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$Bi(OTF)_3$ AS A DUAL ROLE CATALYST. SYNTHESIS OF SUBSTITUTED MORPHOLINE DERIVATIVES VIA CATALYTIC *O*-ALLYLATION

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Abstract – The diastereoselective synthesis of *cis*-1,4-disubstituted morpholines has been accomplished in good to excellent yields via $Bi(OTf)_3$ catalyzed ring-closing *O*-allylation under mild conditions without the need for added base. The bismuth Lewis acid catalyst appeared to play two roles; the mild deprotection of a silyl ether and the Lewis acid activation of an allylic halide for mild nucelophilic cyclization. Substituted morpholines were obtained with diastereoselectivity ranging from 2:1 to >99:1.

INTRODUCTION

Substituted morpholine derivatives are found in many natural and unnatural products and their activity in pharmacology is very attractive.[1] To name a few, they are known to be potentially useful as antidepressants,[2] appetite suppressants,[3] antitumor agents,[4] antibacterials,[5] and antioxidants.[6] Therefore, the efficient synthesis of novel substituted morpholine derivatives opens the door to explore new drug targets. There have been a substantial amount of examples of the synthesis of morpholine derivatives, typically prepared from amino alcohols[7] and epoxides.[8] In order to generate a new carbon-oxygen bond, *O*-alkylation of alcohols with alkyl halides is one of the most useful strategies. *O*-Alkylation generally requires at least a stoichiometric amount of base for both deprotonation and neutralization of acid byproducts (HCl, HBr, HI).[9] Thus, catalytic conditions that require no base are highly desirable.

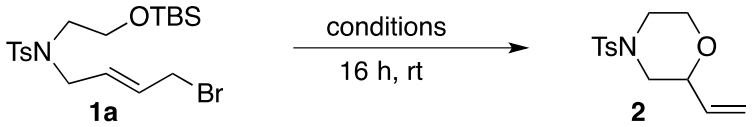
During our studies of mild Lewis acid catalyzed halide activation, we developed an atom transfer cyclization[10] catalyzed by In(III). The reaction was driven by catalytic allylic halide activation under mild conditions. We have also discovered other C-C bonds formations via catalytic halide activation using Lewis acids including ring-closing Friedel-Crafts reactions,[11] intermolecular Friedel-Crafts reactions,[12] and 5-*exo*-*trig* cyclization reactions.[13] However, nucleophilic addition of heteroatoms in this type of

activation has not been demonstrated. Herein, we present a catalytic *O*-alkylation *via* halide activation with Lewis acids in the absence of base[14] for the preparation of substituted morpholine derivatives.

RESULTS AND DISCUSSION

Our initial investigation examined the preparation of 2-vinyl morpholine **2** from compound **1a**, which was prepared in three steps from ethanolamine (Table 1). The first question we addressed was whether a simple cleavage of the TBS group in **1a** would automatically cyclize to yield **2** (Table 1). Unexpectedly, when treated with 1.2 equivalents of CsF in MeCN (entry 1) no reaction was observed. When the reaction was carried out in DMF (entry 2), the starting material decomposed. Using 2 equivalents of TBAF in THF[15] (entry 3) resulted in only 6% yield of the desired morpholine **2**. On the other hand, acidic conditions appeared to be slightly better. Application of a stoichiometric amount of triflic acid[16] (entry 4) resulted in 39% yield of **2**. Clearly simple deprotection of TBS with basic fluoride sources to reveal a nucleophilic alkoxide was not efficient. Acidic conditions afforded an increased yield of **2** but not in a useful range presumably due to the low nucleophilicity of the alcohol. Therefore, we considered that activation of allylic halide **1a** with Lewis acid would enhance the cyclization to yield **2**. In the presence of 10 mol% of $Bi(OTf)_3$[17] in CH_2Cl_2 at room temperature for 16 hours, the target morpholine **2** was produced in an encouraging 56% yield. Interestingly, when 4Å MS were added the reaction did not proceed and **1a** was recovered nearly quantitatively (entry 6). This suggested that trace amounts of water may be required for successful reaction.

Table 1. Intramolecular *O*-allylation conditions



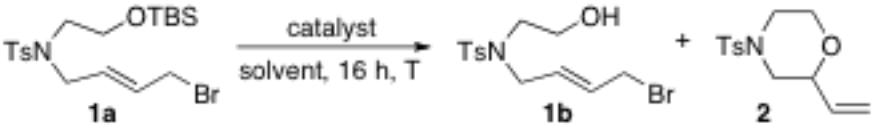
Entry	Conditions	% Yield[a]
1	CsF (1.2 eq); MeCN (0.1*M*)	0[b]
2	CsF (1.2 eq); DMF (0.1*M*)	*dec*
3	TBAF (2 eq); THF (0.1*M*)	6[c]
4	CF_3SO_3H (1 eq); CH_2Cl_2 (0.1*M*)	39[d]
5	$Bi(OTf)_3$ (0.1 eq); CH_2Cl_2 (0.1*M*)	56
6	$Bi(OTf)_3$ (0.1 eq); CH_2Cl_2 (0.1*M*); 4Å MS	0[b]

[a]Isolated yield. [b]Starting material was recovered. [c]32% of the deprotected alcohol was obtained. [d]Trace amounts of the starting material and deprotected alcohol were obtained.

