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

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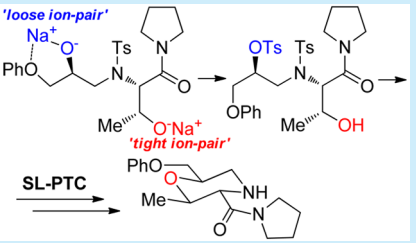
Supporting Information

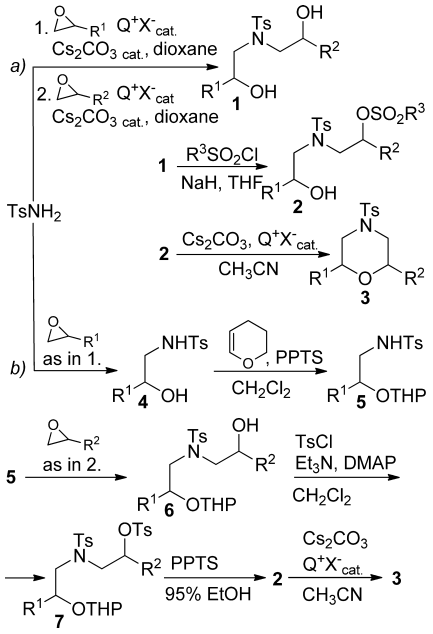
ABSTRACT: The synthesis of enantiopure 2,6-disubstituted morpholines was realized through sequential ring opening of two different optically pure oxiranes by a tosylamide, under solid−liquid phase-transfer catalysis (SL-PTC) conditions, mono-*O*-sulfonylation of the resulting tosylamido-2,2′-diol, and cyclization to the morpholine. The crucial step, the regioselective formation of the monosulfonate, 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 evidence of this, several reviews have been recently published on the regioselectivity of processes such as the manipulation of hydroxy groups in monosaccharide derivatives,[1] addition reactions to allenes,[2] alkenes,[3] and alkynes,[4] transglycosylation of nucleosides,[5] transformations of chiral substrates controlled by a chiral catalyst,[6] cross-coupling reactions carried out in water,[7] Fujiwara−Moritani coupling,[8] Pd-catalyzed cross-coupling of dihaloarenes,[9] and functionalization of heteroaromatics by metal-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 synthesis. Interest in 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 applications 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] therapeutics in the treatment of diabetes and obesity,[17] mental disorders,[18] sexual dysfunction,[19] and tumors,[20] and inhibitors of both tumor necrosis factor-*α*[21] and matrix metalloproteinases.[22]

We previously reported a method for the synthesis of 2,6-disubstituted morpholines **3** (Scheme 1, path b)[23] by intramolecular cyclization of the tosylamidodiol monosulfonate **2**. The latter was prepared through ring-opening reaction of an oxirane under solid−liquid phase-transfer catalysis (SL-PTC) conditions,[24] followed by protection of the hydroxy function of the tosylamido alcohol **4** as the THP derivative **5**. Then, the reaction with a different oxirane, activation of the new formed hydroxy function as an *O*-tosylate (**6** → **7**), and final removal of the protective group afforded the desired intermediate **2**.

Scheme 1. Synthesis of 2,6-Disubstituted Morpholines 3: Direct Regioselective Protocol (a) vs Protection/Deprotection Protocol (b)



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

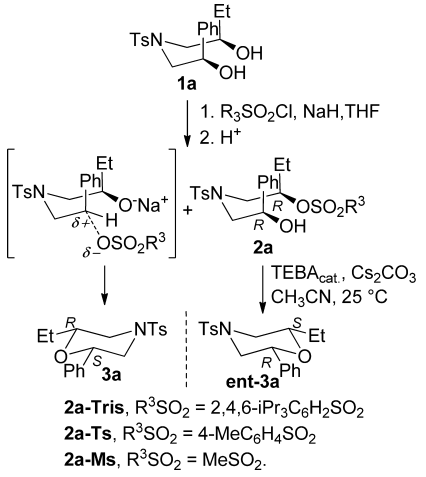
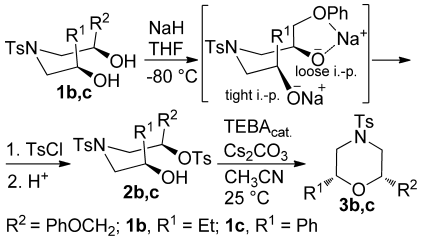


Table 1. Regioselective Sulfonylation of Tosylamidodiol 1a[a]

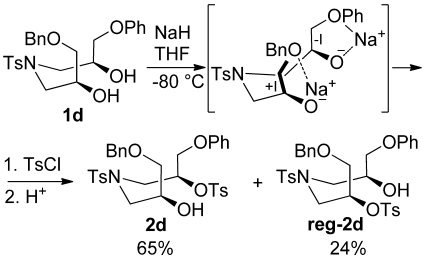
entry	R^3SO_2Cl	temp (°C)	time (h)	yield[b] (%)		ee[c] (%)
1	TrisCl	−80	1.25	**2a-Tris** (72)	**3a** (19)	98
2	TsCl	−80	2.5	**2a-Ts** (57)	**3a** (25)	80
3	TsCl	−65	72	**2a-Ts** (42)	**3a** (52)	65
4	TsCl	25	6		**ent-3a** (80)	25
5	MsCl	−80	4.5	**2a-Ms** (49)	**3a** (31)	65

[a]Reaction conditions: **1a** (1 mmol), R^3SO_2Cl (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.

