Organic Process Research & Development

COMMUNICATION

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Preparative Synthesis via Continuous Flow of 4,4,5,5-Tetramethyl-2-(3-trimethylsilyl-2-propynyl)-1,3,2-dioxaborolane: A General Propargylation Reagent

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Supporting Information

ABSTRACT: A scalable process for the preparation of 4,4,5,5-tetramethyl-2-(3-trimethylsilyl-2-propynyl)-1,3,2-dioxaborolane from trimethylsilylpropyne, isopropyl pinacol borate, and *n*-butyllithium is described. Problems associated with implementing a typical aqueous workup and batch process into production due to borolane "ate" equilibration and protonolysis are presented. To address these issues, a continuous-flow and distillation process was developed which efficiently produced 297 kg of the key propargylation reagent.

INTRODUCTION

Organoboronic acids and esters are valuable synthetic building blocks.[1] Recently, propargyl borolane **1**, 4,4,5,5-tetramethyl-2-(3-trimethylsilyl-2-propynyl)-1,3,2-dioxaborolane,[2] demonstrated significant utility as a versatile reagent for the site-selective propargylations of carbonyl and imine species (Scheme 1). For example, the zinc-catalyzed propargylation of aldehydes and ketones with borolane **1** provided an operationally simple process for the synthesis of homopropargylic alcohols.[3] Additionally, chiral homopropargyl amines were readily accessed through the highly diastereoselective zinc-catalyzed propargylation of *tert*-butanesulfinimines.[4] Through the proper choice of ligands, the copper-catalyzed asymmetric propargylation of aldehydes[5] and ketones[6] was also demonstrated with remarkable functional group tolerance and scope. Alternatively, conversion of the propargyl boronate to the diethanolamine derivative provided facile access to allenyl halides.[7] Synthesis of organoboronate esters may involve the addition of a Grignard reagent to a trialkoxyborate wherein formation of the "ate" intermediate prevents polyalkylation, thereby affording reasonable to high yields for the respective organoborolane.[8] Hoffmann and coworkers employed such a strategy for the synthesis of propargyl borolane **1** with an allenyl Grignard reagent generated from a propargyl bromide (Scheme 2).[9] Although the process provided a gram-scale synthesis of the key borolane, the use of the shock-sensitive propargyl bromide[10] and exothermic, dissolving-metal reduction presents safety and engineering issues that limit the rapid implementation into a pilot plant. Furthermore, the necessary propargyl bromide required either the TMS protection of a propargyl bromide[11] or a sequential TMS protection and substitution of a propargyl alcohol to the bromide intermediate.[12] Alternatively, a Matteson homologation approach has also been pursued for the preparation of propargyl boronates through the iodomethyl pinacol borate intermediate.[13] Direct utilization of trimethylsilylpropyne for the substitution with a borate circumvents the multistep synthesis and purification of a halide intermediate, thereby affording a more cost-effective approach towards the valuable reagent. Herein, we report the multikilogram synthesis of the propargyl borolane **1** through the use of a continuous-flow process from trimethylsilylpropyne and isopropyl pinacol borate.

RESULTS AND DISCUSSION

Initial experiments toward borolane **1** were based on the site selective functionalization of trialkylsilylpropynes through the lithiated species **14** by Corey and Kirst[14] and related addition of lithiated trialkylsilylpropynes to trialkylboranes.[15] NMR and IR characterization of the lithiated propyne **14** by Reich et al. showed a rapid equilibration between the allenyl and propargyl lithium species wherein the allenyl derivate **14b** was favored.[16] Due to the trimethylsilyl substituent, reactions with this organolithium mixture typically strongly favor the acetylenic product.[14,15] Direct addition of the borate **11** to an in situ generated lithiated propyne **14** afforded the borolane **1** in <30% yield. Reversing the addition by charging a solution of lithiated propyne **14** to a solution of borate **11** at −25 °C furnished a reasonable yield of borolane **1** after an aqueous workup (Figure 1). Employing an azeotropic distillation to dry the wet organic layer, typical for production processes, with heptane resulted in significant decomposition and a low yield. Borolane **1** showed reasonable thermal stability[17] but demonstrated susceptibility to protonolysis under control experiments with protic solvents such as isopropanol, that provides a rationalization for the limited stability

