

Supporting Information

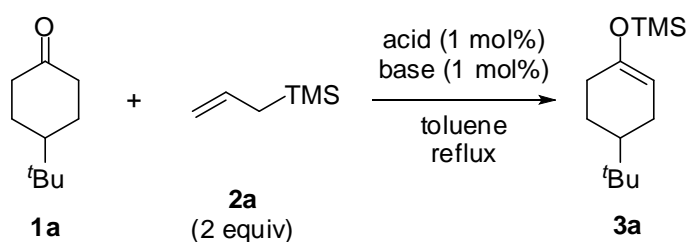
Silyl Enol Etherification by Tf_2NH /Amine Co-catalytic System for Minimizing Hazardous Waste Generation

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Effects of the co-catalyst.

We have examined effects of the catalytic system in the enol silylation of **1a** with trimethylallylsilane (**2a**) into **3a**. The results are summarized in Table S1. The enol silylation of **1a** proceeded smoothly with a combination of Tf₂NH and a variety of amines (entries 1-4). Even with inorganic bases such as Cs₂CO₃, which are insoluble in toluene, the desired silyl enol ether **3a** was obtained in good yield (entry 5). In contrast, Tf₂NH was found to be crucial as an acid catalyst partner. TfOH-NEt₃ co-catalyst (10 mol%) afforded **3a** in moderate yield (entry 6). Although the reaction time was elongated, the chemical yield was not improved. Almost no reaction occurred with MsOH (entry 7).

Table S1. Effects of a Co- catalyst in Enol silylation

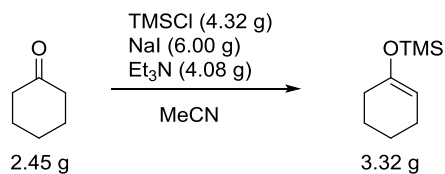


entry	acid catalyst (mol%)	base catalyst (mol%)	% yield ^a
1	Tf ₂ NH (1.0)	NEt ₃ (1.0)	86
2	Tf ₂ NH (1.0)	1-methylimidazole (1.0)	85
3	Tf ₂ NH (1.0)	DABCO	88
4	Tf ₂ NH (1.0)	DBU	88
5	Tf ₂ NH (1.0)	Cs ₂ CO ₃ (20)	79
6	TfOH (10)	NEt ₃ (10)	31
7	MsOH (10)	NEt ₃ (10)	trace

^aYields were determined by GC-MS and ¹H NMR.

Calculation of E-factor values for silyl enol etherification of 1b to 3bf

1, F. C. E. Saraber, S. Dratch, G. Bosselaar, B. J. M. Jansen, A. de Groot, *Tetrahedron*, 2006, **62**, 1717.



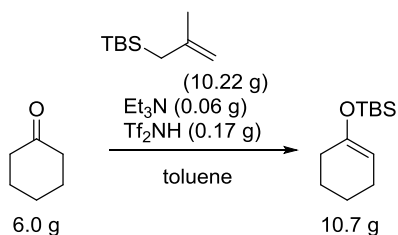
Total amount of reactants: 2.45 g + 4.32 g + 6.00 g + 4.08 g = 16.85 g (solvent has been excluded from this calculation)

Amount of final product: 3.32 g

Amount of waste: (16.85 – 3.32) g = 13.53 g

E-Factor = Amount of waste/Amount of product = 13.53/3.32 = 4.08

2, Our results.



Total amount of reactants: 6.0 g + 10.22 g + 0.06 g + 0.17 g = 16.45 g (solvent has been excluded from this calculation)

Amount of final product: 10.70 g

Amount of waste: (16.45 – 10.70) g = 5.75 g

E-Factor = Amount of waste/Amount of product = 5.75/10.70 = 0.54

Experimental Section

General: All reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents and materials were obtained from commercial suppliers and used without further purification. Column chromatography was performed on Merck silica gel 60 (230–400 mesh). Reactions and chromatography fractions were analyzed employing pre-coated silica gel plate (Merck Silica Gel 60 F254). All melting points were measured on YANACO MP-500P micro melting point apparatus and are uncorrected. IR spectra were measured on JASCO FT/IR-4100. The ¹H and ¹³C NMR spectra were recorded on JEOL AL-400 or JEOL ECP-500 with tetramethylsilane as an internal standard. Low-resolution and high-resolution mass spectra were recorded on JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. Optical rotations were recorded on a JASCO DIP-360 polarimeter with a path length of 1 cm; concentrations are quoted in mg (1 mL). [α]_D values are measured in 10⁻¹ deg cm² g⁻¹. The microfluidic reaction was carried out using KeyChem-Basic system (YMC Co., Ltd., Japan; WWW: <http://www.keyboardchemistry.com/en/custom.html>). The microflow system equip with a Y-shape mixer and pressure/back pressure regulators.

