# Regioselective *O*-Sulfonylation of *N,N*-bis(2-Hydroxyalkyl)-tosylamides as a Synthetic Key-Step to Enantiopure Morpholines

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Supporting Information Placeholder
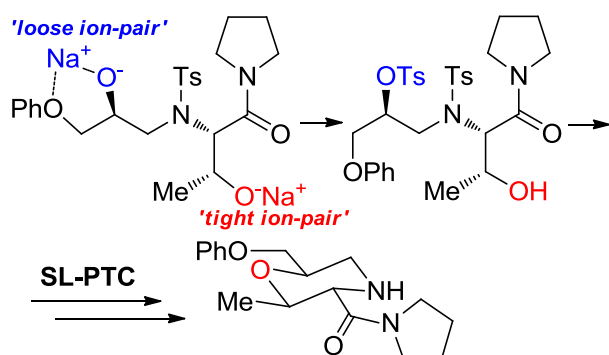
ABSTRACT: The synthesis of enantiopure 2,6-disubstituted morpholines was realized through sequential ring-opening of two different optically pure oxiranes by a tosylamide, under solid-liquid phase transfer catalysis (SL-PTC) conditions, mono-*O*-sulfonylation of the resulting tosylamido-2,2'-diol, and cyclization to the morpholine. The crucial step, that is the regioselective formation of the mono-sulfonate, was controlled by taking advantage of the different stereo, electronic, and coordination properties of the oxirane derived side chains in the diol backbone. As an application of this protocol, a new morpholine-3-carboxamide was synthesized starting from threonine.

Regiochemical control is a stimulating and challenging task in many synthetic transformations of important compounds, and in particular of small molecules. As an evidence of this, several reviews have been recently published on the regioselectivity of processes such as the manipulation of hydroxy groups in mono-saccharide derivatives,[1] addition reactions to allenes,[2] alkenes,[3] and alkynes,[4] the transglycosylation of nucleosides,[5] the trans-formations of chiral substrates controlled by a chiral catalyst,[6] cross-coupling reactions carried out in water,[7] the Fujiwara-Moritani coupling,[8] the Pd-catalyzed cross-coupling of dihal-oarenes,[9] and the functionalization of heteroaromatics by met-al-catalyzed coupling.[10] In the present paper, we describe the regiocontrolled mono-O-sulfonylation of diols, whose hydroxy groups have minimal steric and electronic differences, and the application of this chemistry in an enantiopure morpholine syn-thesis. The interest for the regio- and stereoselective synthesis of optically pure C-substituted morpholines is increasing, due to their wide spectrum of biological activity. In particular, 2,6-disubstituted morpholines have found application in antisense[11] and foldamer chemistry,[12] whereas morpholine 3-carboxylic acids induce β-conformations when they replace proline units in peptide chains.[13] Furthermore, morpholine derivatives have been used as HIV protease inhibitors,[14] anti-inflammatory[15] and antimicrobial agents,[16] as therapeutics in the treatment of diabe-tes and obesity,[17] mental disorders,[18] sexual dysfunctions,[19] and tumors,[20] and as inhibitors of both tumor necrosis factor-α[21] and matrix metalloproteinases.[22]

