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Synthesis of 2-substituted 3,4-dihydro-*2H*-1,4-benzoxazines through ligandless copper-catalyzed cyclization of hydroxysulfonamides under phase-transfer catalysis conditions

D. Albanese [a,*], D. Landini [a], V. Lupi [a], M. Penso [b], D. Scaletti [a]

[a] *Dipartimento di Chimica Organica e Industriale, via Venezian 21, 20133 Milano, Italy*
[b] *Istituto CNR-ISTM, via Golgi 19, 20133 Milano, Italy*

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ABSTRACT

The ring closing under solid–liquid phase-transfer catalysis conditions (SL-PTC) of hydroxysulfonamides **7**, bearing a leaving group in the *ortho* position of the aryl moiety, generates 2-substituted-3,4-dihydro-*2H*-1,4-benzoxazines **4** in good to excellent yields. In the case of hydroxysulfonamides **7** bearing a bromine or iodine atom as a leaving group, a copper(I) salt is used to enable the reaction to occur.

1. Introduction

3,4-Dihydro-*2H*-1,4-benzoxazines have received a great deal of attention due to their wide range of biological and therapeutical properties [1]. For example they have been investigated as intracellular calcium antagonists [2], antihypertensive agents [3], neuroprotective antioxidants [4] and prostaglandin D_2 receptor antagonists [5].

We recently reported a novel two-step synthesis of 2-substituted-3,4-dihydro-2*H*-1,4-benzoxazines **4** through the ring opening of epoxides **1** with *N*-(*o*-fluorophenyl)-toluene-*p*-sulfonamides **2**, followed by intramolecular nucleophilic displacement of the fluoride anion (Scheme 1) [6]. The ring opening step has been carried out without solvent under solid–liquid phase-transfer catalysis (SL-PTC) conditions using solid K_2CO_3 as base, whereas the cyclization was carried out under liquid–liquid PTC conditions by using 50% aqueous NaOH or under SL-PTC conditions by using solid NaOH and THF as solvent [7]. An environmentally friendly synthesis of benzoxazines has also been performed in a sequential fashion through the $R_4N^+F^-$ catalyzed ring opening of epoxides with arylsulfonamides, followed by in situ cyclization of the hydroxysulfonamides **3** thus obtained with 50% aqueous NaOH (Scheme 1) [8]. Under such reaction conditions both steps occurred without organic solvents and benzoxazines could be isolated in excellent yields through filtration of the reaction mixture after dilution with water.

Although the straightforward and high yielding features of this procedure, the latter requires a fluorine atom as a leaving group of an intramolecular aromatic nucleophilic substitution (S_NAr). Therefore, we wondered whether or not the cyclization could also be achieved by replacing the fluorine atom with different leaving groups in order to generate a greater number of variously functionalized benzoxazines.

Here we report that the ring closure of non-fluorinated hydroxysulfonamides **7** to 3,4-dihydro-*2H*-1,4-benzoxazines **4** occurred in good to excellent yields by using solid NaOH under SL-PTC conditions. Cuprous halides were necessary for catalyzing the cyclization of bromo- or iododerivatives **7b**, **c**, **e**–**g**, whereas the cyclization of the tosylate **7d** occurred under the standard SL-PTC conditions without copper(I) (Scheme 2).

2. Experimental

2.1. General remarks

Pellets of NaOH were grounded with a mortar before use. Anhydrous dioxane was purchased from Fluka and used without further purification. Melting points were determined on a BÜCHI

* Corresponding author. Tel.: +39 02 50314165; fax: +39 02 50314159.
E-mail address: domenico.albanese@unimi.it (D. Albanese).

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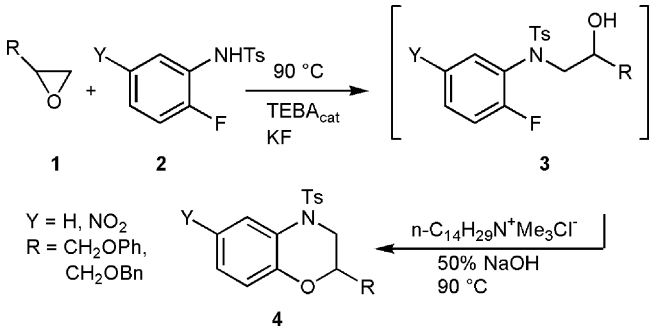


Scheme 1.