General procedure for the synthesis of silyl enol ethers with allylsilanes (Tables 1 and 2).

To a solution of ketone **1** (0.5 mmol) in toluene (5 mL) was added allylsilane (0.75 mmol) at the appropriate temperature. To the resulting mixture were slowly added a stock solution of Tf₂NH in toluene (80 mM solution; 5 μmol) and, then, a stock solution of triethylamine (100 mM solution; 5 μmol) at the same temperature. After stirred for 10 min, the reaction mixture was quenched with saturated NaHCO₃ aq. The mixture was extracted with hexane twice. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. Then, the chemical yield was determined by ¹H NMR using anisole as an internal standard.

The following compounds are known compounds in each reference.

3aa: H. O. House, L. H. Czuba, M. Gall, H. D. Olmstead, *J. Org. Chem.* **1969**, *34*, 2324-2336; H. O. House, A. V. Prabhu, W. V. Phillips, *J. Org. Chem.* **1976**, *41*, 1209-1214.

3ab, 3bb: E. J. Corey, H. Cho, C. Ruecker, D. H. Hua, *Tetrahedron Lett.* **1981**, *22*, 3455-3458.

4aa: M. Kawai, M. Onaka, Y. Izumi, *Chem. Lett.* **1986**, 381-384.

3ba: C. R. Crueger, E. G. Rochow, *J. Organometal. Chem.* **1964**, *1*, 476-483.

3bf: R. E. Donaldson, P. L. Fuchs, *J. Org. Chem.* **1977**, *42*, 2032-2034.

3da: G. M. Rubottom, M. I. Lopez, *J. Org. Chem.* **1973**, *38*, 2097-2099.

3ea, 3ea': H. O. House, L. H. Czuba, M. Gall, H. D. Olmstead, *J. Org. Chem.* **1969**, *34*, 2324-2336.

3fa, 3fa': G. Stork, P. F. Hudrlik, *J. Am. Chem. Soc.* **1968**, *90*, 4462-4464.

3ga: P. Magnus, J. Lacour, P. A. Evans, P. Rigollier, H. Tobler, *J. Am. Chem. Soc.* **1998**, *120*, 12486-12499.

(*Z*)-**3ha:** L. R. Krepski, A. Hassner, *J. Org. Chem.* **1978**, *43*, 3173-3179.

(*E*)-**3ha, (E)**-**3ja:** I. Peterson, I. Fleming, *Tetrahedron Lett.* **1979**, 995-998.

(*Z*)-**3ia**, (*E*)-**3ia**: N. Shimizu, M. Tanaka, Y. Tsuno, *J. Am. Chem. Soc.* **1982**, *104*, 1330-1340.

(*Z*)-**3ja**: E. Nakamura, K. Hashimoto, I. Kuwajima, *Tetrahedron Lett.* **1978**, 2079-2082.

3ka: N. Holy, R. Fowler, E. Burnett, R. Lorenz, *Tetrahedron* **1979**, *35*, 613-619.

9: S. Danishefsky, M. Prisbylla, B. Lipisko, *Tetrahedron Lett.* **1980**, *21*, 805-808.

11: S. E. Barrie, M. Jarman, G. A. Potter, *Brit. UK Pat. Appl.* **1993** (GB 2265624 A 19931006).

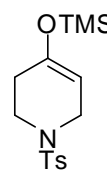
12: G. A. Potter, S. E. Barrie, M. Jarman, M. G. Rowlands, *J. Med. Chem.* **1995**, *38*, 2473-2471.

15a: K. Takasu, M. Ueno, K. Inanaga, M. Ihara, *J. Org. Chem.* **2004**, *69*, 517-521.

16a: A. S. Dreiding, A. J. Tomasewski, *J. Org. Chem.* **1954**, *19*, 241-254.