Having discovered that $Bi(OTf)_3$ could catalyze the cyclization of **1a**, we turned our attention to optimizing conditions using Lewis acid. The results of this investigation are summarized in Table 2. The

use of catalytic In(III) or In(I) salts in dichloromethane resulted in the formation of morpholine **2**, albeit in low to moderate yields (entries 1-4). In all cases the major product obtained was the deprotected alcohol **1b**. As $Bi(OTf)_3$ appeared to be a better catalyst for the reaction we examined the role of catalyst amount, solvent and temperature using this promoter. Using 5 mol% of $Bi(OTf)_3$ at room temperature morpholine **2** was obtained in 31% yield along with 66% of the alcohol **1b** (entry 5). Increasing the catalyst loading to 10 mol% resulted in increased cyclization (56% yield) (entry 6). Other solvents demonstrated variable results. When the reaction was run in THF, DMF and water (entries 7, 12, 13), the starting material was recovered intact. Presumably the overwhelming amount of water in the latter case interfered with the Lewis acid's ability to deprotect the silyl ether. In MeCN and EtOH (entries 8 and 14) at room temperature, deprotection ensued to form about 80% of the free alcohol[18] **1b** along with very low yields of **2**. The use of EtOH at 70 °C resulted in decomposition of the starting material (entry 15). In

Table 2. Lewis acid catalyzed *O*-allylation optimization



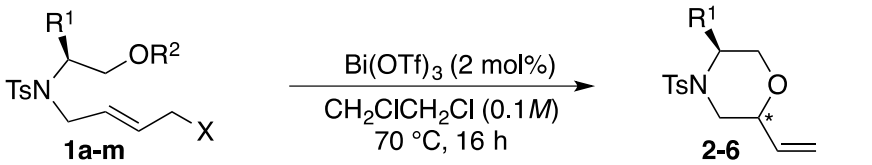
					% Yield[a]		
Entry	Catalyst	mol%	Solvent	T (°C)	**2**	**1b**	**1a**
1[b]	$InCl_3$	5	CH_2Cl_2	rt	21	77	--
2	$InCl_3$	10	CH_2Cl_2	rt	45	50	--
3	$In(OTf)_3$	10	CH_2Cl_2	rt	36	59	--
4	InI	10	CH_2Cl_2	rt	42	50	--
5[b]	$Bi(OTf)_3$	5	CH_2Cl_2	rt	31	66	--
6	$Bi(OTf)_3$	10	CH_2Cl_2	rt	56	40	--
7[b]	$Bi(OTf)_3$	10	THF	rt	9	--	91
8[b]	$Bi(OTf)_3$	10	MeCN	rt	16	80	--
9[b]	$Bi(OTf)_3$	10	$MeNO_2$	rt	50	34	--
10[b]	$Bi(OTf)_3$	10	EtOAc	rt	25	--	--
11[b]	$Bi(OTf)_3$	10	toluene	rt	57	10	10
12[b]	$Bi(OTf)_3$	10	DMF	rt	--	--	100
13[b]	$Bi(OTf)_3$	10	H_2O	rt	--	--	100
14	$Bi(OTf)_3$	10	EtOH	rt	2	81	--
15[c]	$Bi(OTf)_3$	10	EtOH	70	--	--	--
16[b]	$Bi(OTf)_3$	10	CH_2Br_2	rt	69	10	--
17	$Bi(OTf)_3$	10	CH_2ClCH_2Cl	rt	75	--	--
18	$Bi(OTf)_3$	5	CH_2ClCH_2Cl	45	85	--	--
19[d]	$Bi(OTf)_3$	2	CH_2ClCH_2Cl	70	34	62	--
20	$Bi(OTf)_3$	2	CH_2ClCH_2Cl	70	88	--	--

[a]Isolated yield unless otherwise noted. [b]NMR yield (1,2,3-trimethoxybenzene used as internal standard). [c]Starting material decomposed. [d]2 h.

contrast, $MeNO_2$, toluene, dibromomethane, and dichloroethane yielded **2** in moderate to good yield (entries 9, 11, 16 and 17). As dichloroethane seemed to be the optimal solvent for this reaction, we investigated the role of catalytic loading and temperature in this solvent. Utilizing only 2 mol% $Bi(OTf)_3$ in dichloroethane for 2 hours gave the morpholine **2** in only 34% along with 62% of the free alcohol **1b**. Interestingly, simply increasing the reaction time to 16 hours under the same conditions afforded 88% of the pure morpholine **2**. This suggested that the Lewis acid initially catalyzed the deprotection of the silyl ether and cyclization proceeded after formation of the alcohol. The $Bi(OTf)_3$ presumably played a dual role to activate the allylic halide to yield **2**.