Scheme 3. Regioselective *O*-Sulfonylation: Coordination Effect

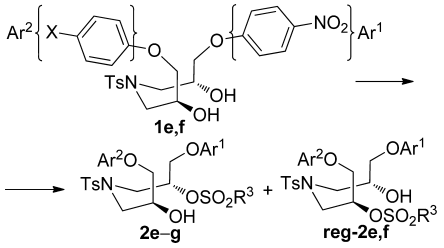


Scheme 4. Regioselective *O*-Sulfonylation: (+I) vs (−I) Effect in the Glycidyl Derivative 1d



Although this multistep protocol gives access to a variety of unsymmetric morpholines, it suffers from the need of additional protection/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

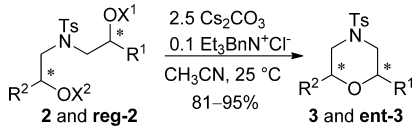
Table 2. Regioselective *O*-Sulfonylation: (+I) vs (−I) Effect in Glycidyl Derivatives 1e,f[a]



entry	substrate	X	R^3SO_2Cl	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), R_3SO_2Cl (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 $LiClO_4$ (8 mmol), at 0 °C, 8 h. [d]In DMF (2.5 mL).

Scheme 5. Stereoselective Cyclization of Monotosylated Compounds to Morpholines under Solid−Liquid PTC Conditions



through the direct and regioselective mono-*O*-sulfonylation of tosylamidodiols **1** (Scheme 1, path a).[25] This reaction was realized on diol **1** via the oxydianion formed in situ. The approach 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 stabilization of the intermediate sodium alcoholate through extra-coordination by the side arm. The tosylamidodiol **1a** was chosen as a model compound to investigate the influence on the regioselectivity of both the steric hindrance and the intramolecular 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 monosulfonate **2a** and (2*R*,6*S*)-2-ethyl-6-phenyl-4-tosylmorpholine (**3a**), deriving from the sulfonylation of the benzylic oxyanion, 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 R^3SO_2Cl. 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 enantiopure morpholine **3a**.

The enantiospecific cyclization to **3a** most probably proceeds through a pseudobimolecular mechanism with inversion of the stereogenic benzylic center (Scheme 2). The smaller TsCl and MsCl gave different product distributions: the less the steric hindrance of the sulfonylating agent the lower the ratio of **2a**/**3a** (entries 1, 2, and 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

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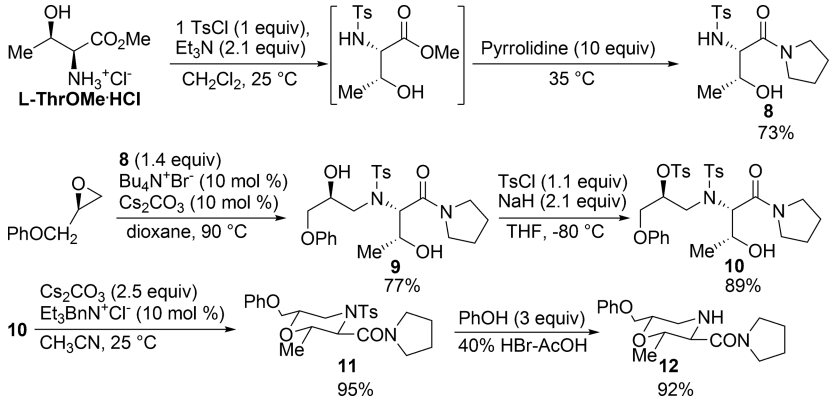
Scheme 6. Example of Regioselective *O*-Tosylation Applied to the Synthesis of 2,6-Disubstitued Morpholine-3-carboxylic Acid Derivative 12



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 of the intermediates **2a** were cyclized to enantiopure morpholine **3a** in good yields (90−93%) under SL-PTC in acetonitrile by using anhydrous Cs_2CO_3 as base in the presence of a catalytic amount of benzyltriethylammonium chloride (TEBA) as phase-transfer agent (see Scheme 5 and the 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 pairs 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.

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 of 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.

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 strongly 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).

Loss of regioselectivity was found by performing the tosylation of **1f** in the presence of $LiClO_4$ (entry 4), which formed "tight ion pairs" with both the oxyanions, smoothing their relative reactivity. The same result was reached in the aprotic dipolar DMF as solvent (entry 5), which solvated both of the sodium alcoholates to generate 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*-tosylmorpholine **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 nonsymmetric 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 electron-donating 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]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03342.

Full experimental details; ^1H and ^{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 the Supporting Information.
(26) For reaction conditions, see footnote a in Table 1.
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