Tetrahedron Letters 69 (2021) 152977

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Borane evolution and its application to organic synthesis using the phase-vanishing method

Nene Soga [a], Tomo Yoshiki [a], Aoi Sato [a], Takuji Kawamoto [b], Ilhyong Ryu [a,c], Hiroshi Matsubara [a,*]

[a] Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan
[b] Department of Applied Chemistry, Yamaguchi University, Ube, Yamaguchi 755-8611, Japan
[c] Department of Applied Chemistry, National Chiao Tung University, Hsinchu 30010, Taiwan

ARTICLE INFO

Article history:
Received 28 December 2020
Revised 27 February 2021
Accepted 2 March 2021
Available online 6 March 2021

Keywords:
Phase-vanishing method
Fluorous solvent
Gaseous reagents
Borane
Hydroboration

ABSTRACT

Although borane is a useful reagent, it is difficult to handle. In this study, borane was generated in situ from $NaBH_4$ or $^{n}Bu_4NBH_4$ with several oxidants using a phase-vanishing (PV) method. The borane generated was directly reacted with alkenes, affording the desired alcohols in good yields after oxidation with H_2O_2 under basic conditions. The selective reduction of carboxylic acids with the evolved borane was examined. The organoboranes generated by the PV method successfully underwent Suzuki–Miyaura coupling. Using this PV system, reactions with borane can be carried out easily and safely in a common test tube.

Introduction

Fluorous solvents, which comprise highly fluorine-substituted compounds, have several specific characteristics; *e.g.*, they are immiscible with general organic solvents and water, and are heavier than typical organic solvents [1]. Utilising these unique features of fluorous solvents, we have developed a novel synthetic methodology using them as a phase screen, known as the ‘phase-vanishing (PV) method’ [2]. The PV method involves a triphasic reaction system, in which fluorous solvents are used as a liquid membrane to steadily transport reagents from the lower (reagent) layer to the upper organic layer containing the substrate. Many organic syntheses have been reported using the PV method [3,4]. For example, we carried out the bromination of alkenes [3a], Friedel-Crafts acylation of aromatic compounds [3c], and Grignard-type reactions [3f], while other groups performed oxidation with MCPBA (*m*-chloroperbenzoic acid) dissolved in 1,2-dibromoethane [4a], chlorination with Cl_2 gas [4b], and bromination with Br_2 using PTFE (Teflon tape) as a phase screen [4h]. The PV method has been used with photo-irradiation to generate HBr in situ from the organic solvents of the top layer in a triphasic system in which Br_2 diffused from the bottom layer, and the evolved HBr was effectively added to alkenes in the organic layer [5]. The photo-irradiative PV method was also used by other researchers for the bromination of carbohydrates [4j]. Gaseous reagents can be gradually evolved in situ using the PV system and consumed in organic reactions [6]. For example, acetylene is generated from calcium carbide and effectively used in the Sonogashira coupling, a Cu-catalysed azide–alkyne cycloaddition and a three-component aldehyde-alkyne-amine (A^3) coupling reaction [6a]. In contrast, hydrogen sulfide is generated from phosphorous pentasulfide and organic sulfides or disulfides are obtained in moderate yields [6b]. Carbon monoxide has also been produced using the PV method and applied in several carbonylation reactions [6c]. When gaseous reagents are used in organic synthesis, special apparatus such as gas cylinders and regulators are usually required. In the PV system, however, gaseous reagents are gradually evolved because the fluorous phase regulates the transport of reagents by passive diffusion. In addition, cooling devices and dropping funnels are not required in the PV method, which makes the PV reaction systems simpler and easier. Moreover, fluorous solvents are easily recovered after the reaction and can be purified by simple distillation for the next reaction.

