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The Hydroxyalkyl Moiety As a Protecting Group for the Stereospecific Alkylation of Masked Secondary Phosphine-Boranes

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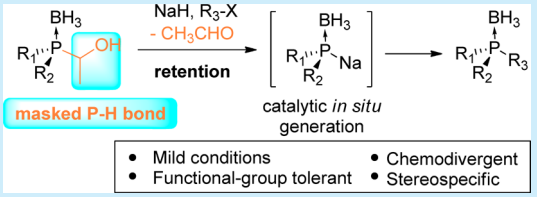
Supporting Information

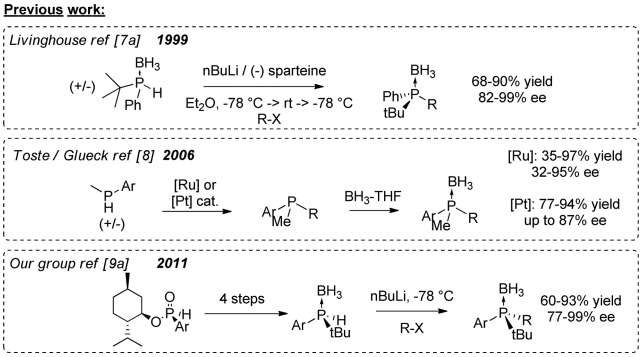
ABSTRACT: The synthesis of functionalized tertiary phosphine-boranes has been developed via a chemodivergent approach from readily accessible (hydroxymethyl) phosphine-boranes under mild conditions. O-Alkylation or decarbonylative P-alkylation product could be exclusively obtained. The P-alkylation reaction was found to proceed in moderate to very good yields and very high enantiospecificity (es >95%) using a variety of alkyl halides as electrophiles. The configurational stability of the sodium phosphido-borane intermediate was also investigated and allowed a deeper understanding of the reaction mechanism, furnishing secondary phosphine-boranes in moderate yield and enantiopurity.



In asymmetric catalysis, the use of chiral phosphines has allowed a wide array of enantioselective transformations, where the phosphine can be used either as a ligand for transition metals[1] or as an organocatalyst.[2] While most of the phosphine ligands used in asymmetric transition-metal catalysis have a chiral backbone,[3] the ones bearing the chiral center at the phosphorus atom (P-stereogenic phosphines) have been given much less attention, mostly due to their difficult asymmetric synthesis. However, in some cases, P-stereogenic phosphines feature better reactivity and/or selectivity than their chiral-backboned counterparts.[4] In this context, the synthesis of P-stereogenic phosphines remains a challenging area of research. Among the numerous methods leading to these chiral compounds, functionalization of secondary phosphines (SPs) or phosphine-boranes (SPBs) has been intensively documented.[5] More specifically, the design of P-stereogenic tertiary phosphines through alkylation of P-chiral secondary phosphines has been investigated[6] (Scheme 1). Indeed, in the late 1990s, Livinghouse described the sparteine-mediated Dynamic Thermodynamic Resolution (DTR) of *tert*-butyl (phenyl) SPB.[7a] The key point of the success of this method was the precipitation of one diastereomer of the lithiated phosphine-borane−sparteine complex at 25 °C, involving probably a crystallization-induced process.[7b] The metal-catalyzed dynamic kinetic resolution (DKR) of secondary phosphine has also been investigated by Toste and Glueck employing chiral ruthenium(II)[8a,b] or platinum(II)[8c−e] complexes as catalysts. Indeed, using methyl (aryl) phosphine, the authors described the preparation of a variety of chiral mono- and bis-phosphines, which may then be quenched by BH_3−THF[8a,b] to yield the corresponding phosphine-boranes. More recently, our group also developed the stereospecific alkylation of enantioenriched *tert*-butyl (aryl) SPB using *n*-BuLi as a base.[9a]

The reaction was found to occur with high conservation of chiral information as long as the reaction was run at −78 °C. Despite the remarkable efficiency of these methods, access to aryl(alkyl) or diaryl SPBs remains difficult, especially for enantioenriched compounds. Furthermore, although the alkylation of configurationally stable dialkylphosphido-boranes proceeds in high conservation of chiral information,[9c] the use of aryl(alkyl) or diaryl SPBs can be problematic, as partial racemization may occur following the alkylation temperature.[9a,b] The use of excess organolithium compounds as a base can also be prejudicial to the functional-group tolerance and, thus, limits the use of functionalized electrophiles (especially with carbonyl and halogen functional groups). Recently, Hayashi described the palladium-catalyzed decarbonylative arylation of (hydroxymethyl) phosphine sulfides in excellent yields[10] (Scheme 2). This retroaddition process had already been observed earlier by Imamoto under basic and thermal conditions,[11] and more recently by Kann, who noted the formation of racemic P-alkylation products.[11c] Pietrusiewicz[12a] and our group[12b] independently reported the stereo-