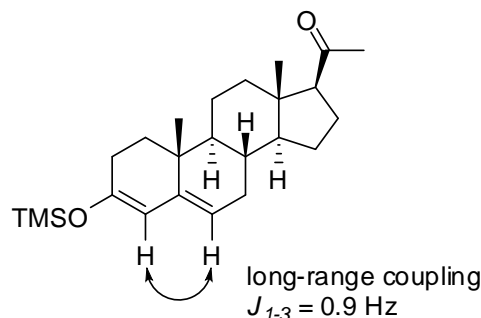
N-(4-Methylphenylsulfonyl)-4-trimethylsilyloxy-1,2,3,6-tetrahydropyridine (**3ca**).

Colorless oil; IR (neat) 2959, 1678, 1346, 1163 cm⁻¹; ¹H NMR (500 MHz) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 4.73 (t, *J* = 3.4 Hz, 1H), 3.60-3.58 (m, 2H), 3.22 (t, *J* = 5.9 Hz, 2H), 2.43 (s, 3H), 2.18-2.15 (m, 2H), 0.15 (s, 9H); ¹³C NMR (126 MHz) δ 148.6, 143.5, 133.6, 129.7, 127.7, 99.3, 43.7, 43.2, 29.9, 21.5, 0.2; LRMS (FAB) *m/z* 326 (M⁺ + 1); HRMS (FAB) calcd for C₁₅H₂₃NO₃SSi (M⁺ + 1): 326.1246, found: 326.1234.



Compound **9**.

Colorless crystals; Mp 102-103 °C; [α]_D²⁶ -36.4 (*c* = 0.8); IR (neat) 2940, 1703, 1655 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.28 (d, *J* = 0.9 Hz, 1H), 5.18-5.19 (m, 1H), 2.54 (dd, *J* = 7.6 Hz, 1H), 2.14-2.28 (m, 2H), 2.13 (s, 3H), 2.04 (dd, *J* = 14.0, 5.3 Hz, 2H), 1.81 (dd, *J* = 10.0, 4.6 Hz, 1H), 1.61-1.72 (m, 5H), 1.46 (dd, *J* = 18.1, 10.3 Hz, 2H), 1.17-1.30 (m, 3H), 1.03-1.09 (m, 1H), 0.96 (s, 3H), 0.65 (s, 3H), 0.21 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 209.5, 150.4, 141.1, 118.4, 108.7, 63.8, 57.1, 48.1, 44.2, 38.9, 34.8, 34.1, 31.9, 31.7, 31.5, 27.6, 24.4, 22.8, 21.2, 18.9, 13.4, 0.39; LRMS (FAB) *m/z* 387 (M⁺ + 1); HRMS (FAB) calcd for C₂₄H₃₈O₂Si (M⁺): 386.2641, found: 386.2639.

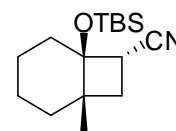


Typical procedure for the domino reaction (Scheme 3).

To a solution of **1g** (0.24 mmol), **2f** (0.60 mmol) and acrylonitrile (**14b**: 0.48 mmol) in toluene-dichloromethane (1 mL, 1 : 1 v/v) were slowly added a stock solution of Tf₂NH in toluene (80 mM solution; 24 μmol) and, then, a stock solution of triethylamine (100 mM solution; 24 μmol) at the ambient temperature. After stirred for 10 min, the reaction mixture was quenched with saturated NaHCO₃ aq. The mixture was extracted with AcOEt twice. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane / AcOEt = 30 : 1) to afford **15b** (63.1 mg, 94%).

(1*S**,6*S**,7*S**)-6-*tert*-Butyldimethylsilyloxy-7-cyano-1-methylbicyclo[4.2.0]octane (**15b**) (as a major diastereomer):

Colorless oil; IR (neat) 2931, 2858, 2233 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.99 (t, *J* = 9.5 Hz,



1H), 1.98-2.02 (m, 1H), 1.90 (dt, $J = 12.6, 3.7$ Hz, 1H), 1.84 (t, $J = 10.3$ Hz, 1H), 1.71 (dd, $J = 10.9, 9.2$ Hz, 1H), 1.43-1.22 (m, 5H), 1.07 (s, 3H) 0.89 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 120.1, 75.6, 43.4, 34.3, 33.6, 32.8, 29.0, 25.6, 23.8, 21.6, 20.0, 18.0, -2.8, -2.9; LRMS (FAB) m/z 280 ($\text{M}^+ + 1$); Anal. calcd for $\text{C}_{16}\text{H}_{29}\text{NOSi}$: C, 68.76; H, 10.46, found: C, 68.91; H, 10.64.

