrate the capacity of BOM-phosphinite **2d** as a P-stereogenic transfer reagent, we next tested the one-pot deprotection/substitution reaction with PhLi using **2d** as starting material (Scheme 3).[17] After deprotection of **2d** in toluene at 80 °C, the reaction was cooled and 2 equiv. of phenyllithium were added. Finally, the resulting tertiary phosphine was protected again and analyzed by chiral HPLC. While addition of PhLi (1.9M in Bu_2O) at room temperature produced the *tert*-butylmethylphenyl phosphine **3a** with suboptimal optical purity, reducing the temperature to -20 °C afforded **3a** in 99% ee and excellent yield. Optical rotation of **3a** and comparison with literature data[18] revealed that the substitution took place with inversion of configuration at the phosphorus center. We believe that chelation of lithium through the BOM oxygen atoms facilitates an efficient substitution process at phosphorus.

Scheme 3. One-pot deprotection/substitution reaction with BOM-phosphinite **2d**.



To demonstrate the utility of **2d** in the synthesis of P-stereogenic tertiary phosphines we tested the scope of the reaction with several organometallic reagents (Scheme 4). The use of phenylmagnesium bromide in the substitution reaction did not allow it to reach completion, which confirmed that organolithium reagents are more efficient in this process. To achieve the highest stereoselectivity in the substitution process, the organolithium reagent was added at -78 °C and the reaction was allowed to warm up to room temperature overnight. In this way, reaction with commercial butyllithium provided **3b** in a highly stereospecific manner. By comparing the sense of rotation of **3b** with the one reported in the literature,[19] it was again confirmed that the substitution reaction with alkyllithiums occurs with inversion of configuration at phosphorus center.

Scheme 4. Reaction scope with different organolithium reagents.



[a] Substitution was carried out at -20 °C for 1.5 h instead.

Next, we tested the reaction with non-commercial organolithiums (Scheme 4). Aryllithiums were generated from the corresponding aryl bromides by metalation with BuLi at low temperature.[20] We observed that in certain instances the choice of solvent (Et_2O, THF or a mixture of both) in which the organolithium was prepared was crucial in the reaction performance. We believe that this solvent effect is not related with the generation of the ArLi, but rather has a strong influence in the P-substitution step. After careful optimization for each case, (aryl)-*tert*-butylmethyl phosphines boranes **3c-i** were prepared in moderate to good yields and very high optical purity, as determined by chiral HPLC. The method proved useful for the formation of intermediates bearing heterocycles (**3h**) or bicyclic rings (**3i**). Phosphine **3j**, bearing an acetylide moiety, was also be prepared efficiently. In contrast with most methods, modification of the last step also allowed the preparation of phosphine oxides. Addition of *tert*-butyl hydroperoxide afforded the corresponding oxides **4a-d**, again with excellent enantiomeric excesses. To prove the usefulness of these intermediates, compound **3d** was used in the synthesis of 1,2-bis(*tert*-butyl(3,5-di-*tert*-butylphenyl)phosphino)ethane (**L5-BH$_3$**) which is a bulkier analog of the C_2-symmetric BisP* ligand described by Imamoto (Scheme 5).[21] Deprotonation of **3d** at the methyl moiety with *sec*-butyllithium followed by oxidative coupling with copper (II) chloride afforded **L5-BH$_3$** in 40% yield. The solid-state structure of the ligand was elucidated by X-ray analysis and is shown in Figure 1.