Having established the conditions for optimal cyclization using $Bi(OTf)_3$ catalysis, we invested the scope and limitation of the substrate with regards to *O*-protecting group and diastereoselectivity (Table 3). First, we investigated the role of the *O*-protecting group. The optimal conditions with the TBS-protected substrate **1a** afforded 88% yield (entry 1). Using the free alcohol **1b** directly (entry 2) provided the cyclized product **2** in quantitative yield supporting our hypothesis that deprotection occured first followed by cyclization of the alcohol. Interestingly, without catalyst, **1b** did provide some morpholine **2** in low

Table 3. *O*-allylation substrate scope

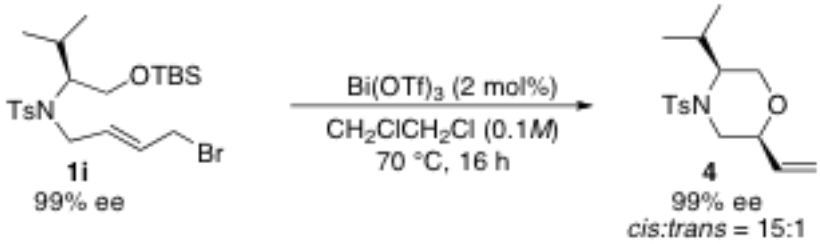


Entry	R^1	R^2	X	1	% Yield[a]	*cis:trans*[b]	Product
1	H	TBS	Br	**1a**	88	--	**2**
2	H	H	Br	**1b**	>99	--	**2**
3[c]	H	H	Br	**1b**	41	--	**2**
4	H	allyl	Br	**1c**	dec	--	--
5	H	benzyl	Br	**1d**	dec	--	--
6	H	TES	Br	**1e**	85	--	**2**
7	H	TBS	Cl	**1f**	77	--	**2**
8[d]	H	TBS	Cl	**1f**	88	--	**2**
9	*t*-Bu	H	Br	**1g**	89	>99:1	**3**
10	*i*-Pr	H	Br	**1H**	97	15:1	**4**[e]
11	*i-Pr*	TBS	Br	**1i**	87	15:1	**4**
12	Me	H	Br	**1j**	86	2:1	**5**
13	Me	TBS	Br	**1k**	93	2:1	**5**
14	benzyl	H	Br	**1l**	88	3:1	**6**
15	benzyl	TBS	Br	**1m**	73	3:1	**6**

[a]Isolated yield. [b]Determined by ^1H NMR. [c]Without catalyst. [d]5 mol% catalyst. [e]Racemic starting material used.

yield (entry 3) but the reaction was not nearly as efficient as that with the catalyst present. Allyl or benzyl protected substrates **1c** and **1d** decomposed under the standard reaction conditions (entries 4 and 5). The TES-protected alcohol **1e** underwent cyclization in good yield (entry 6). Allylic chloride substrates also performed well under the reaction conditions however, the yield was slightly lower (77%, entry 7). Increasing the catalyst loading from 2 to 5 mol% resulted in an increased yield of 88% (entry 8).

Placing substituents α- to the nitrogen resulted in diastereoselective cyclization favoring the *cis* isomer in all cases. A bulky *t*-butyl group was optimal giving rise to a single diastereomer (entry 9). Diastereoselectivity was dependent on the size of the substituent. An isopropyl group afforded a *cis:trans* ratio of 15:1 (entries 10 and 11) while a smaller methyl group only afforded 2:1 selectivity (entries 12 and 13). Benzyl gave 3:1 selectivity (entries 14 and 15). Optical activity was completely preserved using chiral substrates as shown in Scheme 1.

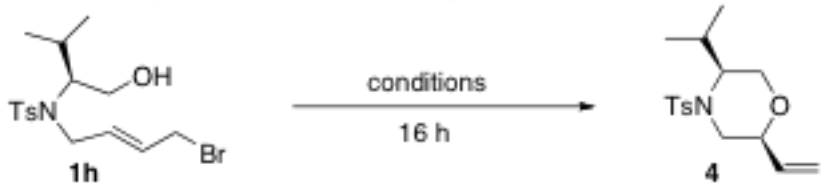


Scheme 1. Retention of optical activity in the cyclization

In order to gain more understanding about the role of the catalyst in the $Bi(OTf)_3$-catalyzed cyclization, we examined the diastereoselectivity of the reaction under different conditions. The results are summarized in Table 4. Interestingly, the cyclization of alcohol **1h** under the reaction conditions *without* the catalyst resulted in the formation of **4** in 60% yield but with lower diastereoselectivity (5:1, entry 1). Under base conditions at room temperature using NaH a similar 6:1 ratio of isomers was obtained (entry 2). Comparing the Bi-catalyzed reaction (entry 3) to these suggests that the catalyst was intimately involved in the cyclization step and probably organized the transition state in a controlled fashion. Based on these observations we hypothesize a reaction with $Bi(OTf)_3$ playing a dual role as described in Scheme 2. Initially the catalyst, most likely with the assistance of a trace of water,[15] catalyzed the deprotection of the silyl ether to form the free alcohol. The Lewis acid could subsequently activate the allylic halide for allylic substitution by the alkoxide. As higher diastereoselectivity was observed in the presence of the Lewis acid, a transition state such as **8** is plausible. The Bi metal could simultaneously coordinate the alcohol (or alkoxide) while activating the halide. A *trans*-decalin-like transition state would explain the preference for the *cis* stereochemistry observed in the product. The R-substituent would prefer an axial orientation due to the bulky equatorial *N*-tosylate group that would disfavor the R-group from adopting an