Scheme 1. Synthesis of 2,6-Disubstituted Morpholines 3: Direct Regioselective Protocol (*a*) *vs* Protec-tion/Deprotection Protocol (*b*).
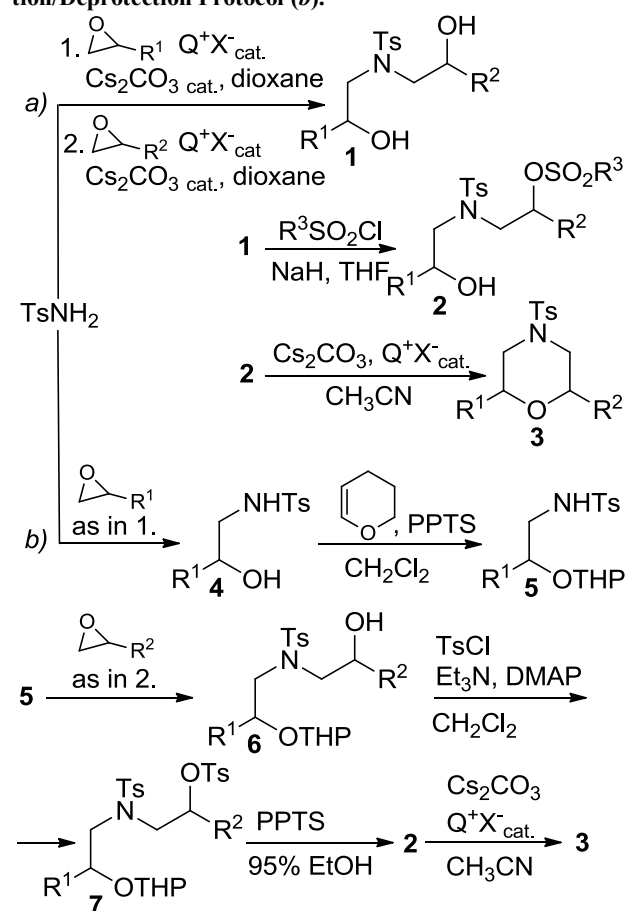
We previously reported a method for the synthesis of 2,6-disubstituted morpholines **3** (Scheme 1, path *b*)[23] by intramo-lecular cyclization of the tosylamidodiol-mono-sulfonate **2**. The latter was prepared through ring opening reaction of an oxirane under solid-liquid phase transfer catalysis (SL-PTC) condi-tions,[24] followed by protection of the hydroxy function of the tosylamido alcohol **4** as the THP derivative **5**. Then, the reac-tion with a different oxirane, activation of the new formed hy-droxy function as an O-tosylate (**6→7**) and final removal of the protective group afforded the desired intermediate **2**. Although this multistep protocol gives access to a variety of unsymmetric morpholines, it suffers from the need of additional protec-tion/deprotection steps, which negatively influences yields and purification operations. Here we report that the same approach to 2,6-disubstituted morpholines can be greatly improved by avoiding the protection/deprotection steps, through the direct and regioselective mono-O-sulfonylation of tosylamidodiols **1** (Scheme 1, path *a*).[25] This reaction was realized on the diol **1** via the oxy-dianion formed in situ (Scheme 2, step *a*). The ap-proach takes advantage of different features such as *i*) the steric hindrance difference between the carbon atoms bearing OH's, *ii*) the formation of a more stable sulfonate, and *iii*) the stabili-zation of the intermediate sodium alcoholate through extra-coordination by the side-arm. The tosylamidodiol **1a** was cho-sen as a model compound to investigate the influence on the regioselectivity of both the steric hindrance and the intramolec-ular nucleophilic ring-closing mechanism (Scheme 2). The O-sulfonylation of the **1a** oxydianion with various sulfonylating agents (TrisCl, TsCl, and MsCl) at -80 °C produced mixtures of the mono-sulfonate **2a** and (2R,6S)-2-ethyl-6-phenyl-4-tosylmorpholine (**3a**), deriving from the sulfonylation of the benzylic oxanion, followed by rapid cyclization (Table 1). The product ratio depends upon the difference in steric hindrance around the hydroxy groups and on the size of the R³SO₂Cl. TrisCl, the largest reagent, preferentially reacted with the less hindered hydroxyl on the carbon atom bearing the ethyl group, giving good yields of **2a-Tris** and minor amounts of enanti-opure morpholine **3a**.

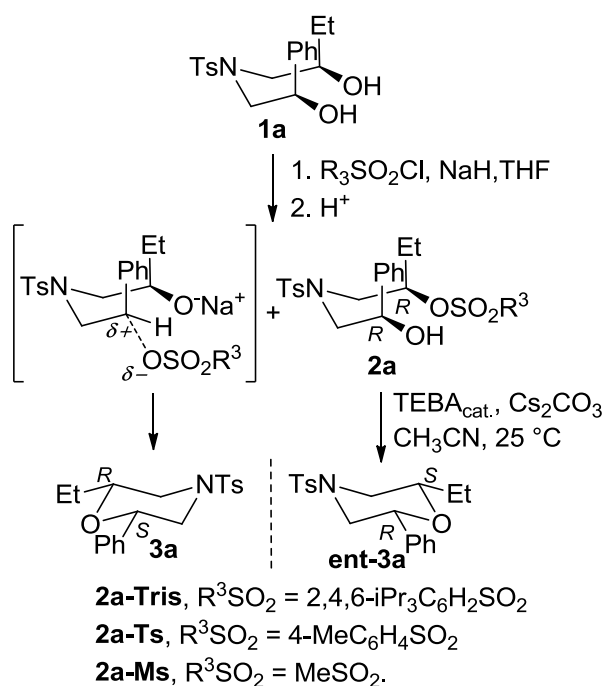**Scheme 2. Regioselective O-Sulfonylation: S_N1 *vs* S_N2 Mech-anism.**

2a-Tris, R³SO₂ = 2,4,6-iPr₃C₆H₂SO₂
2a-Ts, R³SO₂ = 4-MeC₆H₄SO₂
2a-Ms, R³SO₂ = MeSO₂.

