A Facile Synthesis of *N*-[2-(Trifluoromethyl)allyl]amides and Their Transformation into Angularly Trifluoromethylated Bicyclic Cyclopentenones

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(Received September 21, 2006; CL-061101; E-mail: Junji@chem.s.u-tokyo.ac.jp)

On treatment with *sec*-BuLi at −105 °C, 2-bromo-3,3,3-trifluoropropene undergoes rapid lithium–halogen exchange to generate thermally unstable 1-(trifluoromethyl)vinyllithium, which reacts with *N*-tosylimines to afford *N*-[2-(trifluoromethyl)allyl]amides in high yield. Propargylation of the amides, followed by the Pauson–Khand reaction, readily provides pyrrolidine ring-fused cyclopentenones with an angular trifluoromethyl group.

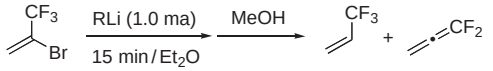
2-Trifluoromethyl-1-alkenes [1-(trifluoromethyl)vinyl compounds] constitute a versatile class of building blocks[1] for the selective introduction of fluorine-containing carbon substituents into bioactive molecules and molecular devices.[2,3] This is due to their electron-withdrawing CF_3 groups, reactive double bonds toward nucleophiles, and allylic fluorine atoms as potential leaving groups. Along this line, we have recently developed flexible synthetic routes to: (i) 1,1-difluoro-1-alkenes via an S$_N$2′-type reaction;[4] (ii) fluorocarbon-substituted heterocycles via intramolecular nucleophilic reactions;[5] and (iii) 5-trifluoromethyl-2-cyclopentenones via a regioselective Nazarov cyclization.[6] Despite the synthetic potential of the 1-(trifluoromethyl)vinyl moiety, its introduction as a C3 unit remains a difficult task, because of the thermal instability of the corresponding reactive metal species, such as a vinyllithium reagent.[7–9]

In our previous paper, we reported the efficient synthesis of [1-(trifluoromethyl)vinyl]-substituted alcohols by the ring opening of cyclic ethers with 3,3,3-trifluoroprop-1-en-2-yllithium (**1**).[8] On treatment of 2-bromo-3,3,3-trifluoroprop-1-ene (**2**) with an equimolar amount of *n*-BuLi at −100 °C, slow lithium–halogen exchange gave rise to a mixture of vinyllithium **1** and *n*-BuLi. We succeeded, however, in the selective trapping of **1** with appropriate electrophiles, such as oxiranes and oxetanes, in the presence of BF_3·OEt_2 by taking advantage of the subtle difference between reactivities of the two lithium species.[10]

On the other hand, 1-(trifluoromethyl)vinylation of highly reactive electrophiles has remained problematic. The vinylation of aldehydes suffers from nonselective addition of both **1** and *n*-BuLi to give a poor yield of the desired allyl alcohols.[7,11] Herein, we report an efficient generation of (trifluoromethyl)vinyllithium **1** to trap with reactive electrophiles, aldehydes and imines, and its application to the construction of angularly trifluoromethylated bicyclic systems, which has been a desirable goal.

We first reexamined the generation of vinyllithium **1** from bromotrifluoropropene **2** by treatment with several alkyllithiums for 15 min. After quenching with methanol, the product distributions were observed by ^{19}F NMR, as shown in Table 1. When the reaction was carried out with *n*-BuLi at −78 °C, the decomposition of vinyllithium **1** occurred to give 1,1-difluoroallene (**4**) in 54% yield, via elimination of lithium fluoride (Entry 1). When carrying out the reaction at −105 °C, we observed only a 14% yield of 3,3,3-trifluoroprop-1-ene (**3**), along with a 76% recovery of **2** (Entry 3). These results indicate that incomplete conversion is inevitable in the reaction with *n*-BuLi, due to the slow exchange rate and the thermal instability of **1**. In contrast, the lithium–halogen exchange reaction with *sec*-BuLi proceeded rapidly even at −105 °C to consume 90% of **2**, which generated **1** in at least 60% yield along with 26% of difluoroallene **4** (Entry 4).

