Preparation of *t*-Butyldimethylphosphine Borane and *t*-Butyldiethylphosphine Borane by Selective Grignard Reagent Substitution of Phosphorus Trichloride

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ABSTRACT
The synthesis of differentially substituted trialkylphosphine boranes from the selective substitution reaction of Grignard reagents with phosphorus trichloride in a single reaction flask was studied. The reaction temperature, stoichiometric loading of the first equivalent of Grignard reagent and reaction time were found to be important for maximizing the yield and selectivity of the reaction. Reaction conditions were optimized to achieve maximum yield of *t*-butyldiethylphosphine borane. The optimized conditions were applied to the syntheses of *t*-butyldiethylphosphine borane and *t*-butyldimethylphosphine borane, which provided 60% and 62% isolated yields respectively. Products were characterized with mass spectrometry, infrared spectroscopy, ^{1}H, ^{13}C, and ^{31}P nuclear magnetic resonance spectroscopy.

KEYWORDS
Synthesis; Trialkylphosphine; Grignard Reagent; Selective; Substitution Reaction; *t*-Butyldiethylphosphine Borane; *t*-Butyldimethylphosphine Borane; Phosphorus Trichloride

INTRODUCTION

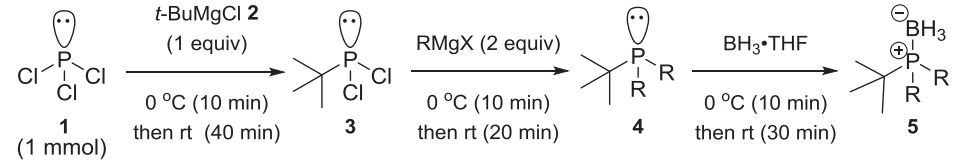
The reactions of Grignard reagents with phosphorus trihalides have been known for over a century.[1–3] Moreover, the alkylated phosphorus products of these reactions are useful as ligands in many transition metal-catalyzed transformations.[3–8] Previous to this work, it has been common to isolate the alkyldichlorophosphine or purchase it from commercial sources before substituting the remaining two chlorides with alkyl nucleophiles.[10–12] For example, *t*-butyldimethylphosphine borane can be prepared from *t*-butyldichlorophosphine and MeMgBr in 60% yield.[13] However, general procedures for the selective one-pot substitution of different alkyl Grignard reagents with phosphorus trichloride to form differentially substituted trialkylphosphines remain unknown.[14] This is despite the fact that this represents the most straightforward way to prepare differentially substituted trialkylphosphines from inexpensive phosphorus trichloride. Herein we report our studies on the synthesis of *t*-butyldimethylphosphine borane and *t*-butyldiethylphosphine borane by selective Grignard reagent substitution reactions with phosphorus trichloride.

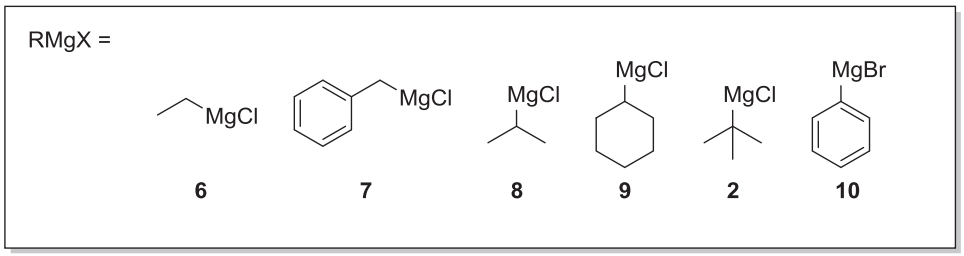
Borane protected trialkylphosphines were used in this work because electron rich trialkylphosphines are reactive with oxygen which makes their handling difficult. Fortunately, borane can be used to protect the readily oxidizable phosphorus atom by simple Lewis base/Lewis acid complexation.[16] This technique has multiple advantages: (1) the phosphine can be protected *in situ* by reaction with borane in tetrahydrofuran (THF), (2) the phosphine-borane adduct is stable to the exposure of ambient oxygen, silica gel chromatography, and aqueous acids; which enables the handling and purification of the phosphine-borane adducts, (3) the borane protecting group can be readily removed by reaction with a Lewis base[17] or strong anhydrous acid.[18,19]

