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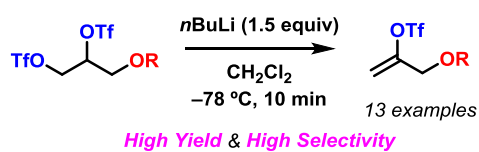
***n*-Butyllithium-promoted regioselective elimination of vicinal bis-triflate having an adjacent ether oxygen**

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ABSTRACT

Regioselective elimination of a vicinal bis-triflate having an adjacent ether oxygen functional group has been developed. Considered in the context of our studies of the regioselective elimination of vicinal dibromide, the key to the mechanism involves the electron-withdrawing inductive effect of the neighboring oxygen functional group. Aliphatic vinyl triflate was shown to be effective in Suzuki–Miyaura cross coupling compared with corresponding aliphatic vinyl bromide.

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Introduction

Vinyl triflates are useful building blocks in a wide range of transition-metal catalyzed C–C bond formations, such as Suzuki–Miyaura coupling, Sonogashira coupling, and Negishi coupling.¹ In consequence of their high reactivity, vinyl triflates are often utilized as the first choice of alternative substrates² when bond-forming reactions using vinyl bromides as the coupling partner do not work well. In some cases, both vinyl triflates and vinyl bromides can be used quite chemoselectively, depending on the synthetic demands, by choosing a suitable catalyst.^{2a,3} In addition, vinyl triflates, which display excellent elimination ability, have also been utilized as precursors for elimination reactions,⁴ nucleophilic substitution reactions,⁵ or fragmentation reactions.⁶ Therefore, vinyl triflates have a great deal of potential in total synthesis of natural products and modern drug discovery research.

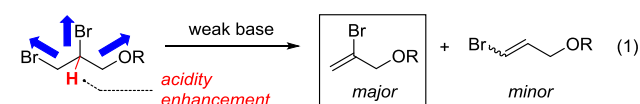
Despite the usefulness of vinyl triflates in organic chemistry, there are few effective versatile synthetic methods. The most popular synthetic routes are transformations from ketones through the corresponding enolate intermediates^{1e,1i,7} or from diols through the geminal bis-triflate intermediate.^{1e,1i,8} In these pathways, regio- and stereocontrol of the double bond in vinyl triflates is a major problem to overcome.^{1e,1i,7c,7d,9} Additionally, other examples of regio- and stereoselective synthesis of vinyl triflates are rarely used in complex molecules because they require harsh reaction conditions.^{9b,10}

Recently, we reported the synthesis of 2-bromo-1-alkenes under mild basic conditions that used the DBU-promoted regioselective HBr-elimination of vicinal dibromides having an adjacent oxygen functional group.¹¹ The key to the high yield and regioselectivity of the HBr-elimination reaction was attributed to

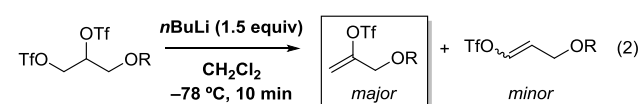
the electron-withdrawing inductive effect of the neighboring oxygen substituent, which enhanced the acidity of the hydrogen at the C2 position, along with the electron-withdrawing inductive

effects of both bromine atoms (Scheme 1, eq. 1).^{11a,11e,11h} Based on this research background, we envisioned regioselective synthesis of vinyl triflates from vicinal bis-triflates having an adjacent oxygen functional group. In the course of our work, we discovered the curious reaction conditions that afforded 2-triflate-1-alkenes (Scheme 1, eq. 2). Herein, we describe the results in detail.

Previous work



This work



Scheme 1. Regioselective HBr-elimination of vicinal dibromide (previous work) and this work.