535 and are corrected. Infrared (IR) spectra were recorded on a Jasco FT/IR 4100 spectrometer. NMR spectra were recorded on Bruker AC 300 or AC 200 spectrometers, operating at 300.13 or 200.13 MHz for ^{1}H NMR and 75.3 or 50 MHz for ^{13}C NMR. Coupling constants *J* are in Hz. Chemical shifts were reported by using $CHCl_3$ as external standards (7.24 ppm for ^{1}H NMR and 77.0 for ^{13}C NMR). Attached Proton Test (APT) experiments were used in the assignment of carbon spectra. Optical rotations were measured with a PerkinElmer 241 polarimeter; the $[\alpha]_D$ values are reported in 10^{-1} ° cm^{-2} g^{-1}, and concentration (*c*) is reported in g/100 mL. Column chromatography on silica gel (230–400 mesh) was performed by the flash technique. Chiral HPLC separations were performed on a Agilent HP 1100 apparatus, equipped with a diode array detector, detection at 230 nm. The flux was set to 1 mL min^{-1} and the volume of injection was 20 μL. Petroleum ether (PE) refers to the fraction boiling in the range of 40–60 °C. Anilines **5a–c** and 2-aminophenol **5d** are commercially available.

2.2. General method for the synthesis of hydroxysulfonamides *7a–c, e–g*

A screw cap vial was charged with sulfonamides **6a–c** (22 mmol), epoxide **1** (20 mmol), K_2CO_3 (276 mg, 2 mmol), and TEBA (456 mg, 2 mmol) and the resultant heterogeneous mixture was stirred at 90 °C for the time indicated in Table 1. Addition of water, extraction with CH_2Cl_2, drying with $MgSO_4$, filtration and solvent removal *in vacuo* gave a residue which was purified by flash column chromatography on silica gel (230–400 mesh) to give hydroxysulfonamides **7**. Yield, chromatographic eluant, and physical and spectroscopic data of compounds **7** are reported in Supplementary Material.

Table 1
Synthesis of hydroxysulfonamides 7[a]

Entry	Sulfonamide	Epoxide	*t* [h]	Yield [%]	Product
1	**6a**	**1a**	4	94	**7a**
2	**6b**	**1a**	7	87	**7b**
3	**6c**	**1a**	3	86	**7c**
4	**6c**	(*R*)-**1a**	2	87	(*R*)-**7c**[b]
5[c]	**6d**	**1a**	24	60	**7d**
6	**6d**[d]	**1a**	3	91	**7d**
7	**6c**	**1b**	2	93	**7e**
8	**6c**	**1c**	4	76	**7f**
9	**6c**	**1d**	3	93	**7g**

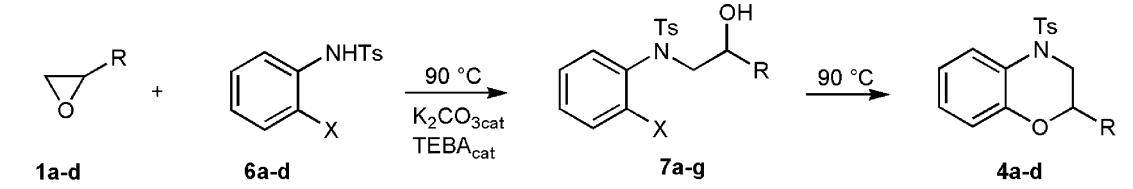
[a] Reaction conditions: sulfonamide (1.1 equiv.), epoxide (1 equiv.), K_2CO_3 (0.1 equiv.), TEBA (0.1 equiv.), 90 °C.
[b] 98% ee (determined by chiral HPLC).
[c] Dioxane 2 M as solvent.
[d] With 2 equiv. of sulfonamide **6d** at 120 °C, without dioxane.