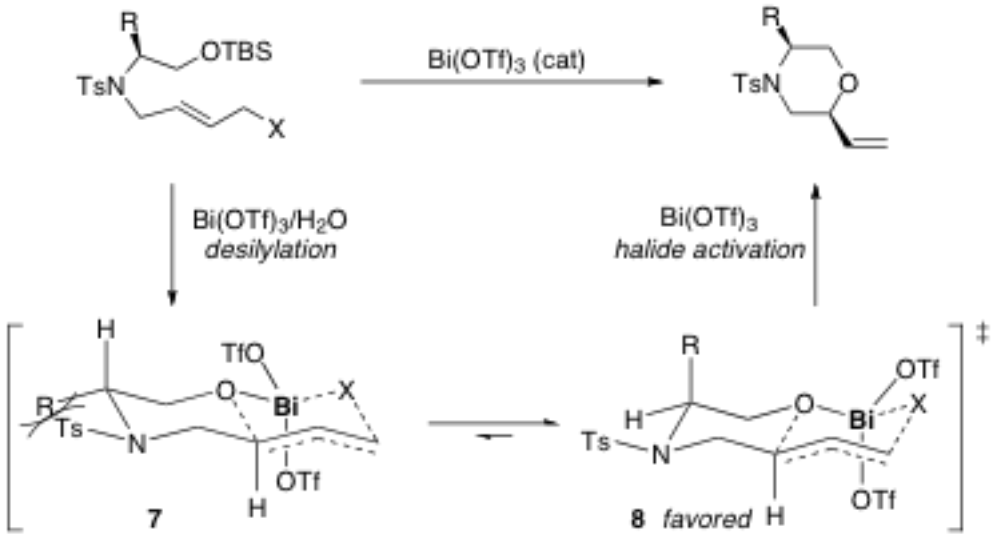
equatorial position (**7**).[19] The axial substituent is further accommodated by the lack of a 1,3-diaxial interaction due to the oxygen in the ring.

Table 4. *O*-Allylation diastereoselectivity under different conditions



Entry	Solvent (0.1*M*)	T (°C)	additive	% Yield[a]	*cis*:*trans*[b]
1	CH_2ClCH_2Cl	70	--	60	5:1
2	THF	rt	NaH (1.2 eq)	54	6:1
3	CH_2ClCH_2Cl	70	$Bi(OTf)_3$ (0.2 eq)	97	15:1

[a]Isolated yield. [b]Determined by ^{1}H NMR.



Scheme 2. Proposed mechanism. Dual role catalyst.

In conclusion, we have demonstrated that $Bi(OTf)_3$ can catalyze the ring-closing *O*-allylation under mild conditions in the absence of base. A variety of substituted morpholine derivatives were prepared from amino alcohols using only 2 mol% of catalyst. When the substituent on the amino alcohol was bulky, good *cis*-diastereoselectivity was obtained Importantly, the $Bi(OTf)_3$ catalyst appeared to play a dual role in this reaction, catalyzing the deprotection of a silyl ether and activating the allylic halide while organizing a tightly controlled transition state.

EXPERIMENTAL

Thin layer chromatography (TLC) was performed on silica gel Whatman-60F glass plates, and

components were visualized by illumination with UV light or by staining with potassium permanganate solution. Chromatography was performed using E. Merck silica gel 60 (230-400 mesh). NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Varian Inova 500 MHz or 400 MHz spectrometer. ^{13}C NMR was recorded using broadband proton decoupling. Chemical shifts are reported relative to TMS and coupling constants in Hz. Optical rotations were recorded on a JASCO-CIP-370 instrument. High-resolution mass spectra (HRMS) [Positive Ion FAB (FAB^+) or Electrospray (ES)] were obtained in the Department of Chemistry and Biochemistry at North Dakota State University. Melting points were determined without correction. Reactions were carried out under an inert atmosphere of nitrogen or argon. Solvents were dried using a nitrogen-pressurized alumina column system from Solvtek.