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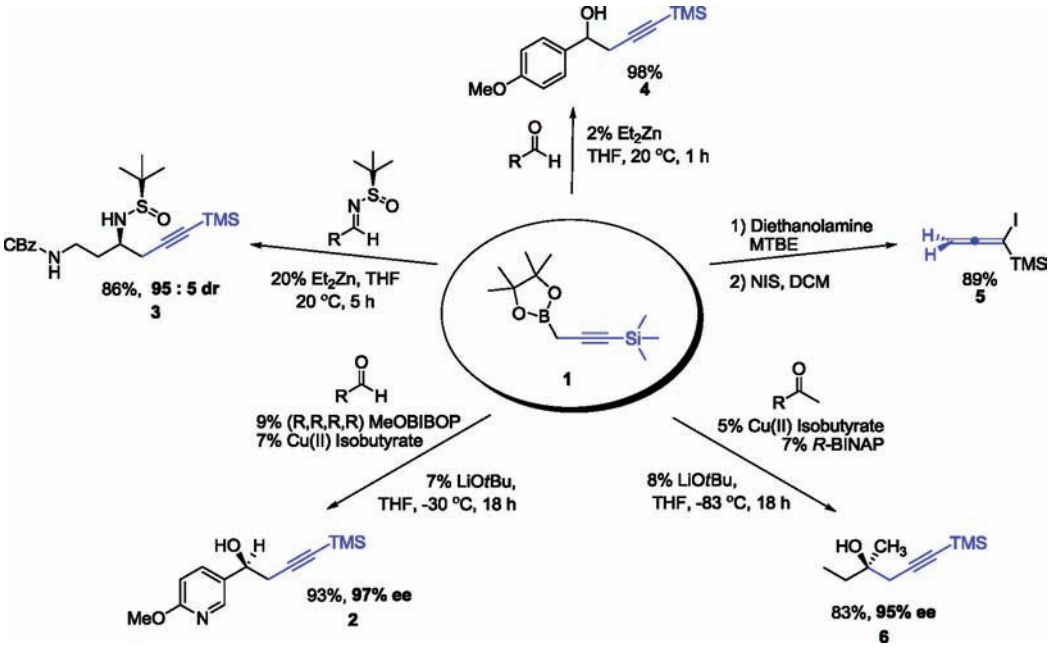
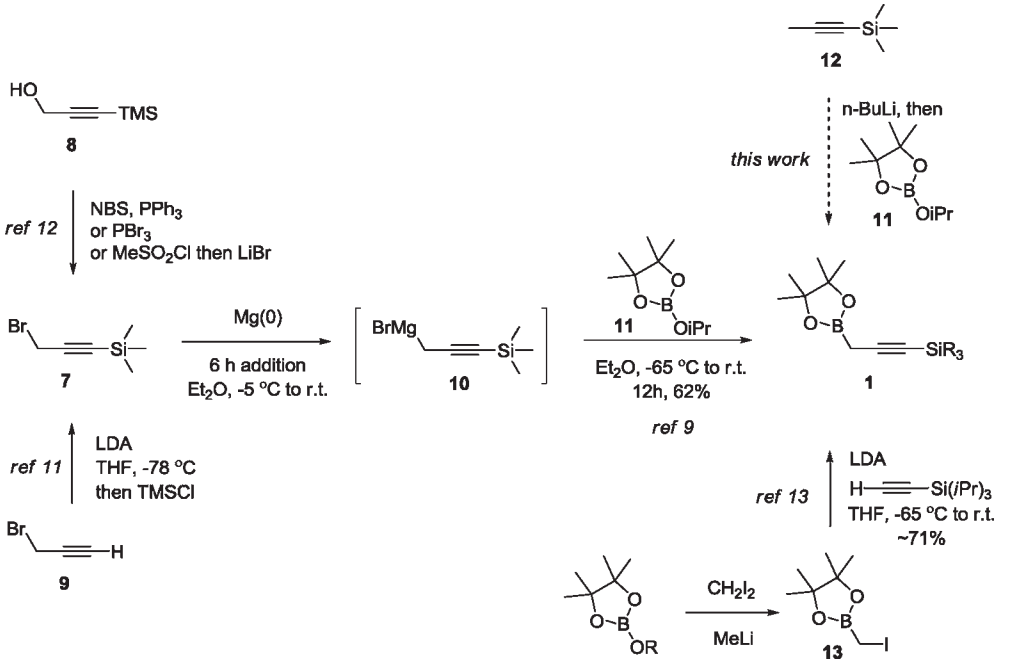
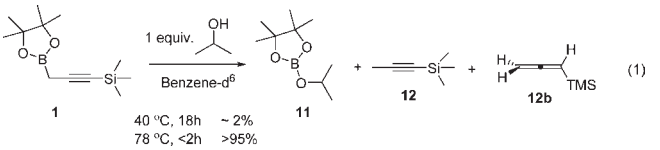
Scheme 1. Applications of propargyl borolane 1



Scheme 2. Synthetic approaches for the preparation of propargyl borolane 1



during azeotropic drying (eq 1).



Although laboratory batches can be readily prepared through workup with a solid desiccant, the use of this technique in production dramatically increases operational costs due to the time-consuming nature of the operation.[18] Accordingly, a nonaqueous workup was pursued.[19] The process required the formal removal of lithium isopropoxide from the borolane "ate" intermediate **15** (Figure 2). To facilitate the workup, the byproducts from the quench should be readily removed by filtration or have a relatively low boiling point to allow removal during the solvent distillation. Accordingly, quenching the reaction with acetic acid, acetyl chloride,[20] methyl iodide and trimethylsilyl chloride[21] were examined (Table 1). Although an acetic acid quench afforded a reasonable yield on a 10-g scale, the yield was significantly affected by the batch size. Alternatively, quenching the process with acetyl chloride provided a

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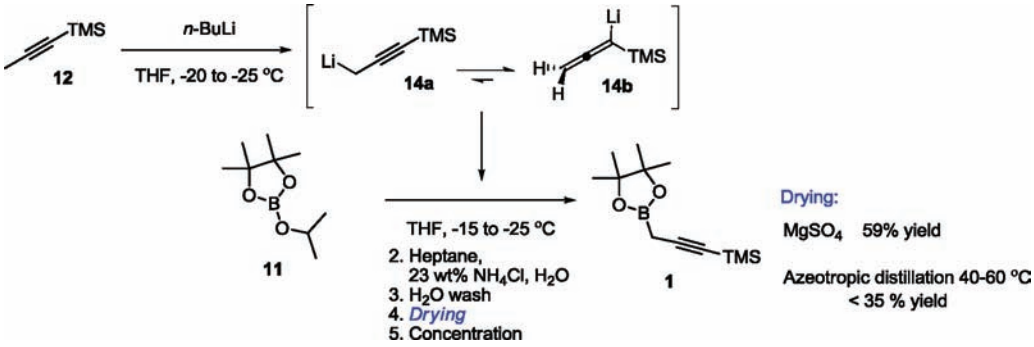


Figure 1. Initial Process for the Preparation of Borolane **1**.

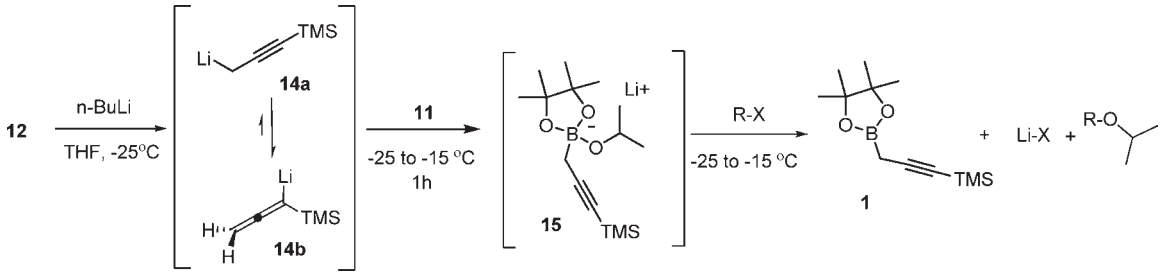
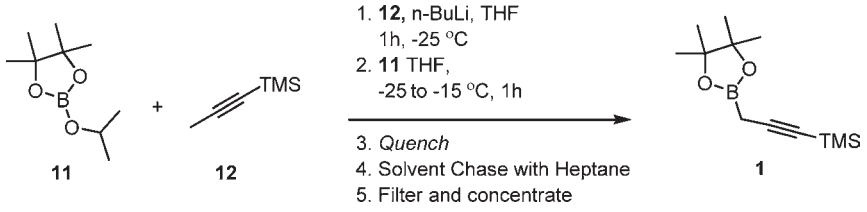


Figure 2. Design of a non-aqueous workup for borolane **1**.