The structure and stereochemistry of both diastereomers of **5b** were determined by comparison with reported data after transformation into **5a** (hydrolysis, followed by methylation).^{S1}

Procedure for silyl enol etherification using microfluidic systems.

The enol silylation was carried out using microfluidic system (KeyChem-Basic, YMC Co. Ltd, Japan) consisting of two multilamination type Y-shaped micromixers (**M1** and **M2**; 500 μm x 100 μm minimum channel width), three syringe pumps, and PTFE (polytetrafluoroethylene) tube reactors (**R1** [500 μm (ϕ) x 100 cm (l)] and **R2** [500 μm (ϕ) x 30 cm (l)]) as shown in Figure 1 (maintext) and Figure S1. A 1.0 M solution of cyclohexanone (**1b**) and *tert*-butylmethallyldimethylsilane (**2f**) in toluene and a 10 mM solution of Tf_2NH in toluene were introduced to the first micromixer (**M1**) at a flow rate of 1 mL/min each. The resulting solution was mixed with a 5.0 mM solution of triethylamine in toluene in the second micromixer. (**M2**) (flow rate: 2.0 mL/min). The resulting solution was concentrated in vacuo. The residue was distilled under reduced pressure (1.3 kPa, 75 $^\circ\text{C}$) to give **3bf** as colorless oil (10.7 g, 84%), whose purity was analyzed by GC to be >99% purity.

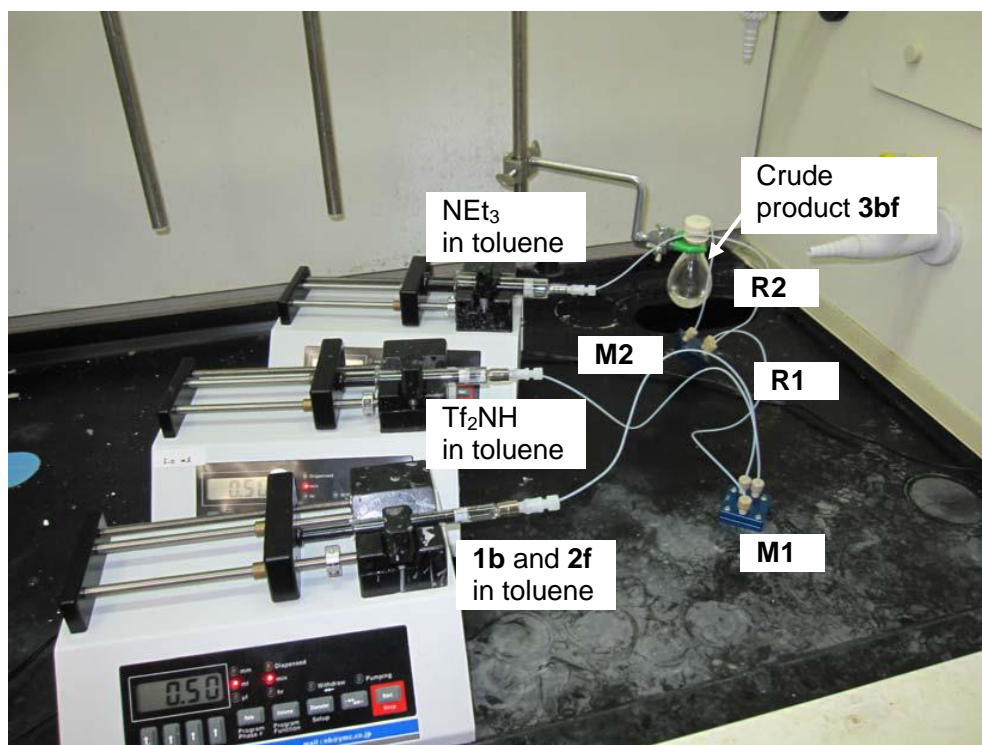


Figure S1. The microreactor system for the Tf_2NH -catalyzed silyl enol etherification.

reference

S1 Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 517-521.