Scheme 5. Synthesis of P-stereogenic bisphosphine ligand **L5-BH$_3$.**

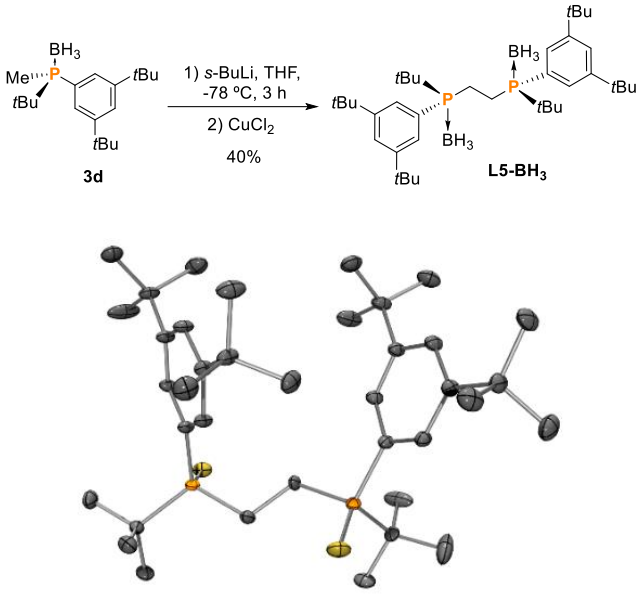
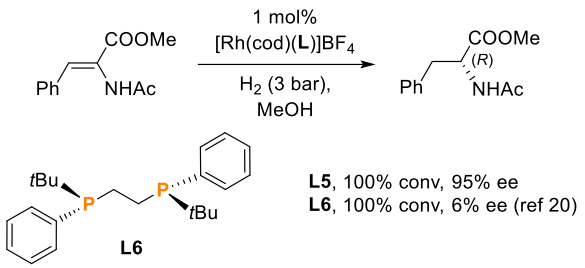


Figure 1. X-ray structure of **L5-BH$_3$**. Ortep diagram shows thermal ellipsoids at 50% probability.

The successful BisP* ligand concept developed by Imamoto is based on the use of a small (Me) group and a bulky (*t*-Bu) to build a large steric bias around the metal center. In contrast, ligand **L5** bears a *tert*-butyl and 3,5-di-*tert*-butylphenyl at the phosphorus atom, which are both very bulky groups. We envisioned that the use of these two very bulky substituents would also result in a promising catalyst design strategy. To test this hypothesis, **L5** was coordinated to rhodium and the resulting catalyst was tested in the asymmetric hydrogenation of the benchmark substrate *Z*-methyl 2-acetamidoacrylate, *Z*-MAC (see the Supporting Information for details of catalyst preparation). Hydrogenation of *Z*-MAC using 1 mol% of cationic [Rh(cod)(**L5**)]BF_4 at 3 bar of hydrogen pressure provided the corresponding dehydroamino acid with 95% ee (Scheme 6). Most interestingly, Mezzetti and co-workers reported that hydrogenation of *Z*-MAC with **L6**, bearing phenyl substituents instead of the 3,5-di-*tert*-butylphenyl moiety, provided almost no selectivity (6% ee).[22] Such a difference in selectivity suggests a strong positive influence of the *tert*-butyl groups in the 3,5 positions of the phenyl ring.[23] The distinct performance between these two ligands could be attributed to the more restricted conformation adopted by **L5** when bound to the rhodium center.[24] Overall, these results confirm that the *tert*-butyl(3,5-di-*tert*-butylphenyl) phosphinyl radical can provide high selectivity in asymmetric catalysis.

Scheme 6. Hydrogenation experiment with **L5** and comparison with the results reported with **L6**.



In summary, we have demonstrated that BOM-*tert*-butylmethylphosphinite borane is an efficient electrophilic P-stereogenic transfer reagent for the synthesis of bulky tertiary phosphines. The novel methodology relies on a one-pot deprotection/substitution process. Substitution of the trivalent phosphinite takes place with exquisite stereospecificity and provides the products with inversion of configuration at the phosphorus atom. The potential of the methodology was confirmed with the synthesis of a wide scope of tertiary phosphines with excellent enantiomeric excess. Also, the bulky P-stereogenic *tert*-butyl(3,5-di-*tert*-butylphenyl)BisP* ligand (**L5**) was synthesized and tested in the Rh-catalyzed asymmetric hydrogenation. The results show that the *tert*-butyl(3,5-di-*tert*-butylphenyl) phosphine moiety is far more selective than the parent *tert*-butylphenylphosphine and therefore emerges as a valuable moiety in ligand design.

ASSOCIATED CONTENT

Supporting Information

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

Experimental details and photocopies of ^{1}H, ^{31}P, and ^{13}C NMR spectra and HPLC chromatograms; experimental procedure for the preparation of [Rh(cod)**L5**]BF_4 (PDF)

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Notes

The authors declare no competing financial interest.

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(14) An extended Table of phosphinite deprotection experiments can be found in the Supporting Information section.

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