General procedure for the synthesis of 1a-1m. Beginning with amino alcohols, the nitrogen was protected by tosylation and the alcohol was protected by silylation according to literature methods.[20] The *N*-tosly-*O*-silyl amino alcohol (1.0 eq) and NaH (1.5 eq.) were stirred in THF (0.5*M*) at 0 ºC for 30 min under argon. 1,4-Dibromobutene (2.5 equiv) in THF (1 *M*) was added dropwise into the mixture and stirred for 16 h (if R was not H, reactions were stirred at 60 ºC). Saturated aqueous NH_4Cl was added and the organic layer separated. The remaining aqueous layer was then extracted with CH_2Cl_2 twice, the combined organic fractions dried with Na_2SO_4, and concentrated in *vacuo*. The crude product was then purified by chromatography over silica gel (10% EtOAc/Hexanes) to afford the *O*-TBS-protected substrates.

General procedure for the synthesis of free alcohols: The *O*-TBS-protected allylic halides **1** and EtOH (0.5*M*) were placed in a small round bottom flask equipped with a magnetic stirring bar. $Bi(OTf)_3$ (5 mol%) was added and the reaction was allowed to stir at rt for 16 h. Saturated aqueous NH_4Cl and CH_2Cl_2 were added and the organic layer separated. The remaining aqueous layer was then extracted with CH_2Cl_2 twice, the combined organic fractions dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel (30% EtOAc/Hexanes) to afford the free alcohol.

(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-4-methylbenzenesulfonamide (1a). IR (neat) cm^{-1}; 2928, 2361, 1598, 1471, 1344, 1256, 1205, 1160, 1091, 1006, 970, 925, 838, 779, 724, 667; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.75 (ddd, *J* = 7.6, 15.2, 22.8 Hz, 1H), 5.61 (ddd, *J* = 6.4, 15.2, 21.6 Hz, 1H), 3.85 (dd, *J* = 6.4, 14.0 Hz, 4H), 3.69 (t, *J* = 6.4 Hz, 2H), 3.20 (t, *J* = 6.4 Hz, 2H), 2.39 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 142.6, 135.8, 135.5, 135.1, 67.8, 55.8, 54.7, 36.8, 31.3, 27.0; HRMS Calcd for $C_{19}H_{32}BrNO_3SSi$ ($M+Na^+$): 484.0953, found 484.0947.

(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (1b). IR (neat) cm^{-1}; 2923, 2291, 1598, 1437, 1336, 1207, 1157, 1089, 817, 722; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.80 (ddd, *J* = 7.6, 15.2, 22.8 Hz, 1H), 5.64 (ddd, *J* = 6.4, 15.2, 21.6 Hz, 1H), 3.86 (d, *J* = 7.2 Hz, 4H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.22 (t, *J* = 5.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 136.4, 130.8, 130.2, 130.1, 127.5, 61.4, 50.7, 50.2, 31.4, 21.7; HRMS Calcd for $C_{13}H_{18}BrNO_3S$ ($M+Na^+$): 370.0088, found 370.0080.

(*E*)-*N*-(2-Allyloxyethyl)-*N*-(4-bromobut-2-enyl)-4-methylbenzenesulfonamide (1c). IR (neat) cm^{-1}; 2922, 1723, 1597, 1494, 1449, 1341, 1159, 1090, 1020, 927, 888, 816, 741, 663; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 2H), 5.91 (m, 1H), 5.79 (m, 1H), 5.68 (ddd, *J* = 6.4, 10.4, 12.8 Hz, 1H), 5.17 (m, 2H), 3.93 (m, 4H), 3.85 (d, *J* = 6.4 Hz, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 3.30 (t, *J* = 6.0 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 133.4, 131.6, 129.9, 128.8, 127.4, 119.1, 70.4, 69.4, 52.0, 46.7, 32.1, 21.7; HRMS Calcd for $C_{16}H_{22}BrNO_3S$ ($M+Na^+$): 410.0401, found 410.1460.

(*E*)-*N*-(2-Benzyloxyethyl)-*N*-(4-bromobut-2-enyl)-4-methylbenzenesulfonamide (1d). IR (neat) cm^{-1}; 2920, 2653, 2245, 1495, 1343, 1163, 1117, 874, 600, 550; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.30-7.24 (m, 7H), 5.80-5.72 (m, 1H), 5.65-5.58 (m, 1H), 4.37 (s, 2H), 3.89 (d, *J* = 7.6, 2H), 3.73 (d, *J* = 5.2, 2H), 3.34-3.26 (m, 4H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 137.3, 136.7, 131.5, 129.9, 128.8, 128.7, 128.6, 128.0, 127.4, 70.3, 68.9, 53.0, 47.2, 32.1, 21.7; HRMS Calcd for $C_{20}H_{24}BrNO_3S$ ($M+Na^+$): 460.0558, found 460.0558.

