Tetrahedron Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

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

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ARTICLE INFO

Article history:
Received 11 August 2017
Revised 7 September 2017
Accepted 14 September 2017
Available online xxxx

Keywords:
Vinyl triflate
Regioselective elimination
Vicinal bis-triflate
Electron-withdrawing inductive effect
Neighboring-group effect

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.

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 substrates[2] 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,i,7] or from diols through the geminal bis-triflate intermediate.[1e,i,8] In these pathways, regio- and stereocontrol of the double bond in vinyl triflates is a major problem to overcome.[1e,i,7c,d,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,e,h] 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.

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 other bases, such

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https://doi.org/10.1016/j.tetlet.2017.09.036
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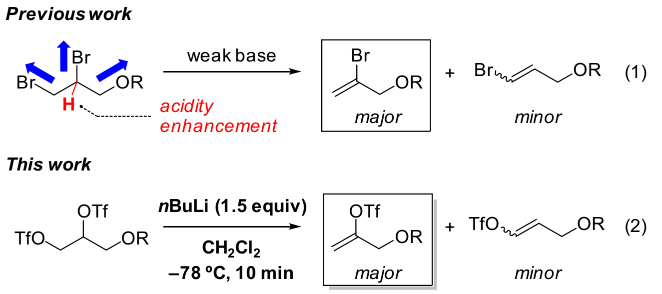


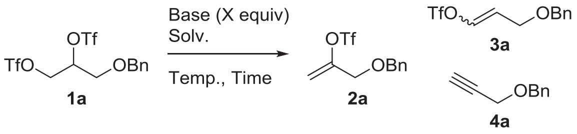
Scheme 1. Regioselective HBr-elimination of vicinal dibromide (previous work) and this work.

as 1,4-diazabicyclo[2.2.2]octane (DABCO), NaOAc, K_2CO_3, 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.

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.

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/H_2O (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 forma-

Table 1
Optimization of reaction conditions.

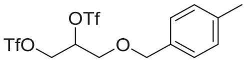
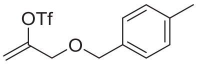
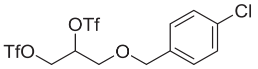
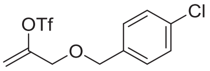
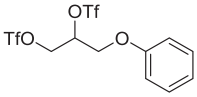
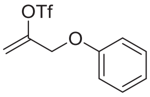
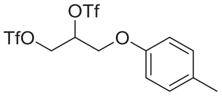
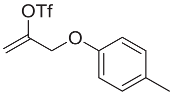
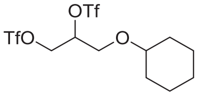
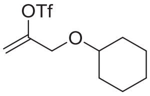
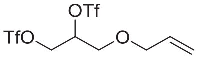
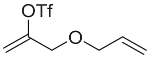
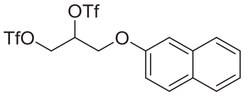
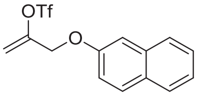
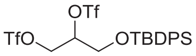
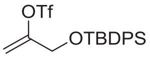
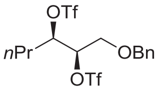
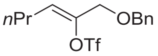
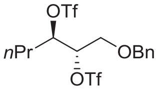
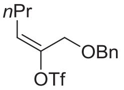
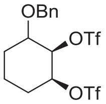
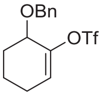
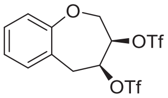
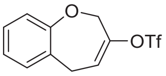
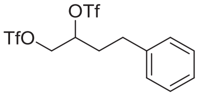
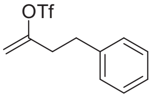
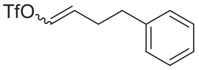


Entry	Base (X equiv)	Solv.	Temp. (°C)	Time (min)	Obtained Product Yield (%)
1	DBU (1.1)	DMF	RT	10	66 (**2a**/**3a** = 1.0/2.7)[d]
2	DBU (1.1)	THF	RT	10	71 (**2a**/**3a** = 1.0/1.3)[d]
3	DBU (1.1)	CH_2Cl_2	RT	60	77 (**2a**/**3a** = 1.0/2.0)[d], 17 (**1a**)
4	DBU (1.1)	CH_2Cl_2	−40	60	57 (**2a**/**3a** = 1.0/2.4)[d], 15 (**1a**)
5	DBU (1.1)	CH_2Cl_2	−78	60	25 (**2a**/**3a** = 1.0/2.1)[d], 48 (**1a**)
6	DABCO (1.1)	CH_2Cl_2	RT	15	Decomp.
7	NaOAc (2.0)	DMF	RT	25	Decomp.
8	K_2CO_3 (2.0)	DMF	RT	20	Decomp.
9	KOH (4.0)	DMF	RT	10	Decomp.
10	KHMDS (1.5)[a]	CH_2Cl_2	−78	10	70 (**2a**)
11	LHMDS (1.5)[b]	CH_2Cl_2	−78	10	18 (**2a**/**3a** = 1.3/1.0)[d], 46 (**4a**)
12	*n*BuLi (1.5)[c]	Et_2O	−78	10	51 (**2a**), 18 (**4a**)
13	*n*BuLi (1.5)[c]	THF	−78	10	44 (**2a**/**3a** = 1.0/1.1)[d], 18 (**1a**), 16 (**4a**)
14	*n*BuLi (1.5)[c]	Toluene	−78	10	82 (**2a**)
15	*n*BuLi (1.5)[c]	CH_2Cl_2	−78	10	94 (**2a**)

