A Facile Synthesis of Optically Active 1,1,1-Trifluoro-3-alkyn-2-ols by Stereospecific Substitution of Optically Active 1-Benzyloxy-2,2,2-trifluoroethyl Tosylate with Lithium Alkynyltriethylaluminates

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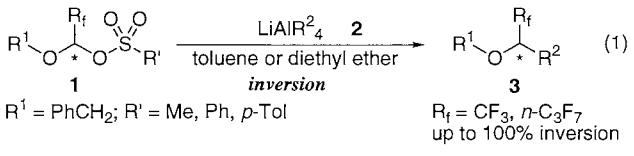
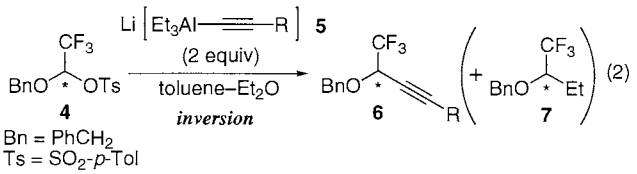
Optically active 1-benzyloxy-2,2,2-trifluoroethyl tosylate reacts with various lithium alkynyltriethylaluminates to give optically active 2-benzyloxy-1,1,1-trifluoro-3-alkynes selectively and stereospecifically with inversion of configuration. Thus, the reaction provides with a novel method for the preparation of various optically active 1,1,1-trifluoro-3-alkyn-2-ols.

Recently, increasing attention is being focused on fluorinated chiral compounds, particularly trifluoromethyl-substituted ones, due to their remarkable biological and physical properties.[1] A straightforward access to such molecules should be stereospecific substitution of optically active compounds bearing a trifluoromethyl group at a chiral carbon. However, only a few works have been successful,[2] since a trifluoromethyl group at an electrophilic center generally interferes with the attack of a nucleophile.

We have demonstrated that an alkoxyl group accelerates such nucleophilic substitution. For example, chiral non-racemic 1-alkoxy(polyfluoro)alkyl sulfonates (**1**) react with lithium tetraalkylaluminates (**2**) stereospecifically with inversion of configuration as shown in eq (1).[3,4] Regarding the reacting alkyl group, only one of four R^2 groups of **2** takes part in the substitution reaction as a nucleophile with the other three R^2s being wasted. We considered the possibility of using lithium alkynyltriethylaluminate[5] (**5**) for the alkynylative substitution reaction[6] of chiral non-racemic 1-benzyloxy-2,2,2-trifluoroethyl tosylate (**4**). Herein, we report that various kinds of previously inaccessible, optically active trifluoromethyl-propargyl benzyl ethers **6** are readily accessible via the following reaction (eq 2).



(1)

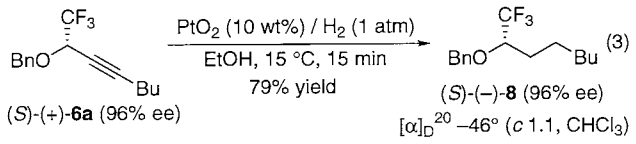


(2)

A typical procedure follows. A commercially available hexane solution of triethylaluminum (0.8 mmol) was added to 1-lithio-1-hexyne (1.0 mmol) in toluene to give lithium 1-hexynyltriethylaluminate (**5a**) slurry, which was dissolved with a small amount of diethyl ether. To a toluene solution of tosylate (*R*)-**4**[3] (0.4 mmol), the aluminate was added dropwise under the indicated conditions to give alkynylated product (*S*)-(+)-**6a** in 77% yield with 97% inversion.[7] This and other results are summarized in Table 1. As readily seen, the present alkynylation reaction is stereospecific and selective with only a small amount of accompanying ethylation product.[8]

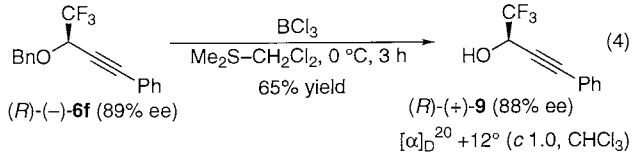
The substitution reaction of (*R*)-**4** with aluminate **5b** prepared from trimethylsilylacetylene gave trimethylsilyl-substituted product (*S*)-**6b** in 60% yield with 95% inversion (entry 2). Terminally functionalized alkynylaluminate **5c** also was applied to the alkynylation to furnish **6c** stereospecifically (95% inversion), although the yield and selectivity remained moderate (entry 3). Lithium [2-(1-alkenyl)ethynyl]triethylaluminates **5d** and **5e** reacted with tosylate (*S*)-**4** to give optically active trifluoromethyl-substituted enynes **6d** and **6e** in good yields, with 97 and 95% inversion respectively (entries 4 and 5). Phenylacetylene and the substituted derivatives were converted into alkynylated products **6f**–**6h** in moderate to good yields with high specificities (entries 6–8). It is worthy to note that bromo and methoxy groups on a benzene ring remained intact throughout the reaction.