2.3. Synthesis of hydroxysulfonamide *7d*

A screw cap vial was charged with **6d** (20 mmol, 8.35 g), **1a** (10 mmol, 1.50 g), K_2CO_3 (1 mmol, 0.14 g), and TEBA (1 mmol, 0.23 g) and the resultant heterogeneous mixture was stirred at 120 °C for 3 h. The residue was chromatographed on silica gel (AcOEt–PE 1–4) to give 5.71 g of the title compound, yield 91%, white solid mp 31–32 °C. ^{1}H NMR ($CDCl_3$): δ, 2.41 (s, 3H), 2.46 (s, 3H), 3.69 (d, 2H), 3.93 (d, 2H), 4.07 (m, 1H), 6.81 (d, 2H, *J* = 8.0 Hz), 6.94 (t, 1H, *J* = 7.2 Hz), 7.18–7.39 (m, 10H), 7.55 (d, 2H, *J* = 8.3 Hz), 7.83 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, selected signals): δ, 21.5 (CH_3), 21.7 (CH_3), 54.4 (CH_2), 68.0 (CH), 69.2 (CH_2). IR (nujol) ν 3442, 3173, 1597, 1298, 1155, 1074 cm^{-1}. Anal. Calcd. for $C_{29}H_{29}NO_7S_2$: C 61.36, H 5.15, N 2.47; found: C 61.50, H 5.16, N 2.46. Sulfonamide **6d** (8 mmol, 3.34 g) was also recovered.

2.4. Typical procedure for the cyclization of hydroxysulfonamides *7* to benzoxazines *4*

A screw cap vial was charged with sulfonamide **7** (2 mmol), NaOH (4 mmol, 0.16 g), $Bu_4N^+Br^-$ (0.2 mmol, 64 mg), CuI (0.2 mmol, 38 mg), and dioxane (2 mL) and heated at 90 °C for the time indicated in Table 2. Addition of water, extraction with CH_2Cl_2, drying with $MgSO_4$, filtration and solvent removal *in vacuo* gave a residue which was purified by column chromatography on silica gel to give benzoxazines **4a–d** whose physical and spectroscopic data match those previously reported [7b].



1a, R = CH_2OPh
1b, R = CH_2OBn
1c, R = CH_2Ot-Bu
1d, R = CH_2OH

6a, X = Cl
6b, X = Br
6c, X = I
6d, X = OTs

7a: X = Cl, R = CH_2OPh
7b: X = Br, R = CH_2OPh
7c: X = I, R = CH_2OPh
7d: X = OTs, R = CH_2OPh
7e: X = I, R = CH_2OBn
7f: X = I, R = CH_2Ot-Bu
7g: X = I, R = CH_2OH

4a, R = CH_2OPh
4b, R = CH_2OBn
4c, R = CH_2Ot-Bu
4d, R = CH_2OH

Scheme 2.

Table 2
Cyclization of hydroxysulfonamides **7b-g**[a]

Entry	Substrate	Base (equiv.)	PTC[b]	Additive (equiv.)	*t* [h]	Yield [%]	Product
1	**7b**	NaOH (2)	**A**	CuBr (0.1)	23	63	**4a**
2	**7b**	NaOH (2)	–	CuBr (0.2)	27	54	**4a**
3	**7b**	*t*-BuOK (3)	–	CuBr (0.2)	7	63	**4a**
4[c]	**7b**	*t*-BuOK (1.5)	–	CuBr (0.1)	22	46	**4a**
5	**7c**	NaOH (2)	**A**	CuI (0.1)	4	84	**4a**
6	(*R*)-**7c**[d]	NaOH (2)	**A**	CuI (0.1)	4	86	(*R*)-**4a**[d]
7[e]	**7c**	NaOH 50% (5)	**B**	CuI (0.1)	48	73	**4a**
8	**7d**	NaOH (2)	**A**	–	3	90	**4a**
9[e]	**7d**	NaOH 50% (10)	**B**	–	25	47	**4a**
10	**7e**	NaOH (2)	**A**	CuI (0.1)	6	90	**4b**
11	**7f**	NaOH (2)	**A**	CuI (0.1)	5	85	**4c**
12	**7g**	NaOH (2)	**A**	CuI (0.1)	20	63	**4d**

[a] Reaction conditions: **A** or **B** (0.1 equiv.), 90 °C, dioxane.
[b] **A**, n-$Bu_4N^+Br^-$ and **B**, n-$C_{14}H_{29}N^+Me_3Cl^-$.
[c] DMF/*t*-BuOH, 110 °C.
[d] 98% ee (determined by chiral HPLC).
[e] Without dioxane.