In this work, we generated borane using the PV method and consumed the reagent in several organic reactions in the same test tube. Although borane is a useful reagent for many organic reactions such as hydroboration of unsaturated bonds [7] and reduction of carboxylic acids [8], it is a noxious (bp −92.8 °C) and highly reactive gas. Borane is usually available as a complex such

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* Corresponding author.
E-mail address: matsu@c.s.osakafu-u.ac.jp (H. Matsubara).

https://doi.org/10.1016/j.tetlet.2021.152977

as BH_3-THF [9] or BH_3-SMe_2 [10]. These complexes are stable and easy to use; however, they are not inexpensive and need to be manipulated under inert atmosphere. Once the bottles storing these complexes are opened, they begin to decompose because of the exposure to air and moisture. As a result, the purity of the reagents decreases. Another method to employ borane is generating it in situ from borohydride salts with oxidants such as sulfuric acid, iodide, or alkyl iodides [11]. Borohydrides should be reacted gradually and carefully with oxidants under inert atmosphere, which is a tedious and exhausting procedure. We herein propose the in situ generation of borane using the PV method with a test tube (Fig. 1).

Results and discussion

Hydroboration of alkenes using borane-evolution PV method

Hydroboration of 4-methylstyrene was carried out using the PV method for borane gas evolution (**1a**). The optimisation of reaction conditions has been provided in detail in the Supplementary Material. 1,2-Dimethoxyethane (DME; $\rho = 0.868\ g\ cm^{-3}$) was employed as the organic phase (top layer), while FC-72 ($\rho = 1.68\ g\ cm^{-3}$), Galden HT-135 ($\rho = 1.72\ g\ cm^{-3}$), or HT-200 ($\rho = 1.79\ g\ cm^{-3}$) was used as the fluorous phase (middle layer) [12]. $NaBH_4$ was used as the borane source, because it is stable, easy to handle, and inexpensive. Fortunately, the density of the reagent is $1.074\ g\ cm^{-3}$, and hence, it can float at the interface of the fluorous and organic phases. Oxidants should sink to the bottom layer, as they are denser than the fluorous phase. Under the standard conditions (Condition A), we used H_2SO_4 ($\rho = 1.83\ g\ cm^{-3}$) as the oxidant and Galden HT-135 as the fluorous phase. However, we slightly modified the conditions from A to E; the results are summarised in Table 1.