Scheme 1. Asymmetric Alkylation of SPs and SPBs



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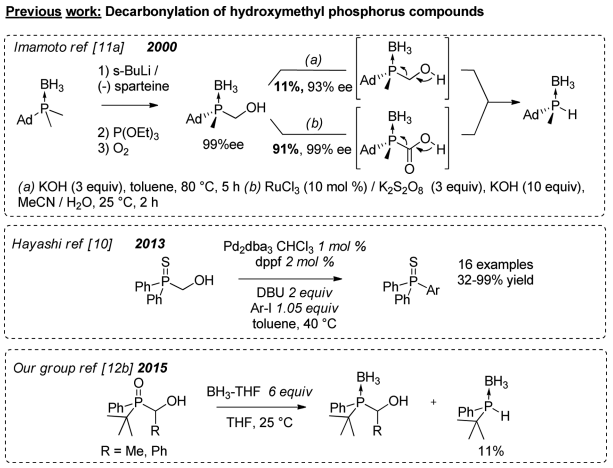
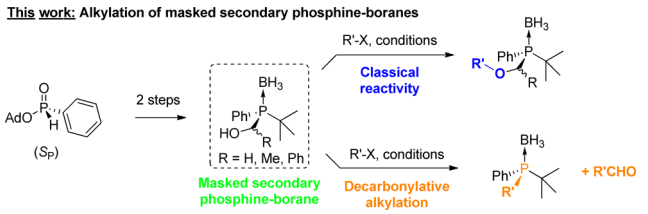
Scheme 2. Decarbonylations of (Hydroxymethyl) Phosphorus Compound



specific reduction of α-hydroxyphosphine oxides under mild conditions (Scheme 2).

When a carbon substituent was present on the α atom, we observed an erosion of the diastereoselectivity, and some SPB was isolated, along with the desired product.[13b] We also attributed this fact to the possible retroaddition of the hydroxyalkyl moiety under borane conditions. On the basis of these observations, we turned our attention to the development of a selective method for the decarbonylative alkylation of hydroxymethyl phosphine-boranes, which are readily obtained from H-adamantylphosphinates[12b,13] (Scheme 3).

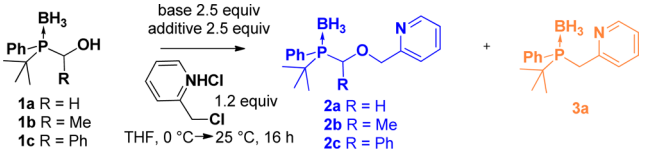
Scheme 3. Envisioned Strategy for the Alkylation of Masked SPBs



To optimize the conditions, we first screened the reaction parameters, using compound **1a** and *o*-(chloromethyl)pyridine hydrochloride as an electrophile. When the reaction was run at room temperature in THF and sodium hydride as the base, a nearly 1:1 mixture of O-alkylation (**2a**) and decarbonylative P-alkylation (**3a**) products was obtained in moderate yield (Table 1, entry 1). The formation of the latter product, resulting from the retro-addition (i.e., decarbonylation) of the α-hydroxyalkyl-phosphine-borane, was postulated to go through a sodium phosphido-borane, which would then be trapped by the electrophile *in situ*. When conducting the reaction on enantioenriched starting material, we obtained 29% of **2a** with nearly fully conserved chiral information (er = 97.5:2.5, entry 2) and 32% of **3a**, also with minor loss of enantiomeric excess (er = 95.5:4.5, entry 2). When looking at the influence of the solvent, we observed that both polar and nonpolar solvents favored the formation of **2a**, although THF gave a nearly 1:1 mixture (entries 2−4).

In the case of DMF, the enantiomeric ratio of **2a** decreased to 83:17 (entry 3), suggesting racemization of the sodium

Table 1. Optimization of the Reaction Conditions



entry	1[a]	base / additive	2/3a[b]	yield [%] (er)
1	(+/-) **1a**	NaH	1.1/1	30 (50:50)
				25 (50:50)
2	(S_P)-**1a**	NaH	1.1/1	29 (97.5:2.5)
				32 (95.5:4.5)
3[c]	(S_P)-**1a**	NaH	2.5/1	26 (83:17)
4[d]	(S_P)-**1a**	NaH	4.1/1	39 (98:2)
				9 (94:6)
5	(S_P)-**1a**	NaH / LiCl	-	-
6	(S_P)-**1a**	NaH / $MgCl_2$	-	-
7	(S_P)-**1a**	NaH / KCl	1.5/1	38 (98:2)
				28 (96:4)
8	(S_P)-**1a**	NaH / CsCl	1/1.5	28 (96.5:3.5)
				40 (97.5:2.5)
9	(S_P)-**1a**	NaH / Bu_4NCl	>1/20	48 (50:50)
10[e]	(S_P)-**1a**	NaH	>20/1	80 (97.5:2.5)
11	(S_P)-**1b**	NaH	>1/20	57 (93:7)
12	(S_P)-**1c**	NaH	>1/20	36 (93:7)
13[f]	(S_P)-**1b**	NaH	>1/20	77 (95:5)
14[f]	(R_P)-**1b**	NaH	>1/20	79 (4.5:94.5)