RESULTS AND DISCUSSION

Initial studies on the selective addition of Grignard reagents to PCl_3 **1** began with the reaction of *t*-BuMgCl **2** and **1** (**Scheme 1**). The Grignard reagent *t*-BuMgCl was chosen because the preparation of *t*-BuPCl_2 suggested that the large size of *t*-BuMgCl would allow for selectivity between the mono, di, and trisubstitution reaction.[11] A second Grignard reagent was then added to substitute the remaining two chlorine atoms and the phosphorus atom was protected with borane prior to workup and analysis by gas chromatography-mass spectrometry (GC-MS). Preliminary experiments evaluated a variety of Grignard reagents as nucleophiles in the second substitution reaction. Grignard reagents with primary, secondary and tertiary sp^3 hybridized C–Mg bonds, as well as

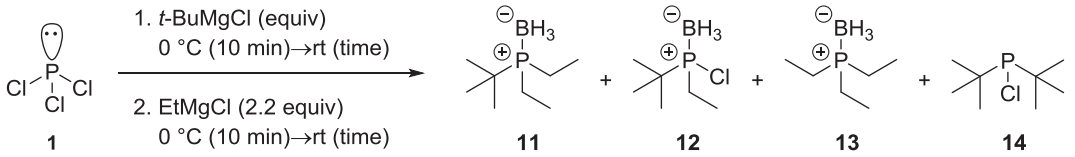
sp² hybridized C–Mg bonds were evaluated. Of these initially evaluated Grignard reagents, only EtMgCl provided clean production of the desired *t*-butyldialkylphosphine **5**. Therefore, EtMgCl was chosen as the second Grignard reagent for studies directed to optimize the yield of the selective substitution reaction.





Scheme 1.

The selective substitution reaction of one equivalent of *t*-BuMgCl and two equivalents of EtMgCl **6** with PCl_3 was optimized by evaluating reagent equivalents and the incubation time between reagent additions (**Table 1**). In all experiments, reagents were added to the reaction mixture once it had been cooled to 0°C in an ice bath.[20] After each reagent addition, the reaction mixture was allowed to stir for 10 min at 0 °C before warming to room temperature for the time specified. The reaction mixture was again cooled to 0°C before the next reagent was added. An experiment following these standard conditions provided 88% of *t*-butyldiethylphosphine borane **11** by GC-MS analysis of the crude reaction mixture (entry 1). Allowing the reaction to immediately warm to room temperature only after the addition of *t*-BuMgCl provided 71% of **11** (entry 2). In addition, allowing reactions to stir for ten minutes at 0°C prior to warming to room temperature decreased the amount of **13** produced, which later proved to be inseparable from **11** via chromatography. These results suggest that the first substitution reaction time of 10 min at 0 °C is important to achieve selectivity for monoaddition. Next, the stoichiometric loading of *t*-BuMgCl (1–1.25 equiv) with respect to **1** was examined (compare entries 1, 3, and 4). The yield of **11** was found to be similar when 1.0 or 1.25 equiv of *t*-BuMgCl was used, however 1.0 equiv of *t*-BuMgCl produced less of the diaddition reaction product **14**.[5] The reaction times at room temperature after the addition of *t*-BuMgCl were then studied (entries 5-9). In these experiments, the yield of **11** increased only slightly from 88% to 90% as the reaction time was increased up to 40 minutes. However, at 60 minutes the yield of **11** began to decrease and production of **14** increased. The reaction times at room temperature after the addition of EtMgCl were also studied (entries 10-14). Unlike the reaction times associated with the addition of *t*-BuMgCl, reaction times of greater than 20 minutes after the addition of EtMgCl showed no significant change in the yield of **11**.



Entry	*t*-BuMgCl (equiv)	*t*-BuMgCl time at rt (min)	EtMgCl time at rt (min)	11 (%)	12 (%)	13 (%)	14 (%)
1	1.0	15	15	88	10	2	0
2[c]	1.0	15	15	71	14	15	0
3	1.1	15	15	89	8	trace	3
4	1.25	15	15	90	trace	trace	10
5	1.0	20	15	88	4	8	0
6	1.0	40	15	90	4	6	0
7	1.0	60	15	82	6.5	7	4.5
8	1.0	80	15	76	5	6	13
9	1.0	100	15	68	6	8	18
10	1.0	40	20	88	0	12	0
11	1.0	40	40	87	0	13	0
12	1.0	40	60	88	0	12	0
13	1.0	40	80	88	0	12	0
14	1.0	40	100	87	0	13	0

Table 1. Optimization of the Selective Grignard Reagent Substitution Reaction.[a,b]
[a]Structure of **12**, **13**, and **14** tentatively assigned by analysis of GC-MS data. [b]Relative peak area ratios. 0°C→room temperature immediately after drop-wise addition of *t*-BuMgCl.