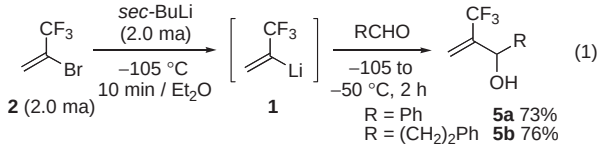
Table 1. Preparation of 1-(trifluoromethyl)vinyllithium **1**



2 ma: molar amount **3** **4**

Entry	R	temp./°C	**3**	**4**	recovery of **2**
1	*n*-Bu	−78	20%	54%	17%
2		−96	31%	11%	58%
3		−105	14%	1%	76%
4	*sec*-Bu	−105	60%	26%	10%
5	*tert*-Bu	−105	50%	35%	5%

We then attempted the reaction of aromatic and aliphatic aldehydes with vinyllithium **1**, generated in situ from 2.0 molar amounts of vinyl bromide **2** and *sec*-BuLi, in consideration of the partial decomposition of **1**. The desired 2-(trifluoromethyl)allyl alcohols **5a** and **5b** were obtained in 73 and 76% yield, respectively (eq 1). Thus, the more rapid lithium–halogen exchange allowed the reaction with reactive electrophiles.



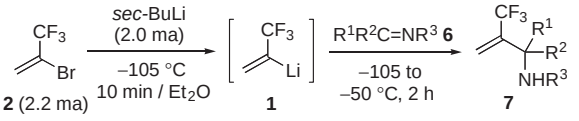
2 (2.0 ma) **1**

R = Ph **5a** 73%
R = $(CH_2)_2$Ph **5b** 76% (1)

Allylamines have been used as useful components for the synthesis of *N*-heterocycles. For the construction of potential trifluoromethylated heterocycles, we pursued the reaction of vinyllithium **1** with imines to prepare 2-(trifluoromethyl)allylamines.[3] Although *N*-benzylimine **6a** was not reactive towards **1**, BF_3·OEt_2 promoted the reaction to afford the desired amine **7a** in 81% yield (Table 2, Entry 1). When *N*-benzoyl- and *N*-tosylimine **6b** and **6c** were employed as the reactive electrophiles, the corresponding *N*-allylamides **7b** and **7c** were obtained in excellent yield (Entries 2 and 3).[12]

We further examined (trifluoromethyl)vinylation of several other *N*-tosylimines **6d–6g** in view of their availability, ease of handling, and the synthetic applicability of the products. All *N*-tosylimines **6c–6g** examined provided the corresponding *N*-[2-(trifluoromethyl)allyl]sulfonamides **7c–7g** in good to excellent yield, as summarized in Table 2. Butanimine **6e** gave **7e** in good yield, even though it had acidic protons α to the imino group (Entry 5). Whereas 1,1-diphenylmethanimine **6g** showed

Table 2. Synthesis of [(trifluoromethyl)allyl]sulfonamides **7**



Entry	R^1	R^2	R^3	7	Yield/%
1[a]	H	Ph	$CH_2C_6H_5$	**7a**	81
2	H	Ph	COC_6H_5	**7b**	97
3[b]	H	Ph	Ts	**7c**	90
4[b]	H	PhCH=CH	Ts	**7d**	89
5	H	*n*-Pr	Ts	**7e**	77
6	H	*t*-Bu	Ts	**7f**	96
7	Ph	Ph	Ts	**7g**	76 (91)[c]

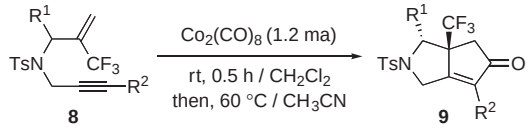
[a]$BF_3 \cdot OEt_2$ (1.5 ma) was added. [b]Solution of **6** was added dropwise over 20 min. [c]Vinyl bromide **2** (3.5 ma) and *sec*-BuLi (3.2 ma) were used.

modest reactivity, employing an excess amount of **1**, generated from **2** (3.5 ma) and *sec*-BuLi (3.2 ma), improved the yield to 91% (Entry 7).