When Condition A was applied, the reaction afforded a quadriphasic system comprising H_2SO_4, Galden HT-135, $NaBH_4$, and DME solution of **1a**, as shown in Fig. S1a in the Supplementary Material (detailed optimisation of this condition is summarised in Table S1 in the Supplementary Material). After degassing the test tube with a syringe, the bottom layer was gently stirred at 25 °C, taking care not to mix the layers. Continuous borane gas evolution was observed, and the bottom layer disappeared after 20 h (Fig. S1b in the Supplementary Material). At a glance, H_2SO_4 worked well to evolve borane, and the desired product, 2-(p-tolyl)-ethan-1-ol (**2a**), was obtained in an acceptable yield after the oxidation of the reaction mixture with H_2O_2 under basic conditions (Table 1, Entry 1, Condition A), compared with the yield of the product obtained using BH_3-THF as the borane source (Table 1, Entry 1, Condition E). However, when alkenes bearing a hydroxy or an ester group (**1j**, **1k**) were employed as the substrate, the yields of the desired alcohols (**2j**, **2k**) decreased (Table 1, Entries 10 and 11, Condition A). A possible reason could be that some of the acid reacted with the substrates in the organic phase, thereby decreasing the amount of borane evolved. Therefore, we attempted to generate borane from $NaBH_4$ and I_2 (Condition B, optimisation of this condition is summarised in Table S2 in the Supplementary Material). Diffusion of I_2 alone into the fluorous phase was too slow to generate borane; therefore, I_2 was dissolved in 1,2-dibromoethane ($\rho = 2.17\ g\ cm^{-3}$) [4a] and FC-72 was employed as the fluorous phase because of its low viscosity. The PV systems employing I_2 at the initial and final stages of hydroboration are shown in Fig. S2a and S2b in the Supplementary Material, respectively. These systems afforded the desired alcohols in better yields with many substrates compared to that obtained using H_2SO_4. As shown in Table 1, I_2 can be used as the oxidant in the PV method for borane evolution with a wide range of substrates. However, their isolated yields sometimes significantly decrease compared to the NMR yields. In addition, products obtained using the PV system with I_2 are always contaminated with 1,2-dibromoethane. Therefore, it is necessary to separate the compound during the workup, which often further lowered the isolated yields of the desired products (Table 1, Entries 1, 10–13, Condition B). Hence, we explored alternative oxidants. As alkyl iodides are known to react with the borohydride and form borane, we examined methyl iodide ($\rho = 2.28\ g\ cm^{-3}$) or ethyl iodide ($\rho = 1.94\ g\ cm^{-3}$) as oxidants because these iodides are denser than fluorous solvents. Methyl iodide diffused quickly into the fluorous phase (even into the more viscose Galden HT-200), evolving a large amount of borane in a short time. However, it was not suitable for the PV hydroboration reaction because a substantial amount of borane escaped from the organic layer without being used in the reaction. Ethyl iodide diffuses into the fluorous phase more slowly than methyl iodide, and hence, it is preferred for application in the PV method. Indeed, when a mixture of Galden HT-135 and HT-200 (2:1 v/v) was employed as the fluorous phase (Condition C, optimisation of this condition is summarised in Table S3 in the Supplementary Material), ethyl iodide worked very well, affording the desired hydroboration products in good yields. The initial and final stages of PV hydroboration using ethyl iodide are shown in Fig. 2a and b, respectively. The organic by-product of the PV reaction using ethyl iodide was ethane. The workup procedure was simpler and easier than that involving iodine. In addition, $^{n}Bu_4NBH_4$ was employed instead of $NaBH_4$ as the borane source (Condition D). THF was employed as the organic phase in this case because the product yields in DME were slightly lower than those in THF. It should be noted that $^{n}Bu_4NBH_4$ dissolved in the solvent. Hence, the PV method with this reagent has three phases at the initial stage of hydroboration (Fig. S3a in the Supplementary Material), and the bottom layer vanishes in 2 h (Fig. S3b in the Supplementary Material). After oxidation with H_2O_2 under basic conditions, the desired alcohols were obtained in good yields as listed in Table 1. PV hydroboration with $^{n}Bu_4NBH_4$ afforded the alcohols in similar yields as that obtained using ethyl iodide.

As summarised in Table 1, we investigated the substrate scope for the hydroboration–oxidation reaction of alkenes using the PV method. Not unexpectedly, anti-Markovnikov products **2** were obtained as the major products, while the Markovnikov products **3** were sometimes observed in trace amounts except for some styrenes described below. Styrene derivatives bearing an electron-donating group afforded the corresponding alcohols in good yields (Entries 1, 2), while non-substituted styrene **1c** provided the desired alcohols in similar yields (Entry 3). Styrenes with a halogen or an electron-withdrawing group afforded the corresponding products in moderate-to-good yields (Entries 4–6). Because hydroboration is an electrophilic reaction, styrene derivatives with an electron-withdrawing group provided slightly lower