*2.4.1. N-(Tosyl)-(2R)-2-phenoxymethyl-3,4-dihydro-2H-1,4-benzoxazine (R)-**4a***

Yield 86%, mp 115–116 °C; $[\alpha]_D^{25}$ + 22.1 (*c* 1, $CHCl_3$). HPLC (Chiralcel OD, EtOH–hexane 5–95), t_R 12.8 min, ee 98%. [t_R (±)-**4a** 12.8, 14.1 min]. ^{1}H NMR ($CDCl_3$): δ, 2.35 (s, 3H), 3.39 (dd, 1H, *J* = 9.9, 14.4 Hz), 3.65–3.69 (m, 1H), 3.92 (dd, 1H, *J* = 6.3, 10.2 Hz), 4.10 (dd, 1H, *J* = 4.5, 10.2 Hz), 4.48 (dd, 1H, *J* = 4.5, 14.4 Hz), 6.83–7.11 (m, 6H), 7.14 (d, 2H, *J* = 8.1 Hz), 7.25–7.32 (m, 2H), 7.49 (d, 2H, *J* = 8.1 Hz), 7.88 (dd, 1H, *J* = 1.5, 8.1 Hz). ^{13}C NMR ($CDCl_3$, selected data): δ, 21.5 (CH_3), 46.2 (CH_2), 67.2 (CH_2), 69.7 (CH).

*2.4.2. N-(Tosyl)-2-benzyloxymethyl-3,4-dihydro-2H-1,4-benzoxazine (**4b**)*

Yield 90%, ^{1}H NMR ($CDCl_3$): δ, 2.37 (s, 3H), 3.28 (m, 1H), 3.51 (m, 3H), 4.34 (dd, 1H, *J* = 2.0, 14.2 Hz), 4.52 (dd, 2H, *J* = 12.4, 14.6 Hz), 6.82 (dd, 1H, *J* = 1.6, 8.1 Hz), 6.92 (m, 1H), 7.05 (m, 1H), 7.20 (d, 2H, *J* = 8.3 Hz), 7.28–7.38 (m, 5H), 7.50 (d, 2H, *J* = 8.3 Hz), 7.83 (dd, 1H, *J* = 1.6, 8.3 Hz). ^{13}C NMR ($CDCl_3$, selected data): δ, 21.5 (CH_3), 46.3 (CH_2), 69.6 (CH_2), 70.7 (CH), 73.5 (CH_2).

*2.4.3. N-(Tosyl)-2-tert-butoxymethyl-3,4-dihydro-2H-1,4-benzoxazine (**4c**)*

Yield 85%, mp 81.5–82 °C ^{1}H NMR ($CDCl_3$): δ, 1.16 (s, 9H), 2.37 (s, 3H), 3.21 (dd, 1H, *J* = 9.6, 14.3 Hz), 3.28–3.41 (m, 2H), 3.47 (dd, 1H, *J* = 3.9, 9.0 Hz), 4.37 (dd, 1H, *J* = 1.8, 14.3 Hz), 6.80 (dd, 1H, *J* = 1.1, 8.1 Hz), 6.91 (m, 1H), 7.04 (m, 1H), 7.21 (d, 2H, *J* = 8.1), 7.52 (d, 2H, *J* = 8.1), 7.85 (dd, 1H, *J* = 1.5, 8.1 Hz). ^{13}C NMR ($CDCl_3$, selected signals): 21.5 (CH_3), 27.3 (CH_3), 46.7 (CH_2), 61.9 (CH_2), 71.2 (CH), 73.5 (C).