[a] **1a**: er = 98:2. **1b**: dr ~1/1, er = 95:5 (both diastereomers). **1c**: dr =2.6/1, er (major dia) = 98.5:1.5 and er (minor dia) = 87:13. [b] Determined by ^{31}P NMR of the crude. [c] DMF used as solvent. [d] Toluene used as solvent. [e] 2-(Bromomethyl)pyridine hydrobromide used as the electrophile. [f] 3 equiv of NaH were used.

phosphido-borane intermediate in a more dissociating solvent.[11c] Then, we turned our attention to the influence of an alkoxide counterion using THF as solvent, and we observed that the more the ion pair was separated, the more formation of **3a** was favored (entries 2, 5−9). However, in the case of the ammonium counterion, this was also accompanied by complete racemization at the phosphorus atom (entry 9). This is consistent with the formation of *tert*-butyl(phenyl)phosphido borane, the configurational stability of which would depend on the counterion.[9b,14] It is worth noting that when using strongly coordinated Mg or Li counterions (entries 5−6), the reaction did not proceed at room temperature. When changing the leaving group on the electrophile from Cl to Br, only product **2a** was obtained in 80% isolated yield and 97:3 er (entry 10). This is also in accordance with retroaddition of the hydroxymethyl group, as when using a better leaving group (X = Br), SN_2 of the alkoxide on the alkyl halide (i.e., "Williamson"-type reaction) may kinetically outcompete the retroaddition, thus allowing the selective formation of **2a**. Finally, we evaluated the influence of substitution on the α-carbon on the selectivity. When a carbon substituent was present (R= Me, Ph, entries 11−12), highly selective formation of **3** was observed. Indeed, the use of methyl substituted substrate **1b** did furnish the desired product **3** without any detectable amount of the O-alkylated product **2b**, in a moderate 57% yield and high enantiomeric ratio (er = 93:7, entry 11). The use of phenyl substituted substrate **1c** gave similar

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reactivity and selectivity for the formation of **3** (36% yield, er = 93:7, entry 12). Finally, when the amount of sodium hydride was raised to 3 equiv, the reaction of **1b** gave the desired compound **3a** in a good 77% yield and very good enantiomeric ratio (er = 95:5, entry 13). The substitution occurred stereospecifically with retention of configuration at the phosphorus atom, as the reaction of the other enantiomer gave a similar yield and afforded the other enantiomer of the product in nearly equal selectivity (entry 14). Unlike previously reported protocols,[11b] the reactions did not lead to detectable amounts of aldehyde reduction products by the sodium phosphido-borane at operating temperature (assessed by the absence of degradation products on ^{31}P NMR). With these optimized conditions in hand, we turned our attention to expanding the scope of the decarbonylative P-alkylation of **1b**, using a variety of alkyl halides (Figure 1). When a variety of benzylic halides were used (Figure 1, **3b**–**f**), electron-donating groups on the aromatic ring favored the reaction.

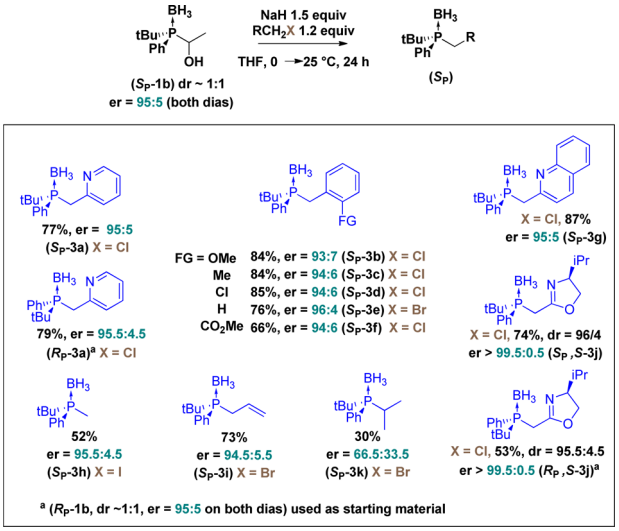
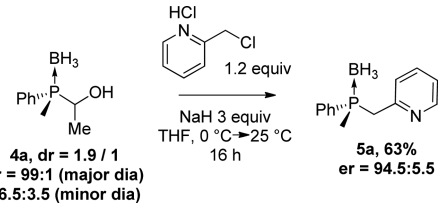


Figure 1. Scope of the P-alkylation of compound **1b** (dr ~1/1, er = 95:5 (both diastereomers)).