An additional set of experiments to evaluate Grignard reagent scope were performed using the previously optimized reaction conditions. In these experiments, *t*-butyldichlorophosphine was prepared *in situ* by reaction of PCl_3 and *t*-BuMgCl at 0°C for 10 min and warming to room temperature and stirring an additional 40 min. The reaction was cooled to 0°C and a Grignard reagent (2.0 equiv) from **Figure 1** was then added drop-wise by syringe. The reaction was stirred for 10 min at 0°C before warming to room temperature and stirring an additional 20 min. The reaction was cooled to 0°C and BH_3•THF was added drop-wise by syringe. The reaction was again stirred for 10 min at 0°C before warming to room temperature and stirring an additional 3 h. In addition to EtMgCl, MeMgCl **15** was also found to provide clean production of the desired *t*-butyldialkylphosphine borane by GC-MS analysis of crude reaction aliquots under the optimized reaction conditions. The optimized reaction conditions were then applied to the 5 mmol preparation of *t*-butyldiethylphosphine borane **11** and *t*-butyldimethylphosphine borane **16**.

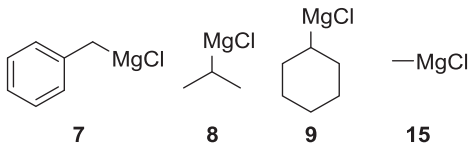
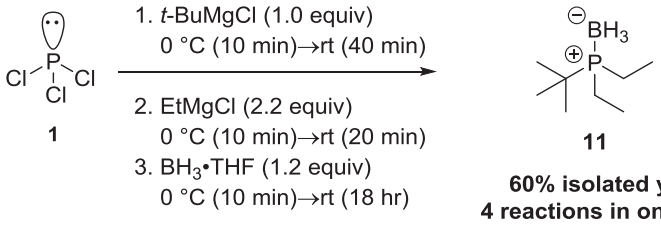


Figure 1. Grignard reagents evaluated under the optimized reaction conditions.

Procedure for the Synthesis of t-Butyldiethylphosphine Borane (11)



Scheme 2.

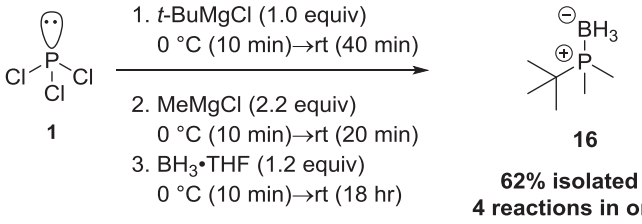
To an oven dried, 50-mL, single neck, round-bottomed flask, containing a magnetic stir bar, capped with a septum that was bound with copper wire, and then evacuated and filled with argon (×3) was added dry THF by syringe. The solvent was purged for 20 min with argon. The flask was cooled to 0°C using an ice bath, followed by the addition of PCl_3 (436 μL, 5 mmol) by syringe. *t*-BuMgCl ([1.7], 2.94 mL, 1.0 equiv) was added drop-wise by syringe and allowed to stir at 0°C for 10 min. The reaction was warmed to room temperature by removal from the cooling bath and stirred for 40 min. The reaction was cooled to 0°C and EtMgCl ([2.7], 4.07 mL, 2.2 equiv) was added drop-wise by syringe. The reaction was allowed to stir at 0°C for 10 min, warmed to room temperature, and stirred an additional 20 min. The mixture was cooled to 0°C and BH_3·THF ([1.0], 6.0 mL, 1.2 equiv) was added drop-wise by syringe. The reaction was allowed to stir at 0°C for 10 min, warmed to room temperature, and stirred at least 30 min. The mixture was quenched by slow addition to a stirred solution of 1 M HCl (60 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solution was concentrated by rotary evaporation at 50°C and 140 torr. Residual solvent was further removed under vacuum at 2 torr for 20 min.