Table 1. Regioselective Sulfonylation of Tosylamidodiol 1a.[a]

entry	R³SO₂Cl	temp (°C)	time (h)	yield (%)[b]		ee (%)[c]
1	TrisCl	-80	1.25	**2a-Tris** (72)	**3a** (19)	98
2	TsCl	-80	2.5	**2a-Ts** (57)	**3a** (25)	80
3	TsCl	-65	72	**2a-Ts** (42)	**3a** (52)	65
4	TsCl	25	6	–	**ent-3a** (80)	25
5	MsCl	-80	4.5	**2a-Ms** (49)	**3a** (31)	65

[a] Reaction conditions: **1a** (1 mmol), R³SO₂Cl (1.1 mmol), NaH (2.1 mmol), THF (2.5 mL). The dianion was generated by reaction of **1a** with NaH at 0 °C for 30 min. [b] Isolated yields. [c] Morpholine **3a** or **ent-3a** ee's, determined by chiral HPLC analysis.

The enantiospecific cyclization to **3a** most probably proceeds though a pseudo-bimolecular mechanism, with inversion of the stereogenic benzylic centre (Scheme 2). The smaller TsCl and MsCl gave different product distributions: the less the steric hindrance of the sulfonylating agent the lower the ratio **2a/3a** (entries 1,2,5). The reaction temperature was a crucial parameter too. Thus, the tosylation of **1a** at -65 °C was less regioselective (entry 3) and, besides, the ee value of the morpholine **3a** dropped to 65%, due to the parallel in situ cyclization of the thermodynamic favored **2a-Ts** to the enantiomeric morpholine **ent-3a**. This ring-closing side-reaction became the main process at 25 °C (entry 4) and the morpholines were the sole products isolated, **ent-3a** being the more abundant enantiomer (er 62:38).

All the intermediates **2a** were cyclized to enantiopure morpholine **3a** in good yields (90–93%) under SL-PTC in acetonitrile, by using anhydrous Cs₂O₃ as base, in the presence of a catalytic amount of benzyltriethylammonium chloride (TEBA) as phase transfer agent (see Scheme 5 and Supporting Information). The effect of coordination on regioselectivity has been proven by direct O-tosylation[26] of the phenylglycidyl ether derived tosylamidodiols **1b,c** (Scheme 3), which gave only the regioisomers **2b** and **2c** in 89% and 91% yield, respectively. These results can be explained by assuming that two different types of ion-pair are present in the intermediate dianions: a poorly nucleophilic 'tight ion-pair' near the alkyl (or aryl) group and a more reactive 'loose ion-pair', formed through coordination of the sodium cation by the glycidyl oxygen atom on the other side arm.

Scheme 3. Regioselective O-Sulfonylation: Coordination Effect.

R² = PhOCH₂; **1b**, R¹ = Et; **1c**, R¹ = Ph
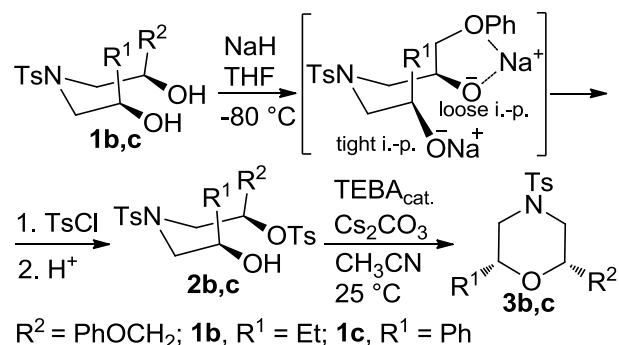
The tosylation regioselectivity of diol **1d** (Scheme 4), which contains the glycidyl derived phenoxy and benzyloxy groups on the side chains, is clearly influenced by the inductive effects of these groups. Whereas both the sodium cations are coordinated by the ether oxygen atoms, the aliphatic benzyl group, through its (+I) effect along the σ bonds, increases the charge of the near oxyanion, which forms a more tight and then less nucleophilic ion-pair with the sodium cation. As a result, even though the regioselectivity was not complete, the tosylate derivative **2d** was the major product.