Table 1. Screen of quenching reagents for the preparation of borolane 1[a]



entry	quench reagent[b]	borate **11** (g)	product **1** (g)	quality (wt %)[c]	yield[d] (%)
1	AcOH	10	10	80	64
2	AcOH	50	39	33	20
3	AcCl	10	13	80	78
4	AcCl	50	64	72	71
5	AcCl	55	77	63	69
6	CH_3I	10	–	–	<20[e]
7	TMSCl	46	–	–	<40[e]

[a] 1.05 equiv *n*-BuLi and 1.05 equiv **12** to borate **11**. [b] 1.05 equiv to borate **11**. [c] Weight percent determined by ^{1}H NMR assay with dimethyl fumarate as an internal standard in C_6D_6. [d] Isolated yield. [e] Assay yield before workup by ^{1}H NMR with dimethyl fumarate as an internal standard in C_6D_6.

consistent high yield for the borolane **1**. The workup using acetyl chloride simply required a solvent switch to heptane, filtration to remove lithium chloride, and concentration to remove the excess solvent and the isopropyl acetate byproduct.[22] Furthermore, the batch after the quench with acetyl chloride can be held at ambient temperature for up to 2 days with no noticeable impact on the yield.

Although a scalable workup for the preparation of borolane **1** was established, the yield was significantly impacted by the batch size. Control experiments revealed a significant effect of the addition time for the charge of the in situ generated lithiated propyne **14** to the borate required to maintain the batch temperature between −15 to −25 °C (Table 2). While a rapid addition in 15 min provided a 78% yield, increasing the addition to an hour dramatically lowered the yield to <50%. Under identical conditions with 150 g batches wherein the addition time was increased from 0.75 to 1.0 h a reduction in the yield from 57 to 48% (entries 3 and 4) was demonstrated. Cooling capacity of pilot-plant reactors vary considerably and slightly exothermic additions in typical production facilities

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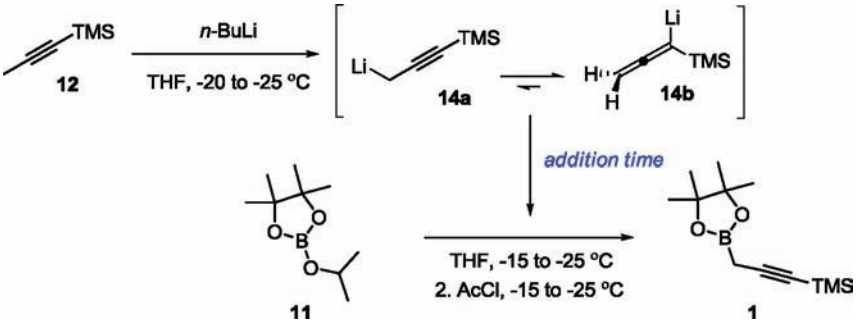
Table 2. Effect of addition time on the preparation of borolane 1[a]

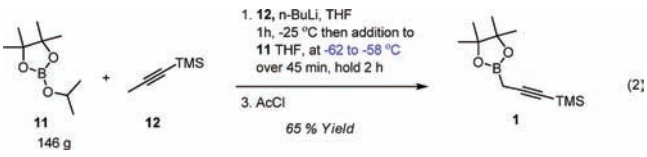


entry	borate **11** (g)	addition time[a] (h)	assay yield[b] **1** (%)
1	10	0.25	78
2	50	0.42	71
3	150	0.75	57
4	150	1	48
5	182	1.25	47

[a] Duration for the addition of the lithiated trimethylsilylpropyne **14** to the borate THF solution. [b] Assay yield after acetyl chloride quench determined by ^{1}H NMR in C_6D_6 with dimethyl fumarate as an internal standard.

at −15 to −25 °C can require several hours. Accordingly, only low to moderate yields are expected for the current process in production.

A reasonable rationalization for the effect of the addition time on the yield for the charge of lithiated trimethylsilylpropyne to isopropyl pinacol borate relates to the limited stabilities of the borolane "ate" intermediates and associated equilibration. After the organometallic addition to the borate, a minimal effect on the yield was observed when the batch was held at −25 °C for up to 2 h. Therefore, the addition time effect must affect the quality of the lithiated propyne or reaction mixture during partial conversion due to increasing the time with which each is held at −25 °C throughout the addition. Although the lithiated propyne has limited stability at −5 °C, a nearly quantitative yield for the addition to *p*-anisaldehyde was obtained after holding the lithiated reagent for 2 h at the reaction temperature of −25 °C (Figure 3). Accordingly, the reduced yield due to the increased addition time is not due to decomposition of the lithiated propyne. Alternatively, organoborone "ate" intermediates derived from the addition with an organolithium reagent are known to dissociate a lithium alkoxide ligand and can lead to polyalkylation.[19,23] Accordingly, the prolonged addition time increases the time when the borolane "ate" intermediate **15** is exposed to the starting borate which due to the dissociation can reasonably enable a borolane "ate" equilibration and generation of the *bis*-isopropoxyborolane "ate" byproduct **17** (Scheme 3). The dissociation and equilibration then establishes a competition for addition to the starting borate **11** and product propargyl borolane **1** upon additional charge of the lithiated propyne to further reduce the yield for the desired product by formation of the byproduct **16**. Complicating the mechanistic analysis is the observation that the starting borate **11** as a solution in THF oligomerizes into a gel upon addition of lithium isopropoxide at the reaction temperature.[24] This oligomerization prevents direct observation of the borolane "ate" intermediates and byproducts and may also promote the decomposition of the desired product **1** to further contribute to the reduced yield with prolonged additions. The borolane "ate" intermediates are typically stabilized with lower reaction temperatures,[19,21,23] but only a marginal improvement in yield to 65% from 57% was obtained by conducting the addition at −60 °C with a 45-min addition (eq 2). Due to the variable yields with different addition times and the decreased efficiency to remove heat from a batch with increasing batch size,[18] the batch process for the preparation of propargyl borolane **1** is unlikely to afford reproducible and reasonable yields upon scale.