Results and discussion

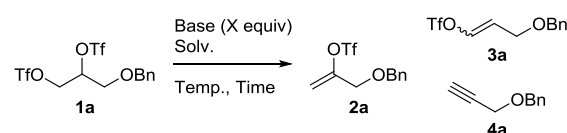
Based on our previous research results,¹¹ we started our study using a benzyl-protected bis-triflate **1a** as a substrate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (Table 1, Entries 1–5). However, the DBU-promoted elimination resulted in unsatisfactory results, particularly in terms of low selectivity of vinyl triflates **2a** and **3a** under the attempted conditions. Some

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other bases, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), NaOAc, K₂CO₃, and KOH, were also examined, but these reactions showed complicated results even at room temperature (Entries 6–9). This outcome seemed to be due to the reaction sensitivity of **1a** at ambient temperature. Therefore, we next evaluated a variety of strong bases at –78 °C for the elimination reaction of **1a**. Interestingly, 2-triflate **2a** was obtained as a single product with 70% yield by using potassium bis(trimethylsilyl)amide (KHMDS, in toluene solution) in dichloromethane, while **2a**, **3a**, and the overreaction product, alkyne **4a**, were obtained by using lithium bis(trimethylsilyl)amide (LHMDS, in THF solution) in the same solvent (Entries 10 and 11). In addition, when *n*BuLi in hexane solution was used in diethyl ether, 2-triflate **2a** was obtained in 51% yield together with **4a** (Entry 12). These results suggested that the solvent effect was involved to a large degree of the elimination reactivity. Hence, *n*BuLi-promoted eliminations of **1a** in THF, toluene, or dichloromethane were carried out (Entries 13–15). As a result, the compound **2a** was solely produced when toluene or dichloromethane was used as a solvent, whereas the reaction system in THF was complicated. The difference of the reactivity and selectivity of the elimination could be caused by the different degrees of association and coordination of *n*BuLi in the solvent. Thus, we selected the optimal conditions as shown in Entry 15.

Table 1

Optimization of reaction conditions.



Entry	Base (X equiv)	Solv.	Temp. (°C)	Time (min)	Obtained Product Yield (%)
1	DBU (1.1)	DMF	RT	10	66 (2a/3a = 1.0/2.7) ^d
2	DBU (1.1)	THF	RT	10	71 (2a/3a = 1.0/1.3) ^d
3	DBU (1.1)	CH ₂ Cl ₂	RT	60	77 (2a/3a = 1.0/2.0) ^d , 17 (1a)
4	DBU (1.1)	CH ₂ Cl ₂	–40	60	57 (2a/3a = 1.0/2.4) ^d , 15 (1a)
5	DBU (1.1)	CH ₂ Cl ₂	–78	60	25 (2a/3a = 1.0/2.1) ^d , 48 (1a)
6	DABCO (1.1)	CH ₂ Cl ₂	RT	15	Decomp.
7	NaOAc (2.0)	DMF	RT	25	Decomp.
8	K ₂ CO ₃ (2.0)	DMF	RT	20	Decomp.
9	KOH (4.0)	DMF	RT	10	Decomp.
10	KHMDS (1.5) ^a	CH ₂ Cl ₂	–78	10	70 (2a)
11	LHMDS (1.5) ^b	CH ₂ Cl ₂	–78	10	18 (2a/3a = 1.3/1.0) ^d , 46 (4a)
12	<i>n</i> BuLi (1.5) ^c	Et ₂ O	–78	10	51 (2a), 18 (4a)
13	<i>n</i> BuLi (1.5) ^c	THF	–78	10	44 (2a/3a = 1.0/1.1) ^d , 18 (1a), 16 (4a)
14	<i>n</i> BuLi (1.5) ^c	Toluene	–78	10	82 (2a)
15	<i>n</i> BuLi (1.5) ^c	CH ₂ Cl ₂	–78	10	94 (2a)

^a 0.5 M in toluene solution^b 1.3 M in THF solution^c 1.6 M in hexane solution^d Ratio of **2a/3a** was determined by ¹H NMR.