The crude product was purified by silica gel column chromatography. The column was prepared using 40 g of silica gel suspended in hexane. The product was loaded neat and the flask was rinsed with minimal dichloromethane. An eluent consisting of a concentration gradient of 100 mL hexane, 100 mL 1% EtOAc/hexane, and 100 mL 2% EtOAc/hexane was used to elute the product. Fractions (2-3 mL each) were collected and analyzed by thin-layer chromatography. Fractions containing the desired product were combined and concentrated as described above to provide 480 mg (60%) of **11** as a white, crystalline solid (**Scheme 2**). The product was stable to exposure to ambient oxygen and was stored in a refrigerator for weeks with no discernible change in purity or reactivity.

Data for t-Butyldiethylphosphine Borane (11)

mp:	42.7–43.5 °C
^{1}H NMR:	(400 MHz, $CDCl_3$) 1.62 (m, 4 H, C***H***$_2$Me), 1.16 (d, *J* = 12.9, 9 H, C(C***H***$_3$)$_3$), 1.18 (dt, *J* = 15.0, 7.5, 6 H, CH_2C***H***$_3$), 0.46 (td, *J* = 94.7, 14.3, 3 H, ***H***$_3$B).
^{13}C NMR:	(130 MHz, $CDCl_3$) 28.1 (d, *J* = 33.1, ***C***$(CH_3)_3$), 25.7 (d, *J* = 1.4, C(***C***$H_3)_3$), 13.2 (d, *J* = 32.7, ***C***H_2CH_3), 8.06 (d, *J* = 1.9, CH_2***C***H_3)
^{31}P NMR:	(162 MHz, $CDCl_3$) 33.7 (q, *J* = 62.2).
IR:	(neat) 2974 (w), 2944 (w), 2882 (w), 2373 (w), 2339 (w), 2317 (w), 2270 (w), 2252 (w), 1466 (w), 1409 (w), 1367 (w), 1273 (w), 1254 (w), 1203 (w), 1132 (w), 1076 (w), 1064 (w), 1043 (w), 1031 (w), 1020 (w), 940 (w), 822 (w), 774 (m), 751 (w), 709 (w).
MS:	(EI, 70 eV) 159 ([M−H]$^+$, 8), 155 (10), 146 ([M−BH_3]$^+$, 100), 130 (3), 116 (9), 102 ([M−*t*-butyl]$^+$, 9), 90 ([M−BH_3, *t*-butyl]$^+$, 98), 74 ([M−*t*-butyl, ethyl]$^+$, 16), 69 (5), 62 ([M−BH_3,*t*-butyl, ethyl]$^+$, 41), 57 (65), 53 (2).
TLC:	R_f 0.43 (95:5 hexane/ethyl acetate) [silica gel, aqueous $KMnO_4$]

Procedure for the Synthesis of t-Butyldimethylphosphine Borane (16)



Scheme 3.

To an oven dried, 50-mL, single neck, round-bottomed flask, containing a magnetic stir bar, capped with a septum that was bound with copper wire, and then evacuated and filled with argon (×3) was added dry THF by syringe. The solvent was purged for 20 min with argon. The flask was cooled to 0°C using an ice bath, followed by the addition of PCl_3 (436 μL, 5 mmol) by syringe. *t*-BuMgCl ([1.7], 2.94 mL, 1.0 equiv) was added drop-wise by syringe and allowed to stir at 0°C for 10 min. The reaction was warmed to room temperature by removal from the cooling bath and stirred for 40 min. The reaction was cooled to 0°C and MeMgCl ([3.0], 3.67 mL, 2.2 equiv) was added drop-wise by syringe. The reaction was allowed to stir at 0°C for 10 min, warmed to room temperature, and stirred an additional 20 min. The mixture was cooled to 0°C and BH_3·THF (1.2 equiv.) was added drop-wise by syringe. The reaction was allowed to stir at 0°C for 10 min, warmed to room temperature, and stirred at least 30 min. The mixture was quenched by slow addition to a stirred solution of 1 M HCl (60 mL) at 0°C. The resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (3 × 20 mL), and dried over anhydrous Na_2SO_4. Et_2O was removed by rotary evaporation at 35 °C and 200 torr. Residual solvent was further removed under vacuum at 2 torr for 20 min.