The formation of organoborolanes typically involves the addition of an organolithium or Grignard reagent to a trialkoxyborate.[8] Lithium and magnesium cations are expected to excerpt different complexations and stabilities between the organotrialkoxyborate and alkoxide intermediates encountered in the batch process.[19] Accordingly, the equilibrium between the intermediate organotrialkoxyborate and organoborolane intermediates encountered during a batch process should be dependent on the countercations utilized in the process. In an effort to shift the equilibrium towards the "ate" intermediate for a batch process (Scheme 3),[19,23] the additive magnesium chloride was included to the isopropyl pinacol borate solution prior to the addition of the in situ generated lithiated propyne **14a**−**b**. The additive magnesium chloride, albeit poorly soluble in the reaction system, appeared to significantly reduce the yield dependence on the addition time of the lithiate propyne to the borate (Table 3). The yield minimally decreased from 78% to 72% upon increasing

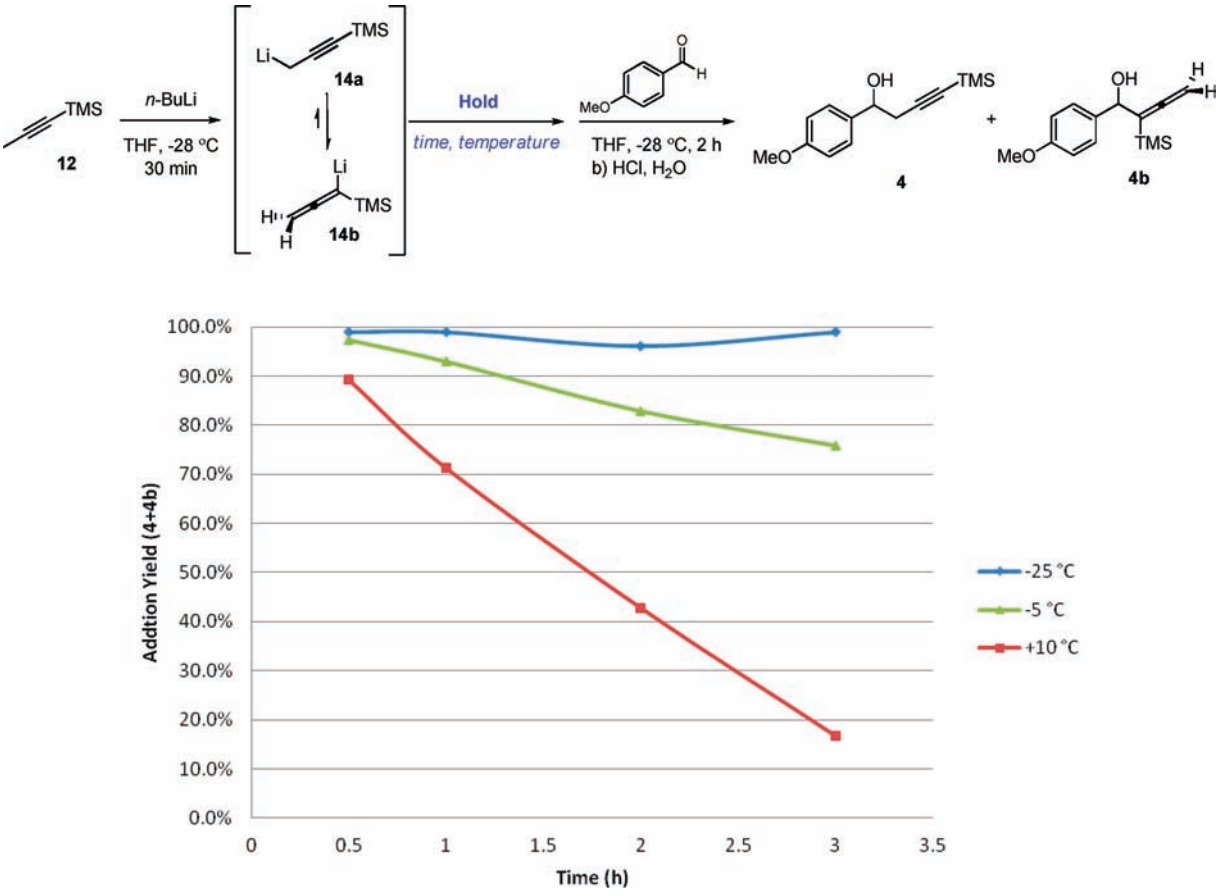
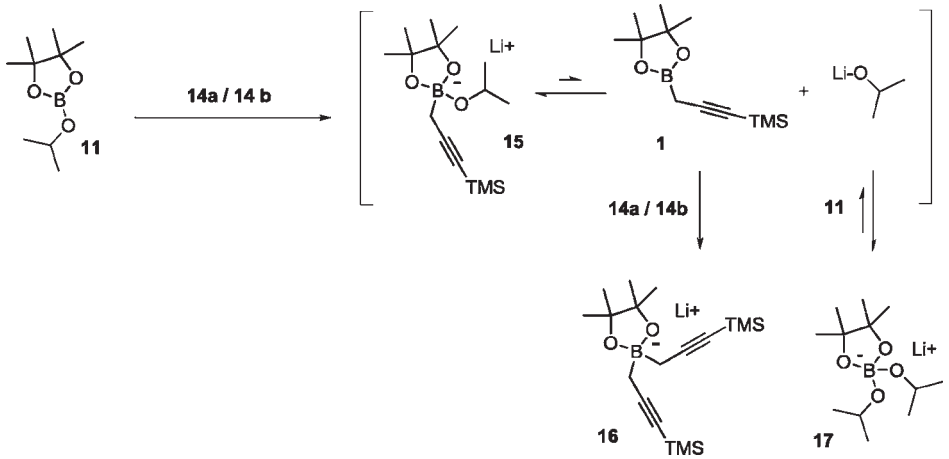


Figure 3. Temperature stability of lithium trimethylsilylpropyne **14a**. HPLC (220 nm) assay yield of **4** and **4b** with toluene as an internal standard (error ±5%). 4−5:1 site selectivity between **4** and **4b**.