To confirm the generality of the regioselective synthesis of 2-triflate-1-alkenes **2**, we examined the elimination reaction of a variety of vicinal bis-triflates **1** under the optimal conditions (Table 2). First, the reactions of the bis-triflates **1** having an adjacent substituted benzyloxy (**1b** and **1c**), phenoxy (**1d** and **1e**), and alkoxy (**1f** and **1g**) groups proceeded smoothly to afford the

corresponding 2-triflates **2b–g** as the sole product (Entries 1–6), while the reaction of **1h** was relatively slow (Entry 7). In addition, the reaction of the silyl-protected **1i** did not give the desired vinyl triflate, although the reason is still under investigation (Entry 8). The regioselective elimination of internally *syn*- and *anti*-bis-triflates **1j** and **1k** proceeded with high *cis–trans* selectivity as a consequence of the *trans* elimination (Entries 9 and 10). Moreover, the reaction of cyclic vicinal bis-triflates **1l** and **1m** also succeeded to give the expected **2l** and **2m**, respectively (Entries 11 and 12). Finally, to confirm the importance of the neighboring oxygen functional group's participation, bis-triflate **1n** was examined (Entry 13). In comparison with the elimination of **1d** (Entry 3), it is clear that the adjacent oxygen functional group is important in determining the elimination reactivity and selectivity.

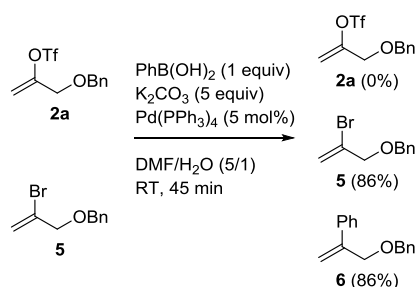
Table 2Regioselective elimination of vicinal bis-triflate **1**.^a

Entry	Bis-triflate 1	Obtained Product	Yields (%)
1			85
2			87
3			85
4			58
5			83
6			76
7			54 ^b
8			N.D. ^c
9			89 ^d
10			84 ^e
11			94
12 ^f			60
13		 	5 ^g

^a *n*BuLi (1.5 equiv, 1.6 M in hexane solution)/CH₂Cl₂, –78 °C, 10 min.^b **1h** was recovered (27%).^c **2i** was not detected, and **1i** was recovered (76%).^d 1-(Benzyloxy)hexane-2-one was obtained as a byproduct (9%).^e **2j** was obtained as a byproduct (4%).^f *n*BuLi (2.0 equiv, 1.6 M in hexane solution)/CH₂Cl₂, –78 °C, 20 min.^g The ratio of **2n/3n** was 2/3 determined by ¹H NMR and **1n** was recovered (80%).

As mentioned above, both vinyl triflates and vinyl bromides can be synthesized chemoselectively by choosing appropriate reaction conditions.³ However, to our knowledge, there have been almost no reports comparing the reactivity of aliphatic vinyl triflates with that of aliphatic vinyl bromides.¹² Thus, the

competition experiment in Suzuki–Miyaura cross coupling was studied using phenylboronic acid (Scheme 2). An equimolar mixture of **2a**, vinyl bromide **5**, and phenylboronic acid was treated in the presence of 5 mol% of tetrakis(triphenylphosphine)palladium and 5 equivalents of potassium carbonate in DMF/H₂O (5/1) at room temperature. After 45 min, the reaction system afforded **5** and the coupling product **6** in good yields along with the recovered **5**, while **2a** was completely consumed. This result implied that aliphatic vinyl triflate **2** might be a better coupling substrate than aliphatic vinyl bromide **5**, without any side-reactions resulting from formation of π -allyl palladium complex by the transition metal under these reaction conditions.^{11g,12,13}



Scheme 2. Competition experiment in the Suzuki–Miyaura cross coupling.

Conclusion

We have developed a new and unique approach to the synthesis of vinyl triflate **2** in high yield and selectivity. The regioselective elimination of vicinal bis-triflate **1** also involved the electron-withdrawing inductive effect of the neighboring ether oxygen functional group. These synthetic studies including our previous research¹¹ should be applicable to the total synthesis of natural products and for use in modern drug-discovery research.

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Supplementary Material

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