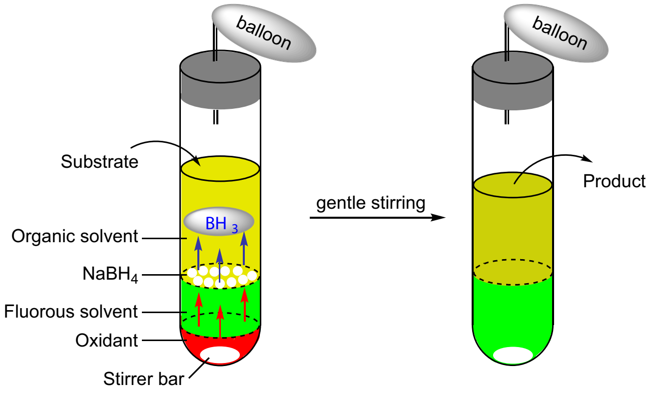
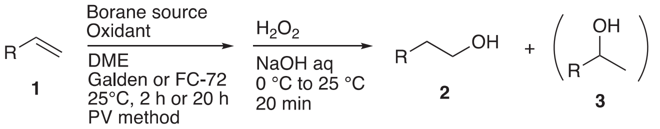
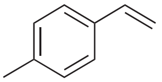
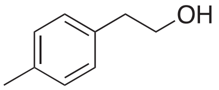
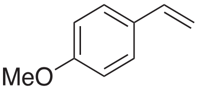
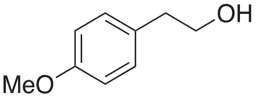
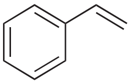
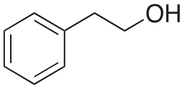
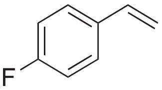
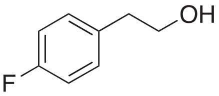
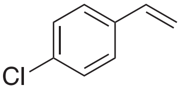
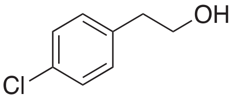
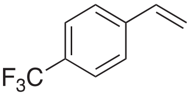
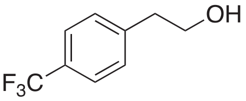
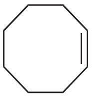
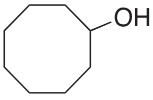
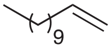
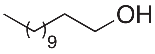
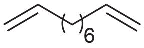
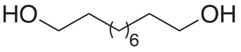
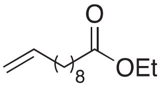
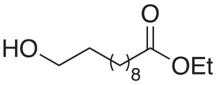
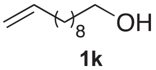
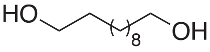
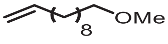
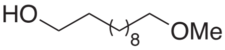
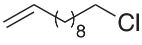
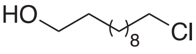


Fig. 1. Concept of borane evolution PV method.

Table 1
Hydroboration–oxidation of alkenes using borane-evolution PV method.



Entry	Substrate	Major product	Condition	Yield/%[b,c]
1	 **1a**	 **2a**	A B C D[d] E	74(85) 63(84) 91(92) 85 84
2	 **1b**	 **2b**	A B C D	75(85) 71(85) 96(98) 91
3	 **1c**	 **2c**	B C	70[61/9][e] 86[74/12][e]
4	 **1d**	 **2d**	B	77[71/6][e]
5	 **1e**	 **2e**	A B C D E	82[73/9][e] 86[69/17][e] 89[76/13][e] 85[72/13][e] 87[72/15][e]
6	 **1f**	 **2f**	A B D	61 59 54
7	 **1g**	 **2g**	A B C D	79(81) 73(86) 85(92) 95
8	 **1h**	 **2h**	B C D	77 96 91
9[f]	 **1i**	 **2i**	B	69
10	 **1j**	 **2j**	A B C	61 79(94) 85
11	 **1k**	 **2k**	A B C D	43 67(98) 94 91
12	 **1L**	 **2L**	B	78(98)
13	 **1m**	 **2m**	B	71(98)