Scheme 3. Proposed equilibration and byproduct formation



the addition time from 0.5 to 2 h. However, when the modified batch process with magnesium chloride was demonstrated on a kilogram scale, the yield decreased to 64% with a 30-min addition in comparison to a 78% yield for a 30 min addition on a 182-g scale (entries 1 and 2). In addition to this drop in yield upon scale-up, the process also presented operational challenges for production. The magnesium chloride additive increased the mass balance for the process and was observed to significantly increase the filtration time for removal of the salts during the workup. These complications and reduced yield upon scale-up presented reasonable concerns to implement the modified batch process with magnesium chloride on a pilot-plant scale.

Continuous-flow processes have gained popularity in chemical production due to the ability to mitigate safety hazards, to

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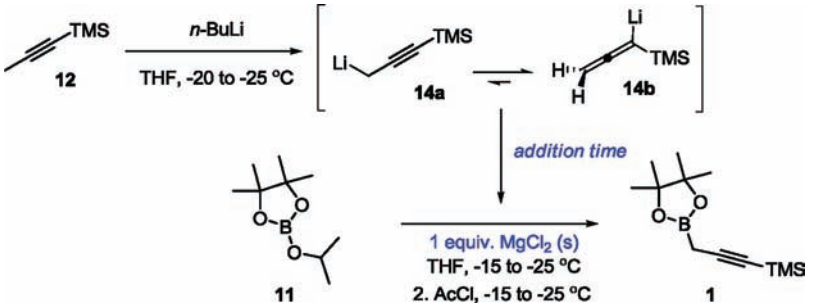
Table 3. Effect of addition time and additive on the preparation of borolane 1[a]



entry	borate **11** (g)	addition time[a] (h)	assay yield[b] **1** (%)
1	182	0.5	78
2	1500	0.5	64
3	68	1.0	73
4	68	1.5	74
5	68	2.0	72

[a] Duration for the addition of the lithiated trimethylsilylpropyne **14** to the borate THF solution. [b] Assay yield after acetyl chloride quench determined by ^{1}H NMR in C_6D_6 with dimethyl fumarate as an internal standard.

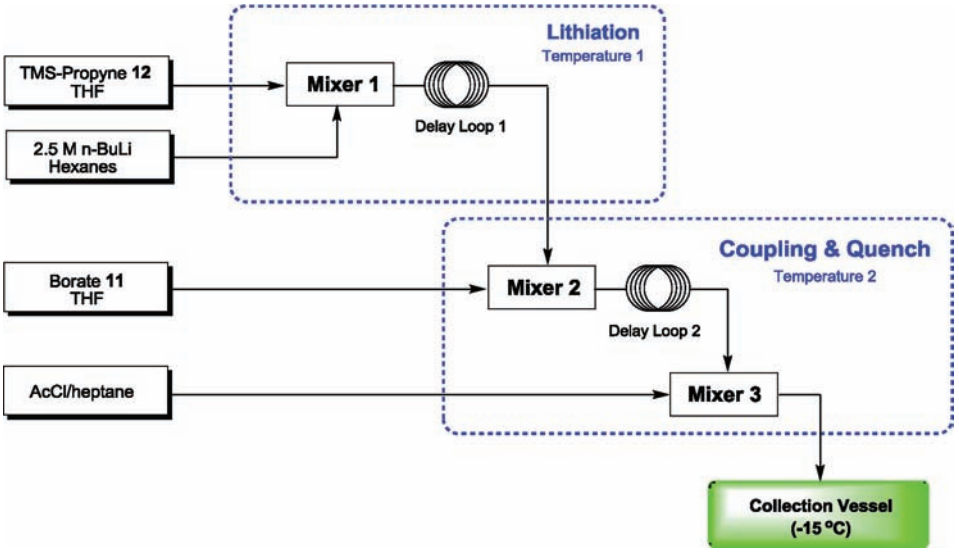
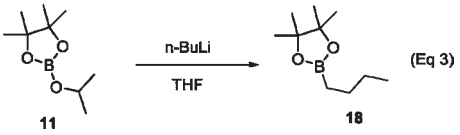


Figure 4. Continuous-flow process for the preparation of borolane **1**.

prepare unstable compounds or intermediates, localize physical effects, and achieve maximum productivity by achieving optimal reaction conditions.[18] Preparation of the propargyl borolane **1** through a continuous-flow process would eliminate the addition time effect observed in a batch process by employing the simultaneous addition of the lithiated propyne **14** and starting borate **11**. This process was designed in three phases (Figure 4). The first phase generates the lithiated propyne **14** by a continuous stream of a THF solution of the starting trimethylsilylpropyne **12** with *n*-butyllithium. A delay loop was installed after the mixture to allow for adequate time for complete lithiation and minimize the formation of the butyl borolane byproduct **18** (eq 3). The second phase conducts the coupling with another delay loop to allow sufficient time for the reaction followed by the quench with acetyl chloride and deposit into a collection vessel.



Optimization of the continuous-flow process focused on reagent stoichiometry, delay loop retention times and respective temperatures. The baseline process utilized a −5 °C bath with 1.13 equiv of *n*-BuLi, 1.07 equiv of starting propyne **12**, 1.13 equiv of acetyl chloride and a retention time of 61 s for the lithiation and 21 s for the coupling. In contrast to a batch process wherein a slight excess of the lithiated propyne was utilized to

Table 4. Stoichiometry optimization for the continuous-flow process[a]

	equiv[b]		GC IPC (A%)[c]		
entry	*n*-BuLi	AcCl	**11**	**18**	**1**
1	1.13	1.13	5.9	6.3	73.4
2	1.1	1.1	5	4.3	74.6
3	1.1	1.03	4.2	4.7	74.8
4	1.03	1.1	5.4	1.7	80
5	1.03	1.03	6	2.1	80.2
6	**1**	**1**	**6.1**	**1**	**82.1**
7	0.93	0.93	8.6	0	81.9

[a] Process conducted in Figure 4 with a −5 °C lithiation, coupling, and quenching temperature and 1.07 equiv of propyne **12** to borate **11**. Delay loop 1 and 2 retention time of 61 and 21 s, respectively. [b] Equivalents to starting borate **11**. [c] GC relative area by FID.