The C≡C bond of (+)-**6a** was easily reduced by catalytic hydrogenation with PtO_2 as a catalyst to furnish (–)-2-benzyloxy-1,1,1-trifluorooctane (**8**), whose sign of $[\alpha]_D$ was identical to (*S*)-(–)-**8**.[4] Thus, the absolute configuration of (+)-**6a** was determined to be *S* (eq 3). The assignment of the absolute configurations of **6b**–**6h** is based on the substrate configuration, as well as the stereochemical course of the reaction.



(3)

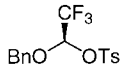
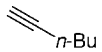
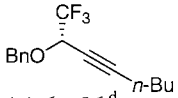
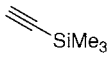
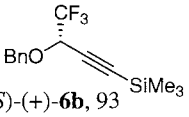
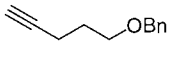
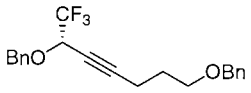
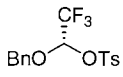
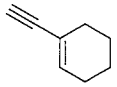
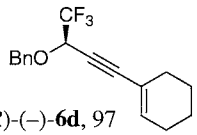
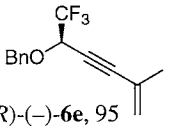
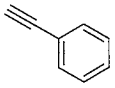
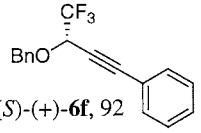
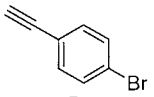
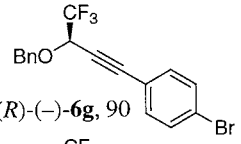
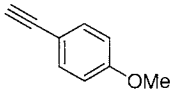
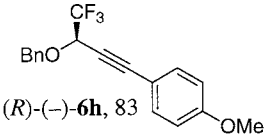
The versatility of the present reaction is demonstrated by the transformation of the products to optically active 1,1,1-trifluoro-3-alkyn-2-ols. Debenzylation of (*R*)-(–)-**6f** with BCl_3[9] in the presence of dimethylsulfide[10] gave (*R*)-(+)-1,1,1-trifluoro-4-phenyl-3-butyn-2-ol (**9**).[11] Noteworthy is that both CF_3 and C≡C functionalities remained totally unaffected by the deprotection procedure.



(4)

According to the novel alkynylation reaction, various novel 1-

Table 1. Ethynylation of Chiral non-Racemic Tosylate **4** with Aluminates **5**

Entry	**4** (Config., % ee)	**5** ≡—R	Temp. (°C)	Time (h)	**6** (Config., % ee)	Yield (%) [a]	% / Inversion [b]	**6** : **7** [c]
1	 (*R*)-**4**, 99	 **5a**	23	2	 (*S*)-(+)-**6a**, 96 [d]	77	97	10 : 1
2	(*R*)-**4**, 98	 **5b**	23	2	 (*S*)-(+)-**6b**, 93	60	95	4 : 1
3	(*R*)-**4**, 98	 **5c**	23	2	 (*S*)-(+)-**6c**, 93	23	95	1 : 1
4	 (*S*)-**4**, 100	 **5d**	23	2	 (*R*)-(−)-**6d**, 97	63	97	4 : 1
5	(*S*)-**4**, 100	 **5e**	23	2	 (*R*)-(−)-**6e**, 95	61	95	5 : 1
6	(*R*)-**4**, 99	 **5f**	40	1	 (*S*)-(+)-**6f**, 92	83	93	6 : 1
7	(*S*)-**4**, 100	 **5g**	40	1	 (*R*)-(−)-**6g**, 90	81	90	5 : 1
8	(*S*)-**4**, 100	 **5h**	40	1	 (*R*)-(−)-**6h**, 83	48	83	2 : 1 [e]

[a] Isolated yield. [b] The ratio of (% ee of **6**)/(% ee of **4**) as expressed in %. [c] Determined by NMR of a crude sample. [d] $[\alpha]_D^{20}$ +134° (*c* 1.0, $CHCl_3$). [e] Isolated product (*R*)-**7** (17% yield) showed 87% ee.

trifluoromethylpropargyl alcohols are now available. These compounds are key chiral building blocks for biologically active and organic functional materials.

References and Notes

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7 See Table 1. Enantiomeric excess (ee) was analyzed by HPLC with CHIRALCEL or CHIRALPAK (both available from Daicel).

8 Isolated ethylation product **7**[3] showed the same configuration and comparable ee to those of **6**. See Table 1, entry 8.

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