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[a] General PV conditions for hydroboration: substrate (2.0 mmol), borane source: $NaBH_4$ (1.1 equiv.), oxidant (0.6 equiv.), organic phase: DME (5.0 mL), fluorous phase: Galden HT-135ss (1.5 mL), 25 °C, 20 h; then $NaOH_{aq}$ (1 M, 1.35 mL), H_2O_2 (30%, 0.5 mL), 0 °C to 25 °C, 20 min. Conditions A: oxidant: H_2SO_4 (0.6 equiv.); Conditions B: oxidant: I_2 (0.6 equiv.) in 1,2-dibromoethane (0.5 mL), fluorous phase: FC-72 (2.0 mL); Conditions C: oxidant: EtI (1.2 equiv.), fluorous phase: Galden HT-135/200 (2.0 mL/1.0 mL); Conditions D: Substrate (1.0 mmol), borane source: $^{n}Bu_4NBH_4$ (1.1 equiv.), oxidant: EtI (1.2 equiv.), organic phase: THF (2.5 mL), fluorous phase: Galden HT-135/200 (1.5 mL/0.5 mL), 2 h; $NaOH_{aq}$ (0.68 mL), H_2O_2 (0.25 mL); Conditions E: borane source: BH_3-THF (1.0 M, 1.1 equiv.), no oxidant, organic phase: THF (5.0 mL), 2 h. [b] Isolated yields. [c] NMR yields are shown in parenthesis. [d] Lower yield (69%) of the product was obtained using DME as the organic phase. [e] Ratios of **2** and **3** were determined by ^1H NMR and shown in brackets. [f] $NaBH_4$ (2.2 equiv.), I_2 (1.2 equiv.).

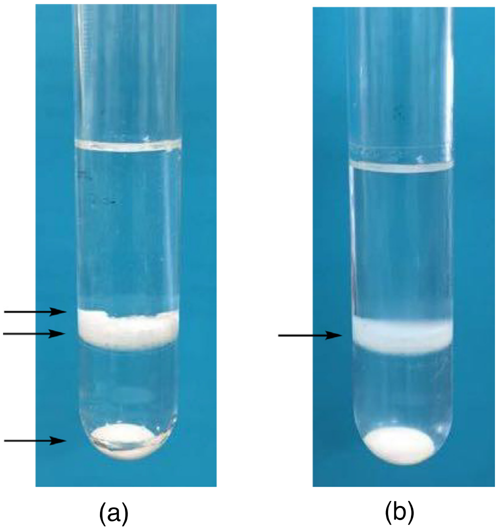


Fig. 2. PV hydroboration of 4-methylstyrene using $NaBH_4$ and ethyl iodide (Condition C). Arrows indicate the phase interface. (a) A quadriphasic system: ethyl iodide, Galden HT-135/200 (Fig. 3), $NaBH_4$, and DME solution of 4-methylstyrene (from the bottom). (b) After 20 h, the ethyl iodide and $NaBH_4$ layers disappeared, affording two phases, Galden and DME phases (from the bottom), respectively, and a white insoluble solid was generated near the interface of the two phases.

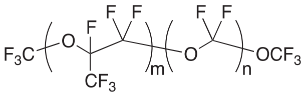


Fig. 3. Structure of Galden.

yields than those with an electron-donating group. Interestingly, styrene (**1c**), 4-fluorostyrene (**1d**), and 4-chlorostyrene (**1e**) afforded Markovnikov alcohols **3c**, **3d**, and **3e** in low yields (6–17%) together with anti-Markovnikov product **2c**, **2d**, and **2d**, respectively [13]. Styrene **1e** was reacted with a conventional borane reagent, BH_3-THF, to afford Markovnikov alcohol **3e** in a yield similar to that obtained by the PV method (Entry 5, Condition E), indicating that the regioselectivity of hydroboration under the PV conditions is hardly different from that of the conventional one [14]. Aliphatic alkenes **1g** and **1h** also underwent hydroboration–oxidation using the PV system, affording desired products **2g** and **2h**, respectively, in good yields (Entries 7, 8). 1,9-Decadiene (**1i**) produced the corresponding diol 1,10-decandiol (**2i**) as the major product (69% yield, Entry 9). As described above, substrates bearing a hydroxy or an ester group afforded the desired products in significantly lower yields when H_2SO_4 was used in the PV method (Entries 10 and 11, Condition A). However, the yields improved when I_2 (Entries 10 and 11, Condition B) or ethyl iodide (Entries 10 and 11, Condition C) was used as the oxidant. $^nBu_4NBH_4$ also worked very well in the reaction, affording a similar yield as ethyl iodide (Entry 11, Condition D).