*2.4.4. N-(Tosyl)-2-hydroxymethyl-3,4-dihydro-2H-1,4-benzoxazine (**4d**)*

Yield 63%, mp 128–129 °C. ^{1}H NMR ($CDCl_3$): δ 1.80 (t, 1H, *J* = 6.5 Hz), 2.38 (s, 3H), 3.37 (dd, 1H, *J* = 9.9, 14.3 Hz), 3.55 (m, 1H), 3.75 (m, 2H), 4.26 (dd, 1H, *J* = 2.4, 14.3 Hz), 6.84–7.82 (m, 8H). ^{13}C NMR ($CDCl_3$, selected signals): 21.5 (CH_3), 45.4 (CH_2), 62.6 (CH_2), 72.0 (CH).

*2.5. Cyclization of hydroxysulfonamide **7c** under solventless conditions*

A screw cap vial was charged with **7c** (0.5 mmol, 262 mg), 50% NaOH (2.5 mmol, 0.13 mL), CuI (0.05 mmol, 10 mg), and n-$C_{14}H_{29}Me_3N^+Cl^-$ (0.1 mmol, 29 mg), and heated at 90 °C for 48 h. Extraction with CH_2Cl_2, drying with $MgSO_4$, filtration and solvent removal *in vacuo* gave a residue which was purified by column chromatography on silica gel (AcOEt–PE 2:7) to give 144 mg of benzoxazine **4a**, yield 73%.

*2.6. Copper(I) free cyclization of hydroxysulfonamide **7d***

A screw cap vial was charged with **7d** (1 mmol, 0.57 g), solid NaOH (2 mmol, 0.08 g), $Bu_4N^+Br^-$ (0.1 mmol, 0.03 g), and dioxane (1 mL) and heated at 90 °C for 3 h. Addition of water, extraction with CH_2Cl_2, drying with $MgSO_4$, filtration and solvent removal *in vacuo* gave a residue which was purified by column chromatography on silica gel (AcOEt–PE 2:7) to give 0.36 g of benzoxazine **4a**, yield 90%.

*2.7. Synthesis of N-(tosyl)-2-hydroxymethyl-3,4-dihydro-2H-1,4-benzoxazine **4d***

A screw cap vial was charged with *N*-(tosyl)-2-*tert*-butoxymethyl-3,4-dihydro-*2H*-1,4-benzoxazine **4c** (1.4 mmol, 0.53 g) and trifluoroacetic acid (3 mL) was dropwise added at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was neutralized with 15% NaOH and extracted with AcOEt, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the title compound (0.42 g, 95% yield), mp 127–128 °C (spectroscopic data match those reported above).

3. Results and discussion

N-Arylsulfonamides **6a–c** have been prepared in good yields by *N*-tosylation of the corresponding commercially available 2-haloanilines with *p*-toluenesulfonyl chloride in pyridine as solvent. The *N*-tosylation of 2-chloroaniline (**5a**) and 2-bromoaniline (**5b**) proceeded at room temperature, whereas better results were obtained at 80 °C in the case of 2-iodoaniline (**5c**). The *N*,*O*-ditosylation of 2-aminophenol (**5d**) was carried out in a dichloromethane–pyridine (1:1) solvent mixture, in the presence of 1.5 equiv. of *p*-toluenesulfonyl chloride [9].

The ring opening of 1,2-epoxy-3-phenoxypropane (**1a**) with *N*-arylsulfonamides **6a–c** was carried out under SL-PTC conditions without solvent at 90 °C, in the presence of catalytic amounts of K_2CO_3 and $Et_3BnN^+Cl^-$ (TEBA), affording excellent yields of hydroxysulfonamides **7a–c** (Table 1, entries 1–3).

Under these reaction conditions *N*-arylsulfonamides **6a–c** melt and can thus be easily deprotonated by solid K_2CO_3 at the solid–liquid phase boundary affording the potassium salt of sulfonamides $ArN(Ts)^-K^+$ (**A**) which are converted into the more reactive

and more soluble [10] quaternary ammonium salts ArN(Ts)$^-$Q$^+$ (**B**) by cation exchange with the PT catalyst [11].

In contrast, under the same reaction conditions sulfonamide **6d** stays solid due to its higher melting point (143 °C) and cannot be easily deprotonated, thus hampering progress of the reaction. As expected, the ring opening proceeded in the presence of dioxane affording hydroxysulfonamide **7d** in 60% yield after heating 24 h (Table 1, entry 5) [12]. However, the melting of sulfonamide **6d** was facilitated by raising the temperature to 120 °C and 91% yield of **7d** was obtained in only 3 h in the presence of 2 equiv. of **6d** and without solvent (Table 1, entry 6).