Scheme 4. Regioselective O-Sulfonylation: (+I) vs (-I) Effect in the Glycidyl Derivative 1d.
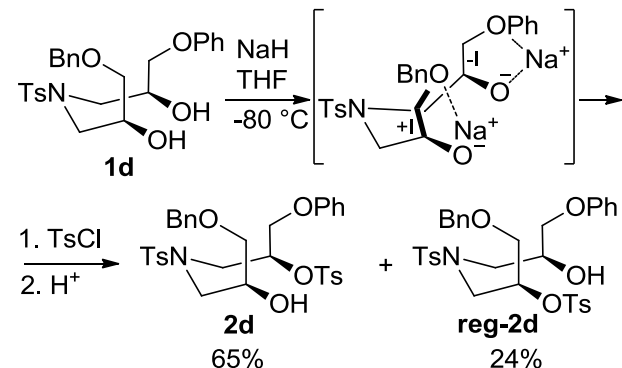
Sulfonylation of the N-tosylamidodiols **1e,f** (Table 2) provided further confirmation that the higher the difference in the inductive effect between the side chains in diols, the higher the regioselectivity. Thus, the hydroxy group in the C-2 position, adjacent to an aryloxymethyl group bearing the strong electron-withdrawing nitro function, was readily tosylated under the optimized reaction conditions to give compounds **2e,f**, which were isolated in good yield, together with minor amounts of the regioisomers **reg-2e,f** (entries 1–3).

Table 2. Regioselective O-Sulfonylation: (+I) vs (-I) Effect in Glycidyl Derivatives 1e,f.[a]
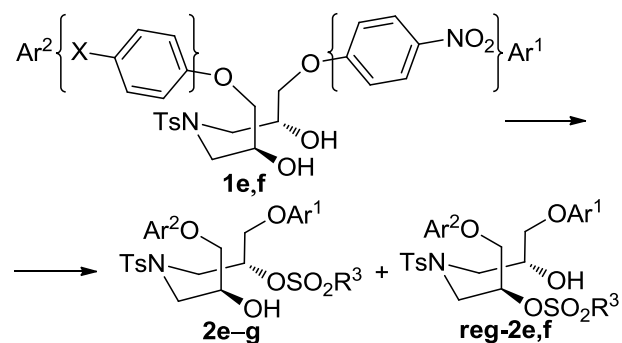
entry	substrate	X	R³SO₂Cl	yield (%)	
1	**1e**	H	TsCl	**2e** (73)	**reg-2e** (20)
2	**1f**	OMe	TsCl	**2f** (78)	**reg-2f** (17)
3	**1f**[b]	OMe	TsCl	**2f** (79)	**reg-2f** (17)
4	**1f**[c]	OMe	TsCl	**2f** (37)	**reg-2f** (34)
5	**1f**[d]	OMe	TsCl	**2f** (41)	**reg-2f** (38)
6	**1f**	OMe	TrisCl	**2g** (90)	–

[a] Reaction conditions: **1** (1 mmol), R₃SO₂Cl (1.1 mmol), NaH (2.1 mmol), THF (2.5 mL), at -80 °C, 1 h. [b] In 20 mL of THF. [c] In the presence of LiClO₄ (8 mmol), at 0 °C, 8 h. [d] In DMF (2.5 mL).

Loss of regioselectivity was found by performing the tosylation of **1f** in the presence of LiClO₄ (entry 4), which formed 'tight ion-pairs' with both the oxyanions, smoothing their relative re-

activity. The same result was reached in the aprotic dipolar DMF as solvent (entry 5), which solvated both the sodium alcoholates generating two 'solvent separated ion-pairs' that had similar enhanced reactivity, i.e. by taking advantage of the opposite effect exerted by the lithium cation. Finally, the reaction of **1f** with TrisCl (entry 6) gave exclusively **2g**. The mono-*O*-sulfonylated derivatives **2** and **reg-2** were cyclized under SL-PTC conditions to the corresponding enantiopure morpholines **3** and **ent-3**, respectively, in yields up to 95% (Scheme 5).[25] The overall process was successfully applied to the synthesis of the new morpholine-3-carboxylic acid derivative **12** starting from L-threonine. Regioselective tosylation of the diol **9** as previously described, gave the sole regioisomer **10** (Scheme 6) which, in turn, was SL-PTC cyclized. The resulting *N*-tosyl morpholine **11** was detosylated to **12** by treatment with 40% HBr-AcOH, in the presence of phenol.