Reduction of carboxylic acids using borane-evolution PV method

Borane is known to reduce carboxylic acids leaving the esters intact [8]. Thus, we carried out the reduction of carboxylic acids **4** using the PV method for borane evolution. Unfortunately, $NaBH_4$ reacts slowly with carboxylic acids. Hence, we employed $^nBu_4NBH_4$ as the borane source. Toluene is often used as the solvent for borane reduction [11b]; however, the yields obtained are considerably low (<20%). Therefore, we used CH_2Cl_2 as the solvent instead [15]. The results are summarised in Table 2. Myristic acid (**4a**) was reduced smoothly to afford the corresponding alcohol **5a** in 84% yield (Entry 1), while ethyl myristate (**4b**) was not reduced, and hence, the ester was recovered quantitatively (Entry 2). Selective reduction of aliphatic carboxylic acid **4c** bearing an ethyl ester was achieved to afford the desired hydroxy ester **5c** in a high yield (Entry 3). Interestingly, whereas diethyl terephthalate (**4d**) was not reduced under the conditions (Entry 4), the ethyl ester in terephthalic monoester **4e** was reduced along with the carboxylic group to furnish diol **5e** (Entry 5) [16]. The cyano group was reacted with borane to afford a complex mixture (Entry 6) [17]. 9-Decenoic acid (**4g**) also produced a complex mixture under the standard reduction conditions (Entry 7). Perhaps, hydroboration to the olefinic moiety in the substrate would compete with the reduction of the carboxylic group. When **4g** was treated under the conditions in which 3 equiv. of borane was generated, both the reduction of the carboxylic group and the hydroboration of the olefinic moiety took place, affording diol **2i** in a good yield (Entry 8).

Suzuki–Miyaura coupling of organoboranes generated in situ using borane-evolution PV method

Finally, we carried out the Suzuki–Miyaura coupling [18] of organoboranes generated in situ using the borane-evolution PV method. Alkenes **1a** and **1h** underwent hydroboration with $^nBu_4NBH_4$ under the PV conditions, followed by the Suzuki–Miyaura coupling with iodobenzene in the presence of a palladium catalyst, affording the corresponding coupling products **6a** and **6h** in the isolated yields of 72% and 75%, respectively (Scheme 1). Importantly, these sequential hydroboration and Suzuki-Miyaura coupling reactions were achieved in a common test tube.

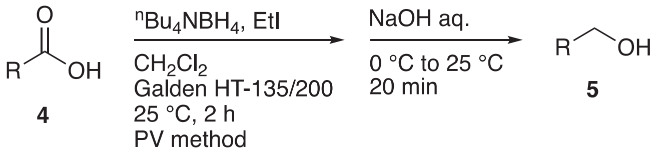
Conclusion

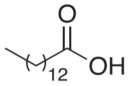
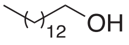
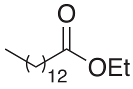
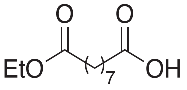
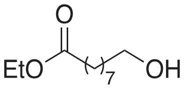
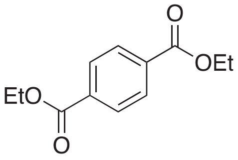
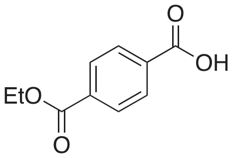
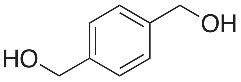
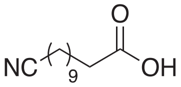
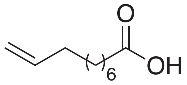
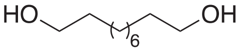
We developed a facile method to evolve borane gas using the PV method, where the gas was generated from $NaBH_4$ with H_2SO_4, I_2, or ethyl iodide in a simple test tube. Hydroboration of alkenes was successfully carried out using the evolved borane, affording the desired products in good yield after treatment with H_2O_2 under basic conditions. The selective reduction of aliphatic carboxylic acids bearing an ethyl ester with borane evolved from $^nBu_4NBH_4$ and ethyl iodide was also achieved under the PV conditions. In addition, the organoboranes generated by hydroboration successfully underwent Suzuki–Miyaura coupling with iodobenzene in the same test tube. Our results show that the borane-evolution PV method is a valid alternative to the method involving the use of borane–THF or borane–Me_2S complex as a borane source. The PV method can be applied to many organic synthesis reactions. Currently, generation of attractive borane derivatives such as 9-BBN and their selective hydroboration using the PV method are under progress, and the results will be reported in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 2
Reduction of carboxylic acids and esters using borane-evolution PV method.[a]