The use of methyl iodide or allyl bromide also allowed the formation of compounds **3h** and **3i**, respectively, in moderate yields. In all these cases, minor to no erosion of the stereochemical information was observed (es >95%).[15] This method also allowed the use of (chloromethyl) chiral oxazoline as an electrophile, to furnish P, C stereogenic phosphine/oxazoline preligands (compounds **3j**) in moderate yields and with high diastereo- and enantioselectivity. Again, no racemization was observed on the product. Indeed, as a chiral electrophile is used in this case, the racemization can be assessed by comparing the er of the starting material with the dr of the product, given that the carbon center does not undergo racemization under these conditions. The use of less reactive secondary alkyl bromide resulted in decreased reactivity and selectivity using the optimized conditions (**3k**, 30% yield, er = 66.5:33.5). In this case, 36% of SPB (resulting from unreacted sodium phosphido-borane) was also isolated.

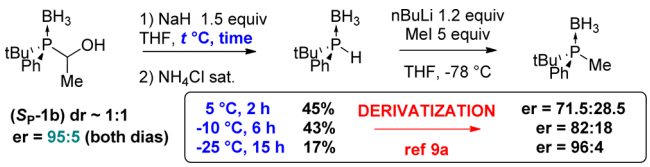
Using methyl(phenyl) masked SPB **4a**, the access to tertiary phosphine **5a** was enabled under the same conditions. In this case, the reaction was found to be slower but occurred in similar enantiospecificity, as only minor racemization occurred (Scheme 4). This remarkable result testifies to the versatility of

Scheme 4. Alkylation of Other Group Functionalized P-Stereogenic Phosphine-Borane



the method, which allows the formation of enantioenriched compounds which are challenging to access using reported methods.[8a] To gain information on the reaction mechanism, we used a proton source as the electrophile. The corresponding SPB was obtained, and its enantiomeric ratio was assessed by derivatizing to the corresponding P-Me compound[9a] (Scheme 5). When the deprotonation was run at 5 °C for 2 h, 45% of

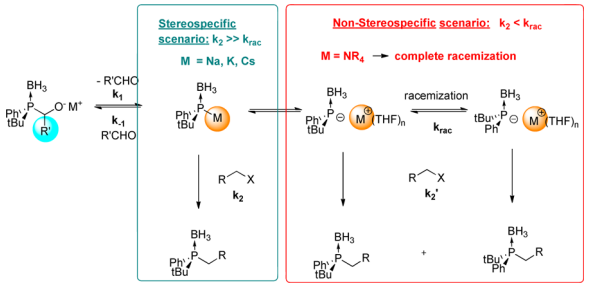
Scheme 5. Configurational Stability of Sodium Phosphido-Borane



SPB was isolated, and substantial racemization occurred. At −10 °C, the reaction outcome was similar to the case for 5 °C, although racemization was diminished. At −25 °C, the reaction provided desired SPB in low yield (17%) but without erosion of enantiomeric ratio, accounting for the higher stability of the alkoxide at low temperature.

These results suggest that the sodium secondary phosphido-borane seems to be configurationally more stable than its lithium counterpart.[9b,14] However, as detectable racemization occurs despite the temperature, this does not explain the complete stereospecificity observed during the alkylation process. To rationalize this result, we propose a mechanism where the sodium phosphido-borane would be generated in a catalytic amount through the reaction time, and in the presence of the electrophile, alkylation at the phosphorus atom would be faster than racemization of the anionic intermediate ($k_2 \gg k_{rac}$, Scheme 6). This mechanism would also explain complete racemization using the ammonium counterion, as in this case of $k_2 < k_{rac}$. In the case of a less electrophilic secondary alkyl halide, a diminished k_2 value may account for the decrease in stereoselectivity of the process ($k_2 \approx k_{rac}$).

Scheme 6. Proposed Reaction Scenario



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In conclusion, we have synthesized a variety of functionalized tertiary phosphine-boranes by a straightforward approach, with moderate to good yields and excellent enantiomeric ratios. In the present report, the configurational instability of alkyl(aryl)-phosphido-boranes has been circumvented by catalytic *in situ* generation of these reactive species under mild conditions via decarbonylation of hydroxyalkylphosphine-borane. The synthesis of these compounds has been achieved in a three-step enantiospecific sequence, from readily available, enantiopure H-adamantyl phosphinate (which are separated via semipreparative chiral HPLC).[13a]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03450.

Experimental procedures, products characterization, NMR spectra, and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Enantiospecificity es = ee (product)/ee (starting material). The absolute stereochemistry was determined by comparing the sign of optical rotation of compound **3e** with ref 9a, confirming the retention of configuration at the phosphorus atom.

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