Table 5. Temperature and retention time optimization for the continuous-flow process[a]

	temperature (°C)		delay loop (s)		GC IPC (A%)[d]		
entry	**1**[b]	**2**[c]	**1**[b]	**2**[c]	**11**	**18**	**1**
1	0	0	45	21	9.3	1.7	80.6
2	−5	−5	45	21	8.4	3.1	79.8
3	−2	−5	45	21	10.1	1.8	78.8
4	0	−5	45	21	12.5	1.4	77.2
5	5	−5	45	21	6.5	0.5	84.7
6	−5	−5	62	0	12.8	1	77.4
7	−5	−5	53	5	9.7	1.1	77.5
8	−5	−5	62	21	6.1	1	82.1
9	**5**	−5	**40**	**21**	**6.5**	**0.5**	**84.7**[c]
10	5	−5	40	31	7.1	1	83.8

[a] Process conducted in Figure 4 with 1.07 equiv of propyne **12** and 1 equiv of *n*-BuLi and AcCl to starting borate **11**. [b] Temperature and retention time for the lithiation. [c] Temperature and retention time for the coupling. [d] GC relative area by FID.

compensate for the decomposition pathways, the optimal stoichiometry for a continuous-flow process was the desired 1 equiv of lithiated propyne and 1 equiv of acetyl chloride to starting borate **11** (Table 4). The reaction temperatures and retention times for the lithiation and coupling were subsequently optimized (Table 5). Complete lithiation of trimethylsilylpropyne as indicated by <0.5 A% butyl adduct formation was achieved with a lithiation temperature of 5 °C and a retention time of 40 s. The optimal conditions for the coupling utilized a 21 s delay loop at −5 °C before the acetyl chloride quench at the same temperature. After the quench, the reaction mixture can be held in the collection vessel for up to 24 h at −5 °C. The lab-scale continuous-flow process on a 50−100-g scale afforded a consistent 64−70% yield for the propargyl borolane **1** before distillation and after workup to remove the salts and solvents.

After preparation of the borolane **1** through a continuous-flow process, the crude material was purified by distillation. The crude material from the continuous-flow reaction was mixed with heptane to precipitate the salts (LiCl), filtered, and the filtrate concentrated to remove the majority of the solvents. For smaller batches (<10 kg), a batch distillation was employed. The filtrate from the filtration was distilled through a short path distillation apparatus to remove the heavy impurities and distillation through a fractional distillation column provided the borolane **1** in >95 A% (GC-FID) and 88 wt % with an 82% distillation recovery (Figure 5). For production batches (>10 kg), pot distillation was not practical and exposes the product to prolonged heating due to the time required to distill the large volumes. Accordingly, a continuous distillation process was developed with a series of thin film distillation apparatuses to provide the propargyl borolane with reproducible quality (Figure 6). Due to the large capacity of the continuous distillation equipment, hold up loss was inevitable with larger losses with smaller batches. Distillation of the largest batch (∼200 kg) afforded a 70% recovery, and larger batches are expected to yield better recoveries.

The continuous-flow process for the preparation of borolane **1** reproduced well from lab scale to production to afford an average yield of 64−75% after workup to remove the salts and most of

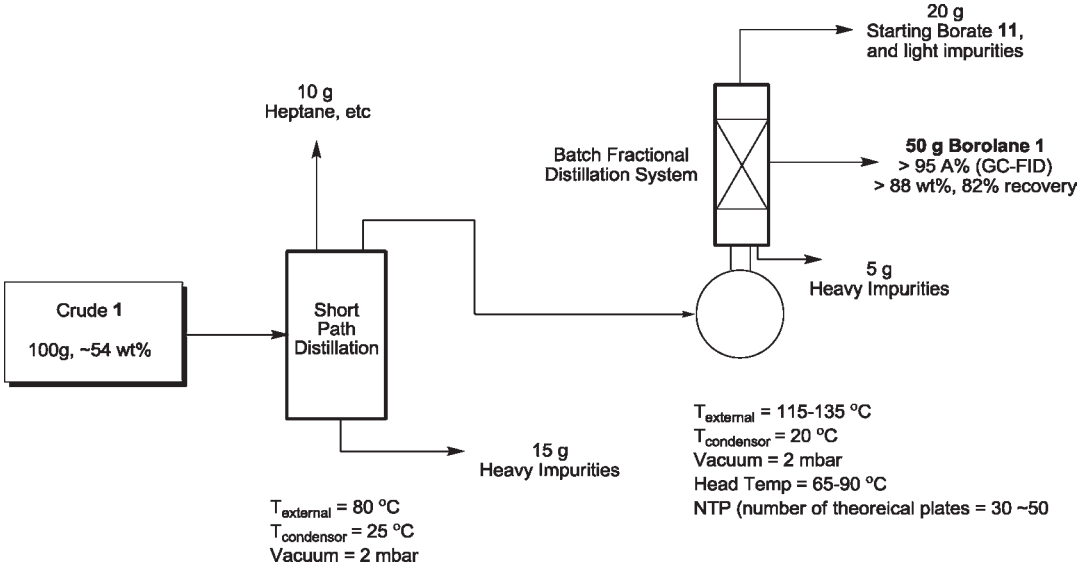


Figure 5. Lab-scale batch distillation of borolane **1**.