(*E*)-*N*-(4-Bromobut-2-enyl)-4-methyl-*N*-2-(triethylsilyloxy)benzenesulfonamide (1e). IR (neat) cm^{-1}; 2956, 1458, 1342, 1158, 1090, 1005, 921, 815, 756, 720, 653, 550; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.76 (ddd, *J* = 7.6, 15.2, 22.8 Hz, 1H), 5.63 (ddd, *J* = 6.4, 15.2, 21.6 Hz, 1H), 3.86 (dd, *J* = 5.6, 12.0 Hz, 4H), 3.69 (t, *J* = 6.4 Hz, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 2.40 (s, 3H) 0.91 (t, *J* = 8.0 Hz, 9H), 0.58 (q, *J* = 9.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 137.3, 130.5, 130.4, 130.0, 127.4, 62.2, 50.5, 49.5, 31.5, 29.9, 21.7, 6.9, 4.5; HRMS Calcd for $C_{19}H_{32}BrNO_3SSi$ ($M+Na^+$): 484.0953, found 484.0959.

(*E*)-*N*-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-*N*-(4-chlorobut-2-enyl)-4-methylbenzenesulfonamide (1f). IR (neat) cm^{-1}; 2929, 2857, 1598, 1471, 1444, 1343, 1305, 1256, 1160, 1091, 1006, 971, 927, 837, 779, 727, 651; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.69 (ddd, *J* = 6.4, 15.2, 21.6 Hz, 1H), 5.63 (ddd, *J* = 6.0, 15.2, 21.2 Hz, 1H), 3.96 (d, *J* = 6.8 Hz, 2H), 3.88 (d,

J = 7.2 Hz, 2H), 3.70 (t, *J* = 6.0 Hz, 2H), 3.21 (t, *J* = 6.4 Hz, 2H), 2.4 (s, 3H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 137.4, 130.1, 130.0, 129.9, 127.4, 62.6, 50.6, 49.4, 44.1, 26.1, 21.7, 18.4; HRMS Calcd for $C_{19}H_{32}ClNO_3SSi$ ($M+Na^+$): 440.1458, found 440.1460.

(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-(1-hydroxymethyl-2,2-dimethyl-propyl)-4-methylbenzenesulfonamide (1g). IR (neat) cm^{-1}; 3530, 2965, 2254, 1598, 1495, 1477, 1436, 1330, 1204, 1156, 1090, 1021, 911, 886, 815, 735, 660; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.81-5.71 (m, 2H), 3.86 -3.60 (m, 7H), 2.37 (s, 3H), 1.76 (s, 1H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 143.6, 137.8, 132.9, 129.6, 128.9, 128.2, 68.1, 60.6, 59.3, 45.8, 34.8, 32.0, 29.3, 28.5, 21.7, 21.2, 14.4; HRMS Calcd for $C_{17}H_{32}BrNO_3S$ ($M+Na^+$): 426.0714, found 426.0704; $[\alpha]_D^{25}$ -6.0726 (c 0.46, CH_2Cl_2).

(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-(1-hydroxymethyl-2-methylpropyl)-4-methylbenzenesulfonamide (1h). IR (neat) cm^{-1}; 3521, 2967, 1599, 1470, 1332, 1215, 1152, 1093, 1011, 890, 815, 754, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.87-5.76 (m, 2H), 3.97 (dd, *J* = 5.2, 16.8 Hz, 1H), 3.88 (d, *J* = 6.4 Hz, 2H), 3.78 (m, 2H), 3.59 (m, 2H), 2.43 (s, 3H), 1.82-1.73 (m, 2H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 132.7, 129.8, 129.4, 127.6, 66.5, 62.3, 45.7, 31.8, 28.2, 21.7, 20.8, 20.3; HRMS Calcd for $C_{16}H_{24}BrNO_3S$ ($M+Na^+$): 412.0558, found 412.0567.

(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-[1-(*tert*-butyldimethylsilanyloxymethyl)-2-methylpropyl]-4-methylbenzenesulfonamide (1i). IR (neat) cm^{-1}; 2929, 2360, 1464, 1338, 1154, 1090, 1009, 979, 895, 866, 838, 755, 686, 655; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.80-5.70 (m, 2H), 4.04-3.98 (m, 1H), 3.87-3.83 (m, 3H), 3.64 (dd, *J* = 4.8, 10.8 Hz 1H), 3.52-3.41 (m, 2H), 2.40 (s, 3H), 2.03-1.90 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.80 (s, 9H), -0.07 (d, *J* = 4.8, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 138.8, 133.6, 129.6, 128.3, 127.6, 65.8, 63.5, 46.3, 32.1, 27.6, 26.0, 21.6, 20.8, 20.1, 18.4; HRMS Calcd for $C_{22}H_{38}BrNO_3SSi$ ($M+Na^+$): 526.1423, found 526.1415; $[\alpha]_D^{25}$ -72.149 (c 0.91, CH_2Cl_2); the enantiomeric purity was determined by HPLC (254 nm, 25 ºC) t_R = 47.3 min (minor); t_R = 49.6 min (major) [Chiralcel AD-H + AD-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99/1, 1.0 ml/min] as 99% ee.