In summary, we have described a rapid and efficient regioselective mono-*O*-sulfonylation of oxa-dianions derived from non-symmetric 3-tosylamido-1,5-diols. This selective reactivity,

which to the best of our knowledge is unexplored, depends on both the stability and the nucleophilicity of the oxa-dianion ion-pairs: the combination of steric hindrance and electrodonating effects generate a reactive "loose ion-pair" that is preferentially tosylated. The 5-hydroxy-sulfonates prepared through the reported procedure are key intermediates for the direct synthesis of enantiopure polysubstituted morpholines, such as **12**, that can be used for the preparation of anti-HBV agents.[27]

Scheme 5. Stereoselective Cyclization of mono-Tosylated Compounds to Morpholines, Under Solid-Liquid PTC Conditions.
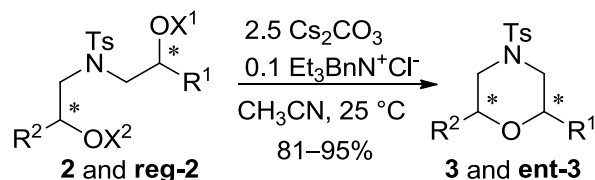
Scheme 6. Example of Regioselective *O*-Tosylation Applied to the Synthesis of 2,6-Disubstitued Morpholine-3-Carboxylic Acid Derivative 12.
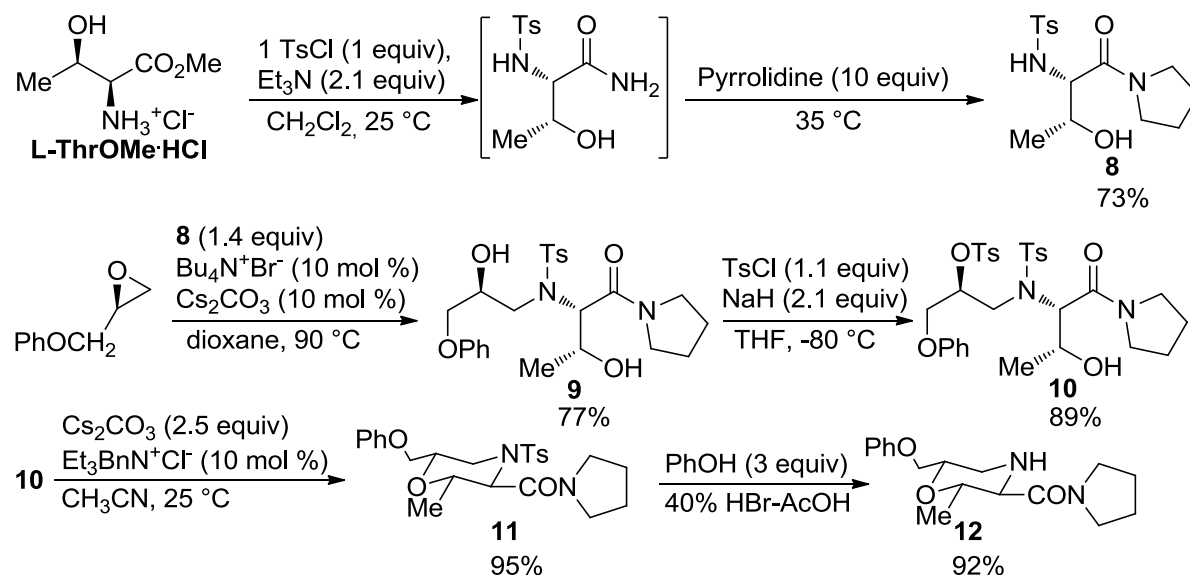
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full experimental details; ^{1}H, ^{13}C NMR spectra (PDF).

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Notes
The authors declare no competing financial interest.

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(25) For experimental details, see Supporting Information.

(26) For reaction conditions see note *a*) in Table 1.

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