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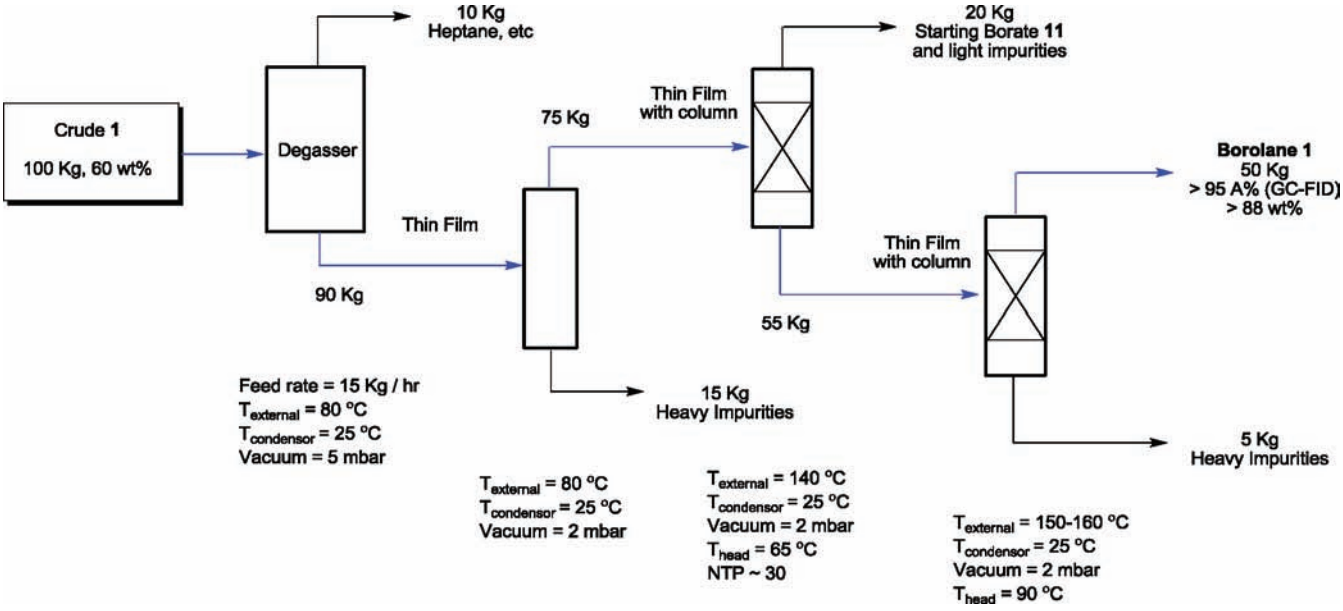

Figure 6. Continuous distillation of propargyl borolane **1** through a series of thin film distillation apparatuses.

Table 6. Continuous-flow batches for propargyl borolane 1

Reaction		Lab Batches 1	Lab Batches 2	Production Batches 1	Production Batches 2	Production Batches 3	Production Batches 4
IPC[a]	**11**	7.7%	9.3%	3-10%	1-6%	ND	ND
	18	1.0%	0.4%	0.2-5%	1-2%	ND	ND
	1	83.1%	83.3%	75-82%	79-86%	ND	ND
Crude Product[b]	**11**	10.2%	7.9%	5.0%	9.4%	5.1%	9.3%
	18	1.0%	0.4%	1.1%	1.7%	1.9%	1.0%
	1	78.7%	82.4%	79.7%	77.6%	74.9%	74.3%
	Assay[c]	61.5 wt%	67.0 wt%	63.7 wt%	65.3 wt%	63.4 wt%	66.3 wt%
	Yield	64.3%	70.4%	71.6%	74.9%	66.6%	66.4%
Distillation		Continuous SPD & Batch Distillation		Continuous Distillation			
	Yield[d]	82%	-	70.0%[e]		37.2%[e]	61.8%[e]
	Light Cut T_{bath}	115-120 °C	-	140 °C			
	Heavy Cut T_{bath}	120-135 °C	-	150-160 °C			
	Pressure	2 mbar	-	2-5 mbar			
Total							
	Product	52.8 g	-	211.1 kg		34.3 kg	72.9 kg
	Yield[f]	53%	-	51.1%		24.8%	41.0%
	Assay[c]	88.0 wt%	-	92.7 wt%		91.0 wt%	96.2 wt%

[a] GC-IPC by FID (A%). [b] Crude product after concentration, heptane chase, and filtration. Percent **11**, **18** and **1** by GC-FID (A%). [c] Weight percent assay determined by ^{1}H NMR in C_6D_6 with dimethyl fumarate as an internal standard. [d] Distillation recovery yield. [e] Due to large capacity of distillation equipment, hold up loss was inevitable with larger losses with smaller batches. [f] Overall yield for reaction and distillation. ND = not determined. SPD = short path distillation.

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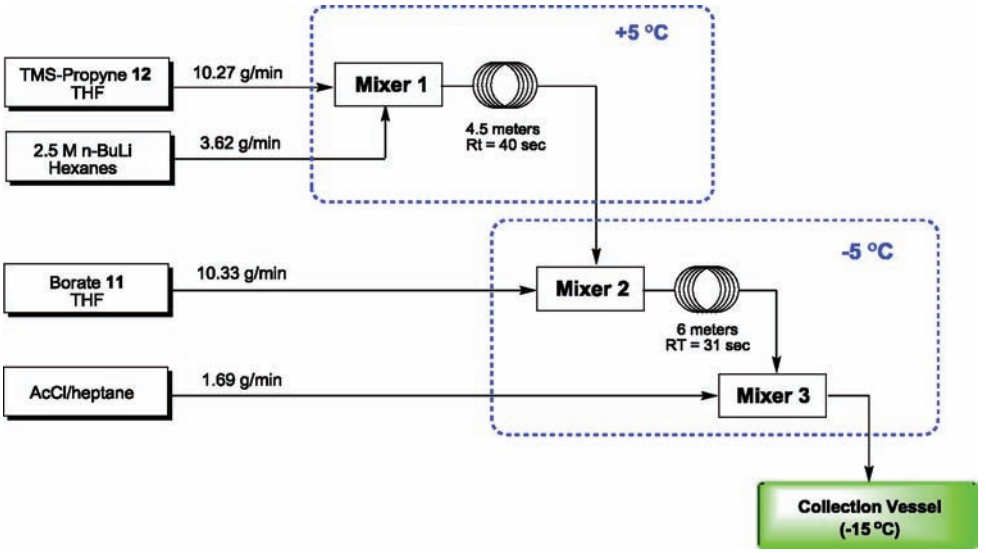

Figure 7. Continuous-flow system for lab-scale batches.

the solvents (Table 6). Due to the hold-up loss in the continuous distillation process and relatively small batches in relation to the equipment design, a moderate distillation recovery was obtained in the production batches that were ~100 kg. Overall, the continuous-flow process and distillation produced 318 kg of the propargyl borolane **1** in >91 wt % purity (297 kg at 100 wt %).