Having accomplished the synthesis of 2-(trifluoromethyl)-allylamides **7**, we turned our attention to the construction of fused-ring systems involving an angular trifluoromethyl group,[2,13] whose framework might be constructed by an intramolecular Pauson–Khand reaction.[14,15] Introduction of an angular trifluoromethyl group can be an attractive tool for the analog synthesis of steroids and alkaloids, and remains a challenging task. Furthermore, very few examples of 1,6-enynes bearing a electron-withdrawing group at the C-2 vinylic carbon have been reported in the Pauson–Khand reaction.[16] These facts prompted us to investigate the Pauson–Khand reaction of *N*-propargyl-*N*-[2-(trifluoromethyl)allyl]amides **8**, readily prepared by propargylation (with a propargyl bromide and NaH in DMF at rt) of the above-obtained amides **7** in 84–92% yield.

Enyne **8a** was treated with dicobalt octacarbonyl to generate the cobalt–yne complex. Heating the complex at 60 °C in acetonitrile promoted the desired Pauson–Khand reaction of a CF_3-substituted terminal alkene, to afford the pyrrolidine ring-fused cyclopentenone **9a** bearing an angular trifluoromethyl group in 81% yield with high diastereoselectivity (*anti*:*syn* = 94:6) (Table 3, Entry 1).[17,18] Substrates **8b** and **8c** with an internal alkyne moiety or an alkyl group at the allylic position also readily underwent the cyclization to give trifluoromethylated pyrrolidines **9b** and **9c** in 85 and 71% yield, respectively (Entries 2 and 3).

Table 3. Synthesis of 3a-CF_3-cyclopenta[*c*]pyrroles **9**



Entry	R^1	R^2	Time/h	9	Yield/%	*anti*:*syn*[a]
1	Ph	H	3	**9a**	81	94:6[b]
2	Ph	Et	2	**9b**	85	83:17[c]
3	*n*-Pr	H	3	**9c**	71	86:14[c]

[a]Determined by ^{19}F NMR. [b]See Ref. 17. [c]Configuration was determined in analogy with **9a** by comparing ^1H and ^{19}F NMR data of each isomer.

The sequence of (i) (trifluoromethyl)vinylation of imines, followed by (ii) propargylation and (iii) the cobalt-mediated intramolecular Pauson–Khand reaction, successfully provides a facile entry to the fused *N*-heterocycles bearing an angular trifluoromethyl group.

We thank Dr. N. Kanoh (the University of Tokyo) for the X-ray crystal structure analysis.

The present work is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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11 When a 1:1 mixture of **2** and *n*-BuLi was kept at −100 °C for 15 min and then treated with benzaldehyde, two alcohols, derived from vinyllithium **1** and *n*-BuLi, were obtained in 25 and 64% yield, respectively.
12 To a solution of **2** (0.13 mL, 1.24 mmol) in Et_2O (10 mL) was added *sec*-butyllithium (1.07 M in cyclohexane, 1.05 mL, 1.13 mmol) in Et_2O (5 mL) at −105 °C under Ar. After stirring for 10 min, **6c** (146 mg, 0.56 mmol) in Et_2O (10 mL) was added over 20 min. The reaction mixture was allowed to warm to −50 °C over 2 h, and the reaction was quenched with phosphate buffer (pH 7, 10 mL). Organic materials were extracted with EtOAc three times, and the combined extracts were washed with brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (hexane–EtOAc, 10:1) to give **7c** (180 mg, 90%) as colorless crystals.
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Published on the web (Advance View) December 2, 2006; doi:10.1246/cl.2007.22