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 past decade, our group has developed the synthesis of P-stereogenic synths 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 Ms₂O 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 alkylithium or aryllithium reagents was unproductive.7

To address this shortcoming, here we report on the efficiency of benzoxymethyl 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.

Previous Work

This Work

We began this project by testing whether the simple methyl tert-butylmethylphosphinite borane 2a could undergo nucleophilic substitution with phenyllithium (Scheme 2). We also hope to receive feedback from the community on our approach to this challenging problem.
demonstrated that methyl phosphinite boranes provide clean substitution reaction with organolithium reagents.\textsuperscript{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. 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.\textsuperscript{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 phosphorines are more reactive when compared to borane-protected ones.\textsuperscript{12} To this end, deprotection of 2a with 1,4-diabicyclo[2.2.2]octane (DABCO) was examined (Scheme 2). As determined by \textsuperscript{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.

**Table 1.** Highlighted protection assays with different phosphinites.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>substrate\textsuperscript{a}</th>
<th>base\textsuperscript{a}</th>
<th>conditions</th>
<th>conversion\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH\textsubscript{3}</td>
<td>2b</td>
<td>DABCO</td>
<td>80 °C, 4 h</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>C\textsubscript{6}F\textsubscript{5}CH\textsubscript{2}</td>
<td>2c</td>
<td>DABCO</td>
<td>60 °C, 4 h</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>C\textsubscript{6}F\textsubscript{5}CH\textsubscript{2}</td>
<td>2c</td>
<td>DABCO</td>
<td>80 °C, 4 h</td>
<td>Decomp.</td>
</tr>
<tr>
<td>4</td>
<td>BuOCH\textsubscript{2}</td>
<td>2d</td>
<td>DABCO</td>
<td>80 °C, 4 h</td>
<td>85%</td>
</tr>
<tr>
<td>5</td>
<td>BuOCH\textsubscript{2}</td>
<td>2d</td>
<td>Quinuclidine</td>
<td>80 °C, 4 h</td>
<td>98%</td>
</tr>
<tr>
<td>6</td>
<td>MeOCH\textsubscript{2}</td>
<td>2e</td>
<td>Quinuclidine</td>
<td>80 °C, 4 h</td>
<td>90%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}NMR tube experiments, concentration: 2 (0.39 M) and base (1.2 M).

\textsuperscript{b}Conversion was determined by \textsuperscript{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).\textsuperscript{13} 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 (1.9 M in BuO) 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\textsuperscript{14} 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 4.** Reaction scope with different organolithium reagents.
Next, we tested the reaction with non-commercial organolithiums (Scheme 4). Aryllithiums were generated from the corresponding aryl bromides by metathesis with BuLi at low temperature. We observed that in certain instances the choice of solvent (EtO, 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(3,5-di-tert-butylphenyl)phosphinoethane \( \text{L5-BH}_3 \) which is a bulkier analog of the \( C_2 \)-symmetric BisP* ligand described by Imamoto (Scheme 5). Deprotonation of \( 3d \) at the methyl moiety with sec-butyllithium followed by oxidative coupling with copper (II) chloride afforded \( \text{L5-BH}_3 \) 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 \( \text{L5-BH}_3 \).

Figure 1. X-ray structure of \( \text{L5-BH}_3 \). Ortep diagram shows thermal ellipsoids at 50% probability.

The successful BisP* ligand concept developed by Imamoto is based on the use of a small \( (\text{Me}) \) group and a bulky (t-Bu) to build a large steric bias around the metal center. In contrast, ligand \( \text{L5} \) 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, \( \text{L5} \) was coordinated to rhodium and the resulting catalyst was tested in the asymmetric hydrogenation of the benchmark substrate 3-methyl-2-acetamido-3-acylate, Z-MAC (see the Supporting Information for details of catalyst preparation). Hydrogenation of Z-MAC using 1 mol% of cationic [Rh(cod)(L5)]BF₄ 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 \( \text{L6} \), bearing phenyl substituents instead of the 3,5-di-tert-butylphenyl moiety, provided almost no selectivity (6% ee). Such a difference in selectivity suggests a strong positive influence of the tert-butyl groups in the 3,5 positions of the phenyl ring. The distinct performance between these two ligands could be attributed to the more restricted conformation adopted by \( \text{L5} \) when bound to the rhodium center. 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 \( \text{L5} \) and comparison with the results reported with \( \text{L6} \).
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) phosphate moiety is far more selective than the parent tert-butylphenylphosphate 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 ¹H, ³¹P, and ¹³C NMR spectra and HPLC chromatograms; experimental procedure for the preparation of [Rh(cod)L₅]BF₄ (PDF)

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Notes
The authors declare no competing financial interest.

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REFERENCES

(8) Recently, the Pd-catalyzed coupling of tert-butylmethylphosphine borane with different arylhalides has been reported. However, some degree of racemization is observed; see: Wang, C.; Yue, C. D.; Yuan, J.; Zheng, J. L.; Zhang, Y.; Yu, H.; Chen, J.; Meng, S.; Yu, Y.; Yu, G. A.; Che, C. M. Synthesis of P-Chiral Phosphine Compounds by Palladium-Catalyzed C-P Coupling Reactions. *Chem. Commun.*, 2020, 56, 11775-11778.
(9) For the synthesis of 2a, see ref. 5.
(11) Reaction of PhMe(O)P-BH₃ with ArLi provides clean substitution reaction with inversion of configuration, see ref. 10.
(14) An extended Table of phosphinite deprotection experiments can be found in the Supporting Information section.
(15) When using DABCO, either increasing the reaction time or number of equivalents of base did not afford complete conversion as monitored by ³¹P NMR (see SI for details).
(17) The use of toluene in the deprotection proved to be equivalent to benzene-d₆ in terms of reaction performance.
(20) For in situ generated ArLi, 5 equivalents of organometallic reagent were employed to ensure complete conversion. We think that the need for extra equivalents of ArLi reagents is due to a combination of insoluble and dilution effects.