(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-(1-hydroxypropan-2-yl)-4-methylbenzenesulfonamide (1j). IR (neat) cm^{-1}; 3527, 2977, 2361, 1598, 1494, 1437, 1333, 1206, 1152, 1091, 1050, 1008, 969, 911, 870, 815, 728, 657; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.89 (ddd, *J* = 7.5,

15.5, 22.0 Hz, 1H), 5.83 (ddd, *J* = 6.5, 15.5, 22.0 Hz, 1H), 4.04-3.92 (m, 4H), 3.79 (dd, *J* = 7.0, 16.5 Hz, 1H), 3.59-3.51 (m, 2H), 2.44 (s, 3H), 2.00 (s, 1H), 0.98 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 138.0, 132.8, 130.0, 129.4, 127.4, 64.8, 55.7, 44.8, 31.8, 21.8, 14.9, 14.4; HRMS Calcd for $C_{14}H_{20}BrNO_3S$ ($M+Na^+$): 384.0245, found 384.0245; $[\alpha]_D^{25}$ 46.491 (c 0.33, CH_2Cl_2).

(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-1-methylethyl]-4-methylbenzene-sulfonamide (1k). IR (neat) cm^{-1}; 3031, 2929, 2857, 2359, 1599, 1495, 1471, 1336, 1258, 1215, 1154, 1092, 1006, 968, 914, 838, 757, 654, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 6.0 Hz, 2H), 5.88-5.75 (m, 2H), 4.02-3.82 (m, 5H), 3.60 (dd, *J* = 5.5, 10.0 Hz, 1H), 3.52 (dd, *J* = 6.0, 10.0 Hz, 1H), 2.43 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.02 (d, *J* = 2.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 143.3, 133.6, 129.8, 128.6, 127.4, 66.1, 55.3, 45.3, 32.1, 26.1, 21.7, 15.9; HRMS Calcd for $C_{20}H_{34}BrNO_3SSi$ ($M+Na^+$): 498.1110, found 498.1116; $[\alpha]_D^{25}$ -2.454 (c 1.82, CH_2Cl_2).

(*E*)-*N*-(4-Bromobut-2-enyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (1l). IR (neat) cm^{-1}; 3527, 3028, 2924, 2252, 1598, 1495, 1454, 1333, 1205, 1157, 1094, 911, 815, 732, 701, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.24-7.17 (m, 5H), 7.04 (d, *J* = 6.4 Hz, 2H), 5.86 (ddd, *J* = 4.6, 15.2, 22.8 Hz, 1H), 5.76 (ddd, *J* = 6.0, 15.2, 21.2 Hz, 1H), 4.06-3.94 (m, 2H), 3.89-3.83 (m, 3H), 3.66-3.56 (m, 2H), 2.75 (dd, *J* = 4.8, 13.6 Hz, 1H), 2.67 (dd. *J* = 7.6, 13.6 Hz, 1H), 2.39 (s, 3H), 1.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 137.8, 137.7, 132.6, 129.9, 129.5, 129.3, 128.8, 127.5, 126.9, 62.7, 62.0, 46.0, 36.7, 31.8, 21.7; HRMS Calcd for $C_{20}H_{24}BrNO_3S$ ($M+Na^+$): 460.0558, found 460.0558; $[\alpha]_D^{25}$ -14.090 (c 0.15, CH_2Cl_2).

(*E*)-*N*-[1-Benzyl-2-(*tert*-butyldimethylsilanyloxy)-ethyl]-*N*-(4-bromobut-2-enyl)-4-methylbenzene-sulfonamide (1m). IR (neat) cm^{-1}; 2930, 1736, 1334, 1155, 838, 699, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.26-7.21 (m, 5H), 7.18-7.16 (m, 2H), 5.62-5.46 (m, 2H), 5.04 (t, *J* = 6.8 Hz, 1H), 4.11 (m, 1H), 4.00 (m, 1H), 3.77 (d, *J* = 7.2, 2H), 3.63 (m, 1H), 2.4 (s, 3H), 0.80 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.5, 137.1, 132.9, 129.8, 128.8, 128.7, 128.5, 128.0, 127.6, 63.5, 62.0, 46.3, 32.0, 26.0, 21.7, 18.4; HRMS Calcd for $C_{26}H_{38}BrNO_3SSi$ ($M+Na^+$): 574.1423, found 574.1419; $[\alpha]_D^{25}$ -20.548 (c 0.34, CH_2Cl_2).

General procedure for the $Bi(OTf)_3$-catalyzed cyclization: Substrates **1** (0.1 – 0.3 mmol) and CH_2Cl_2 (0.05*M*) were placed in a small round bottom flask equipped with a condenser and a magnetic stir bar. $Bi(OTf)_3$ (2 to 5 mol%) was added and the reaction was allowed to stir at 70 ºC. Upon completion of the reaction (16 h), the mixture was loaded on to a silica gel column directly and isolated using 10:1

hexane-EtOAc solution to afford morpholine product.