Entry	Substrate	Product	Isolated yield//%
1	 **4a**	 **5a**	84
2	 **4b**	—	NR
3	 **4c**	 **5c**	82
4	 **4d**	—	NR
5	 **4e**	 **5e**	75
6	 **4f**	Complex mixture	–
7 8[b]	 **4g**	Complex mixture  **2i**	– 79

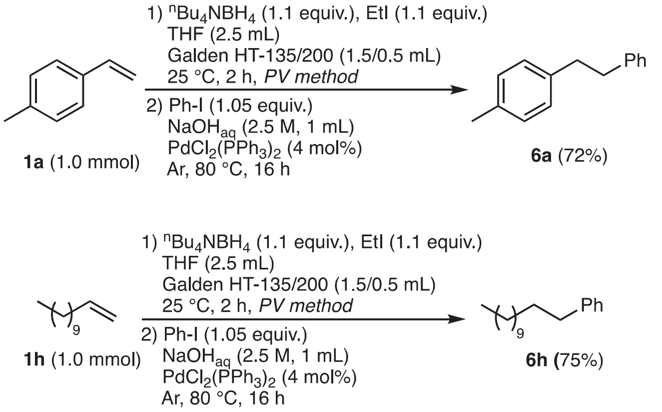
[a]Substrate (1.0 mmol), $^{n}Bu_4NBH_4$ (2.0 equiv.), EtI (2.0 equiv.), CH_2Cl_2 (2.5 mL), Galden HT-135/200 (1.5 mL/0.5 mL), 25 °C, 2 h; then $NaOH_{aq}$ (1 M, 0.7 mL), 0 °C to 25 °C, 20 min. [b] $^{n}Bu_4NBH_4$ (3.0 equiv.), EtI (3.0 equiv.); then $NaOH_{aq}$ (0.68 mL), H_2O_2 (0.25 mL), 0 °C to 25 °C, 20 min.

Acknowledgments

This study was partially supported by JSPS KAKENHI Grant Number JP16K05755. We acknowledge Tosoh Finechem Corp. for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152977.



Scheme 1. Suzuki–Miyaura coupling of organoboranes generated using borane-evolution PV method.

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[12] Galden HT-135 and HT-200 are polyether-type perfluorinated solvents (see Fig. 3), which are commercially available from Solvay Solexis Inc. HT-200 has higher boiling point and viscosity than HT-135.

[13] Anti-Markovnikov products were isolated together with Markovnikov products. Their separation was not performed in this study. The product ratios were determined by ^1H-NMR.

[14] The regioselectivity for the addition of borane to 4-substututed styrene is strongly influenced by the substituent; see Ref. 8a.

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[16] Reaction of monoester **4e** with 1 equiv. of borane provided a mixture of diol 5e and unreacted **4e**. Using THF and toluene as the organic phase, **5e** was obtained in lower yields along with **4e**.

[17] Reduction of **4f** with 1, 2 or 3 equiv. of borane afforded complex mixtures invariably.

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