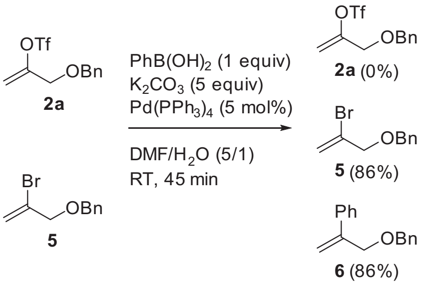
[a] 0.5 M in toluene solution.
[b] 1.3 M in THF solution.
[c] 1.6 M in hexane solution.
[d] Ratio of **2a**/**3a** was determined by ^1H NMR.

Please cite this article in press as: Kutsumura N., et al. Tetrahedron Lett. (2017), https://doi.org/10.1016/j.tetlet.2017.09.036

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

Entry	Bis-triflate **1**	Obtained Product	Yields (%)
1	 **1b**	 **2b**	85
2	 **1c**	 **2c**	87
3	 **1d**	 **2d**	85
4	 **1e**	 **2e**	58
5	 **1f**	 **2f**	83
6	 **1g**	 **2g**	76
7	 **1h**	 **2h**	54[b]
8	 **1i**	 **2i**	N.D.[c]
9	 **1j**	 **2j**	89[d]
10	 **1k**	 **2k**	84[e]
11	 **1l**	 **2l**	94
12[f]	 **1m**	 **2m**	60
13	 **1n**	 **2n**  **3n**	5[g]

[a] nBuLi (1.5 equiv, 1.6 M in hexane solution)/CH_2Cl_2, −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] nBuLi (2.0 equiv, 1.6 M in hexane solution)/CH_2Cl_2, −78 °C, 20 min.
[g] The ratio of **2n**/**3n** was 2/3 determined by ^{1}H NMR and **1n** was recovered (80%).



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

tion of π-allyl palladium complex by the transition metal under these reaction conditions.[11g,12,13]

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 research[11] should be applicable to the total synthesis of natural products and for use in modern drug-discovery research.

Acknowledgments

This work was partly financially supported by the Central Glass Co., Ltd. (Central Glass Co., Ltd. Award in Synthetic Organic Chemistry, Japan), Tokyo Ohka Foundation for The Promotion of Science and Technology, and JGC-S Scholarship Foundation.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.09.036.