The crude product was purified by column chromatography. The column was prepared using 40 g of silica gel suspended in hexane. The product was loaded neat and the flask was rinsed with minimal dichloromethane. An eluent consisting of a concentration gradient of 200 mL hexane, 50 mL 1% Et_2O/hexane, 50 mL 2% Et_2O/hexane, 100 mL 4% Et_2O/hexane, and 100 mL 6% Et_2O/hexane was used to elute the product. Fractions (2-3 mL each) were collected and analyzed by thin-layer chromatography. Fractions found to contain the desired product were combined and concentrated as described above to provide 411 mg (62%) of **16** as a white, crystalline solid (**Scheme 3**). The product was stable to exposure to ambient oxygen and was stored in a refrigerator for weeks with no discernible change in purity or reactivity.

Data for t-Butyldimethylphosphine Borane (16)

mp:	160.5–161.0 °C
^{1}H NMR:	(400 MHz, $CDCl_3$)
	1.24 (d, *J*= 9.9, 6H, C$\underline{\boldsymbol{H}}_3$) 1.17 (d, *J*=13.5, 9H, C(C$\underline{\boldsymbol{H}}_3$)$_3$) 0.5 (qd *J*= 95.3, 15.4, 3H, $\underline{\boldsymbol{H}}_3$B)
^{13}C NMR:	(130 MHz, $CDCl_3$)
	26.65 (d, *J*= 35.09, 1C, $\underline{\boldsymbol{C}}$(CH$_3$)$_3$) 24.77 (d, *J*= 2.45, 3C, C($\underline{\boldsymbol{C}}H_3$)$_3$) 7.30 (d *J*=35.97, 2C, $\underline{\boldsymbol{C}}H_3$)
^{31}P NMR:	(162 MHz, $CDCl_3$)
	20.3 (q, *J*= 38 Hz)
IR:	(neat)
	2965 (w). 2869 (w), 2376 (m), 2256 (w), 1474 (w), 1463 (w), 1422 (w), 1290 (w), 1137 (w), 1068 (w), 1018 (w), 942 (w), 918 (w), 851 (w), 820 (w), 756 (w).
MS:	(EI 70eV)
	131 ([M−H], 12). 118 ([M−BH_3], 100), 88 ([M−BH_3, methyl, methyl, 19), 74 ([M−*t*-butyl, H], 24), 62 (68), 57 (50).
TLC:	R_f: 0.20 (97:3 hexanes/diethyl ether) [silica gel, aqueous $KMnO_4$]

CONCLUSIONS

The *t*-butyldialkylphosphine boranes, *t*-butyldiethylphosphine borane and *t*-butyldimethylphosphine borane, were prepared by selective Grignard substitution reaction of PCl_3. The highlights of this method include the use of inexpensive PCl_3 and a one-pot experimental procedure. Reaction temperature and time were found to be important for maximizing the yield and selectivity of the reaction. A stoichiometric loading of 1 equivalent of *t*-BuMgCl was found to be optimal. The optimized reaction conditions were demonstrated in the 5 mmol preparation of *t*-butyldiethylphosphine borane and *t*-butyldimethylphosphine borane in 60% and 62% yields respectfully. We currently work to transform the phosphine boranes into phosphonium tetrafluoroborate salts and use them in transition metal-catalyzed reactions.

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Matthew Prater graduated Magna Cum Laude from Southern Utah University in 2015 with a B.S. degree in chemistry with an emphasis in professional chemistry. While at SUU, Matthew was the recipient of the Walter Maxwell Gibson Research Fellowship, and the L.S. and Aline W. Skaggs Research Grant. He currently pursues a graduate degree in chemistry at the University of Utah.

PRESS SUMMARY

Trialkylphosphines are commonly used as ligands in the transition metal-catalyzed reactions that produce a number of fine chemicals and pharmaceuticals. These reactions often require tuning of the catalyst by subtle variation in the ligand structure to maximize yield and selectivity. This work describes the discovery and optimization of an efficient synthesis of *t*-butyldimethylphosphine and *t*-butyldiethylphosphine, protected as their borane adducts, by a one-pot, selective Grignard reagent substitution reaction of inexpensive phosphorus trichloride.