■ CONCLUSIONS

In conclusion, an efficient process for the production of 4,4,5,5-tetramethyl-2-(3-trimethylsilyl-2-propynyl)-1,3,2-dioxaborolane from trimethylsilylpropyne, *n*-butyllithium, and isopropyl pinacol borate was developed. The development of a nonaqueous continuous-flow process circumvented the issues with borolane "ate" intermediate equilibration and protonolysis associated with a batch process, and typical aqueous workup afforded over 300 kg of the propargylation reagent. Due to the synthetic value of organoboronic esters in process chemistry, continuous-flow technologies that provide a robust process for the production of these valuable yet often relatively unstable reagents are of significant utility.

■ EXPERIMENTAL SECTION

Batch Process with $MgCl_2$. Anhydrous THF (<500 ppm water, 733 mL) followed by 1-trimethylsilyl-1-propyne (154 mL, 117 g, 1.05 mol) were charged to a dried reactor under argon. The batch was cooled to T_{int} = −25 °C. *n*-BuLi (2.5 M in hexanes, 404 mL, 1.01 mol) was charged to the trimethylsilylpropyne solution at a rate to maintain T_{int} = −20 to −25 °C. The reaction was aged for 1 h at T_{int} = −25 °C to afford the lithiated propyne solution as a homogeneous yellow to orange solution. While maintaining the lithiated propyne solution at T_{int} = −25 °C, the lithiated propyne solution was charged to an anhydrous mixture of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (200 mL, 182 g, 0.980 mol) and anhydrous magnesium chloride (93.3 g, 0.980 mol) in THF (<500 ppm water, 1.0 L) at a rate to maintain the borolane solution at T_{int} = −25 to −15 °C. The reaction was aged for 1 h at T_{int} = −25 °C. An anhydrous solution of acetyl chloride (71.8 mL, 79.3 g, 1.01 mol) in MTBE (72 mL) was charged to the reaction at a rate to maintain T_{int} = −20 to −15 °C. The quenched reaction was aged for 1 h at T_{int} = −20 to −15 °C, then warmed to ambient temperature over 0.5 to 1 h. The batch was concentrated in vacuo to remove 1.82 L of solvent. The resulting mixture was charged then distilled with MTBE (1 × 1.0 L, 1 × 700 mL) followed by heptane (1 × 1.0 L, 1 × 350 mL). The solids were removed by filtration and rinsed with heptane (2 × 100 mL). The filtrate was concentrated in vacuo to provide the crude borolane **1** as a homogeneous orange oil (225.1 g). 1H NMR in C_6D_6 with dimethyl fumarate as an internal standard showed 80.8 wt % for a reaction yield of 78%.

The crude borolane **1** (747.6 g, 53.8 wt %) was distilled through a fractional distillation system with ~3−5 theoretical plates at ~2 mbar. Collection of the fractions with T_{vap} = 68−79 °C with T_{bath} = 108−135 °C provided borolane **1** as a yellow oil (260 g) in 92.8 wt % with a 60% distillation recovery. ^{1}H NMR (400 MHz, C_6D_6) 1.92 (2H, bs), 0.971 (s, 12 H), 0.189 (s, 9 H). ^{13}C NMR (100 MHz, C_6D_6) 104.16, 83.80, 83.17, 24.70, 3.7 (b), 0.46. EI-HRMS calcd for $[M]^+$ $C_{12}H_{23}BO_2Si$ 238.1560, found 238.1577; calcd for $[M - CH_3]^+$ $C_{11}H_{20}BO_2Si$ 223.1326, found 223.1331.

Continuous-Flow Process. The four feed solutions were prepared in dried vessels under argon. In the first vessel, a solution of 1-trimethylsilyl-1-propyne (56.5 g, 0.503 mol) was prepared in THF (<500 ppm water, 313 g). The second vessel was charged with *n*-BuLi (2.5 M in hexanes, 134.4 g, 194 mL, 0.485 mol). The third vessel was charged with THF (<500 ppm water, 284.4 g) followed by 2-isopropoxy-4,4,5,5 tetramethyl-1,3,2-dioxaborolane (87.6 g, 0.471 mol). The fourth vessel was charged with heptane (<100 ppm water, 24.6 g) and acetyl chloride (38.0 g, 0.484 mol).

A continuous-flow system was constructed as delineated in Figure 7. The indicated mixers and delay loops were immersed into two separate chillers adjusted to the respective temperatures. The four feed streams were charged into the specified mixtures with nitrogen pressure at the respective flow rates metered by mass flow controllers. The final mixed streams were collected into a vessel under nitrogen with agitation at T_{int} NHT −15 °C. After completion of the continuous-flow process, the reaction solution was agitated at T_{int} NHT −15 °C for 1 h. The solution

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was warmed to ambient temperature and can be held at this point for up to 18 h.

The reaction was concentrated to ~450 mL by distilling 475 mL of solvent to afford an orange to red mixture. The mixture was charged and then distilled with heptane (500 mL); this chase was repeated until the relative area ratio of heptane to THF by GC-FID of the reaction mixture was >4: 1. The resulting mixture was cooled to ambient temperature. The solids were removed by filtration and rinsed with heptane (275 mL). The filtrate was concentrated to a cloudy red oil (117.3 g, 61.5 wt %). ^{1}H NMR in C_6D_6 with dimethyl fumarate as an internal standard showed 61.5 wt % for a reaction yield of 64.3% yield.

The crude borolane **1** (92.6 g, 61.5 wt %) was distilled under the conditions and equipment setup as depicted in Figure 5 to afford the borolane **1** as a yellow oil (52.8 g, 88.0 wt %, 81.6% distillation recovery).

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, complete characterization data for propargyl borolane **1**, and copies of ^{1}H and ^{13}C NMR spectra. This material is free of charge via the Internet at http://pubs.acs.org.

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