***Cis*-5-*tert*-butyl-4-(toluene-4-sulfonyl)-2-vinylmorpholine (3).** IR (neat) cm^{-1}; 2965, 2256, 1736, 1598, 1477, 1401, 1342, 1290, 1110, 1030, 966, 939, 813, 739, 672; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.65 (ddd, *J* = 5.6, 10.8, 16.4 Hz, 1H), 5.19-5.11 (m, 2H), 4.05 (d, *J* = 12.4 Hz, 1H), 3.68 (dd, *J* = 2.8, 18.0 Hz, 1H), 3.43 (d, *J* = 4.4 Hz, 1H), 3.35-3.25 (m, 2H), 3.20 (dd, *J* = 11.6, 14.8 Hz, 1H), 2.41 (s. 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 138.8, 135.2, 130.1, 127.3, 117.5, 65.1, 59.1, 47.2, 36.1, 29.3, 21.7; HRMS Calcd for $C_{17}H_{25}NO_3S$ ($M+Na^+$): 346.1453, found 346.1457; $[\alpha]_D^{25}$ 5.294 (c 0.39, CH_2Cl_2).

***Cis*-5-isopropyl-4-(toluene-4-sulfonyl)-2-vinylmorpholine (4).** IR (neat) cm^{-1}; 2967, 1464, 1342, 1280, 1216, 1159, 1092, 1019, 971, 940, 909, 815, 756, 680, 557; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.69 (ddd, *J* = 5.6, 10.8, 16.4 Hz, 1H), 5.25-5.14 (m, 2H), 3.89 (dd, *J* = 2.4, 13.2 Hz, 1H), 3.68 (dd, *J* = 3.2, 14.8 Hz, 1H), 3.58-3.53 (m, 1H), 3.30 (dd, *J* = 2.8, 12.8 Hz, 2H), 2.94 (dd, *J* = 11.2, 14.4 Hz, 1H), 2.41 (s, 3H), 2.23-2.20 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 138.9, 135.1, 130.1, 127.2, 117.8, 66.3, 59.2, 45.6, 25.5, 21.7, 20.2, 20.0; HRMS Calcd for $C_{16}H_{23}NO_3S$ ($M+Na^+$): 332.1294, found 332.1294; $[\alpha]_D^{25}$ 7.692 (c 0.25, CH_2Cl_2); the enantiomeric purity was determined by HPLC (254 nm, 25 ºC) t_R = 81.8 min (major); t_R = 84.6 min (minor) [Chiralcel AD-H + AD-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99/1, 1.0 ml/min] as 99% ee.

(Mixture of 1:2 *cis/trans)*-5-methyl-4-(toluene-4-sulfonyl)-2-vinylmorpholine (5). IR (neat) cm^{-1}; 3033, 2980, 2864, 1918, 1599, 1494, 1444, 1341, 1161, 966, 815, 680, 550; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.86-5.74 (m, 1H), 5.39 (dd, *J* = 7.5, 25.0 Hz, 1H), 5.29-5.24 (d, *J* = 13.5 Hz, 1H), 4.00 (q, *J* = 6.5 Hz, 1H), 3.88-3.86 (m, 1H), 3.73-3.57 (m, 3H), 2.89 (t, *J* = 12.0 Hz), 2.45 (s, 3H), 1.12 (d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 143.7, 137.8, 135.0, 134.8, 134.7, 130.2, 130.1, 130.0, 127.9, 127.3, 118.4, 118.0, 75.2, 72.4, 71.8, 71.4, 70.5, 51.8, 49.0, 48.5, 44.5, 43.9, 21.8, 15.8, 13.9 d; HRMS Calcd for $C_{14}H_{19}NO_3S$ ($M+Na^+$): 304.0983, found 304.0976; $[\alpha]_D^{25}$ 7.692 (c 0.25, CH_2Cl_2).

***Cis*-5-benzyl-4-(toluene-4-sulfonyl)-2-vinylmorpholine (6).** IR (neat) cm^{-1}; 3028, 2925, 2865, 2254, 1733, 1599, 1496, 1455, 1342, 1304, 1163, 1112, 1090, 1054, 959, 911, 815, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.31-7.12 (m, 7H), 5.83 (ddd, *J* = 5.6, 10.8, 16.4 Hz, 1H), 5.39 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 4.00 (dd, *J* = 3.6, 8.0 Hz, 1H), 3.88-3.85 (m, 1H), 3.71-3.55 (m,

2H), 3.47 (dd, J = 2.8, 11.6 Hz, 1H), 3.04 (q, J = 10.4 Hz, 2H), 2.69 (dd, J = 4.8, 12.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 138.0, 137.8, 135.0, 130.0, 129.7, 129.6, 128.9, 127.5, 127.3, 126.8, 119.2, 118.1, 72.7, 67.3, 62.2, 55.9, 54.3, 45.1, 34.4, 34.2, 21.7 4 d ; HRMS Calcd for $C_{20}H_{23}NO_3S$ ($M+Na^+$): 380.1296, found 380.1302; $[\alpha]_D^{25}$ 37.008 (c 0.36, CH_2Cl_2).

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