References

1. (a) Scott WJ, Crisp GT, Stille JK. *J Am Chem Soc*. 1984;106:4630–4632;
   (b) Echavarren AM, Stille JK. *J Am Chem Soc*. 1987;109:5478–5486;
   (c) Scott WJ, McMurry JE. *Acc Chem Res*. 1988;21:47–54;
   (d) Lipshutz BH, Elworthy TR. *J Org Chem*. 1990;55:1695–1696;
   (e) Ritter K. *Synthesis*. 1993;735–762;
   (f) Crisp GT, Meyer AG. *Tetrahedron*. 1995;51:5585–5596;
   (g) Busacca CA, Eriksson MC, Fiaschi R. *Tetrahedron Lett*. 1999;40:3101–3104;
   (h) Halbes U, Bertus P, Pale P. *Tetrahedron Lett*. 2001;42:8641–8644;
   (i) Chassaing S, Specklin S, Weibel JM, Pale P. *Tetrahedron*. 2012;68:7245–7273;
   (j) Vila C, Hornillos V, Giannerini M, Fañanás-Mastral M, Feringa BL. *Chem Eur J*. 2014;20:13078–13083;
   (k) McCammant MS, Sigman MS. *Chem Sci*. 2015;6:1355–1361;
   (l) Shvartsbart A, Smith III AB. *J Am Chem Soc*. 2015;137:3510–3519.
2. (a) Nicolaou KC, Bulger PG, Sarlah D. *Angew Chem Int Ed*. 2005;44:4442–4489;
   (b) Chinchilla R, Nájera C. *Chem Rev*. 2007;107:874–922.
3. (a) Kamikawa T, Hayashi T. *Tetrahedron Lett*. 1997;38:7087–7090;
   (b) Kamikawa T, Hayashi T. *J Org Chem*. 1998;63:8922–8925;
   (c) Littke AF, Dai C, Fu GC. *J Am Chem Soc*. 2000;122:4020–4028;
   (d) Wang J, Seefeld MA, Luengo J. *Tetrahedron Lett*. 2011;55:6346–6348.
4. (a) Brummond KM, Gesenberg KD, Kent JL, Kerekes AD. *Tetrahedron Lett*. 1998;39:8613–8616;
   (b) Navarro-Vázquez A, Alonso-Gómez JL, Lugtenburg J, Cid MM. *Tetrahedron*. 2010;66:3855–3860;
   (c) Maity P, Lepore SD. *J Org Chem*. 2009;74:158–162.
5. (a) Liu JF, Heathcock CH. *J Org Chem*. 1999;64:8263–8266;
   (b) Lipshutz BH, Vivian RW. *Tetrahedron Lett*. 1999;40:4;
   (c) Rawat DS, Gibbs RA. *Org Lett*. 2002;4:3027–3030.
6. (a) Kamijo S, Dudley GB. *J Am Chem Soc*. 2005;127:5028–5029;
   (b) Kamijo S, Dudley GB. *Org Lett*. 2006;8:175–177;
   (c) Tummatorn J, Dudley GB. *J Am Chem Soc*. 2008;130:5050–5051;
   (d) Kurosawa F, Nakano T, Soeta T, Endo K, Ukaji Y. *J Org Chem*. 2015;80:5696–5703;
   (e) Kawamoto T, Sasaki R, Kamimura A. *Angew Chem Int Ed*. 2017;56:1342–1345.
7. (a) McMurry JE, Scott WJ. *Tetrahedron Lett*. 1983;24:979–982;
   (a) Comins DL, Dehghani A. *Tetrahedron Lett*. 1992;33:6299–6302;
   (b) Foti CJ, Comins DL. *J Org Chem*. 1995;60:2656–2657;
   (c) Babinski D, Soltani O, Frantz DE. *Org Lett*. 2008;10:2901–2904;
   (d) Specklin S, Bertus P, Weibel JM, Pale P. *J Org Chem*. 2008;73:7845–7848.
8. (a) Stang PJ, Treptow W. *Synthesis*. 1980;283–284;
   (b) Wright ME, Pulley SR. *J Org Chem*. 1989;54:2886–2889.
9. (a) Keck D, Muller T, Bräse S. *Synlett*. 2006;3457–3460;
   (b) Vasilyev AV, Walspurger S, Chassaing S, Pale P, Sommer J. *Eur J Org Chem*. 2007;5740–5748.
10. (a) Summerville RH, Schleyer PVR. *J Am Chem Soc*. 1974;96:1110–1120;
    (b) Olah GA, Spear RJ. *J Am Chem Soc*. 1975;97:1845–1851;
    (c) Crisp GT, Meyer AG. *Synthesis*. 1994;667–668;
    (d) Al-huniti MH, Lepore SD. *Org Lett*. 2014;16:4154–4157.
11. (a) Ohgiya T, Nishiyama S. *Chem Lett*. 2004;33:1084–1085;
    (b) Ohgiya T, Kutsumura N, Nishiyama S. *Synlett*. 2008;3091–3105;
    (c) Kutsumura N, Niwa K, Saito T. *Org Lett*. 2010;12:3316–3319;
    (d) Kutsumura N, Kubokawa K, Saito T. *Synlett*. 2010;2717–2720;
    (e) Kutsumura N, Iijima M, Toguchi S, Saito T. *Chem Lett*. 2011;40:1231–1232;
    (f) Kutsumura N, Kubokawa K, Saito T. *Synthesis*. 2011;2377–2382;
    (g) Kutsumura N, Matsubara Y, Niwa K, Saito T. *Eur J Org Chem*. 2013;3337–3346;
    (h) Kutsumura N, Toguchi S, Iijima M, Tanaka O, Iwakura I, Saito T. *Tetrahedron*. 2014;70:8004–8009.
12. Jutand A, Négri S. *Organometallics*. 2003;22:4229–4237.
13. (a) Organ MG, Miller M. *Tetrahedron Lett*. 1997;38:8181–8184;
    (b) Organ MG, Miller M, Konstantinou Z. *J Am Chem Soc*. 1998;120:9283–9290;
    (c) Organ MG, Arvanitis EA, Dixon CE, Cooper JT. *J Am Chem Soc*. 2002;124:1288–1294;
    (d) Organ MG, Arvanitis EA, Villani A, Majkut Y, Hynes S. *Tetrahedron Lett*. 2003;44:4403–4406;
    (e) Comer E, Organ MG, Hynes SJ. *J Am Chem Soc*. 2004;126:16087–16092.

Please cite this article in press as: Kutsumura N., et al. Tetrahedron Lett. (2017), https://doi.org/10.1016/j.tetlet.2017.09.036