The presence of complicated splitting patterns in ^{1}H NMR spectra of bromo- and iododerivatives **7b**, **c**, **e**–**g** suggested hindered rotation due to the presence of a bulky group in the *ortho* position of the aryl moiety. Moreover two singlets for the methyl group clearly indicated the presence of two rotamers generally in a nearly 1:1 ratio (determined by ^{1}H NMR spectroscopy).

Hydroxysulfonamides **7a**–**c** were chosen as model substrates to investigate the ring closure to benzoxazine **4a** (Scheme 2). The cyclization of hydroxysulfonamides **7a**–**c** under SL-PTC conditions, as previously described for the ring closing of fluorinated hydroxy sulfonamides [6–8], afforded only trace amounts of 2-phenoxymethylbenzoxazine **4a**, even after prolonged heating. Therefore, a different approach was required in order to fulfill our goal. A literature search revealed that the intramolecular copper-catalyzed C–O bond formation between aryl halides and alcohols has been used to assemble heterocycles such as dihydrobenzofuran and chroman [13]. The cyclization of various haloalcohols, leading to benzodioxanes and benzoxazines, has also been carried out by using expensive palladium catalysts in the presence of expensive phosphine ligands [14]. The copper-catalyzed ether formation by displacement of aryl bromides [15] and heteroaryl bromides [16] has also been reported.

On the basis of these previous results, the SL-PTC ring closure of **7a**–**c** was attempted in the presence of catalytic amounts of cuprous salts under ligandless conditions. Although the addition of cuprous salts was ineffective in the cyclization of the chloro derivative **7a**, it proved to be beneficial in the case of bromo and iodo derivatives **7b** and **c** (Scheme 2).

The cyclization of the less reactive *N*-(2-bromophenyl)-*N*-(2-hydroxy-3-phenoxypropyl)-4-methylbenzenesulfonamide (**7b**) was chosen as a model reaction in order to find the best reaction conditions; the most significant results are reported in Table 2. The expected benzoxazine **4a** was obtained in 63% yield by stirring a heterogeneous mixture of **7b**, solid NaOH (2 equiv.), $Bu_4N^+Br^-$ (0.1 equiv.) and CuBr (0.1 equiv.) in dioxane as solvent at 90 °C (Table 2, entry 1). Similar results were reached by using stoichiometric amounts of CuBr or under inert atmosphere.

The reaction was slower in the absence of the PTC catalyst, providing a lower yield of **4** even in the presence of twice the amount of CuBr (Table 2, entry 2). The cyclization proceeded also under homogeneous conditions by using *t*-BuOK as base, affording benzoxazine **4a** in 63% after 7 h (Table 2, entry 3). When the reaction was carried out at higher temperatures in a solvent mixture (DMF/NMP or *t*-BuOH/DMF) lower yields of **4a** were obtained (Table 2, entry 4). The CuI (0.1 equiv.) catalyzed ring closure of 2-iodophenyl hydroxysulfonamide **7c**, in the presence of solid NaOH (2 equiv.), $Bu_4N^+Br^-$ (0.1 equiv.) in dioxane, occurred in a short time affording benzoxazine **4a** in 84% yield after 4 h only (Table 2, entry 5) [17].

It is worth noting that the cyclization of **7c** can also be carried out in the absence of organic solvent by using 50% aqueous NaOH as base in the presence of *n*-$C_{14}H_{29}N^+Me_3Cl^-$ as catalyst (Table 2, entry 7). Under these reaction conditions 73% of **4** has been obtained, although in a longer reaction time.

The scope of the copper-catalyzed cyclization was extended to hydroxysulfonamides **7e**–**g**. These have been prepared in good yields through the ring opening of differently protected glycidol derivatives such as benzylglycidol (**1b**), *t*-butylglycidol (**1c**), and glycidol (**1d**) with **6c** under SL-PTC conditions, as previously described (Table 1, entries 7–9) (Scheme 2). The CuI catalyzed cyclization generated the corresponding benzoxazines **4b**–**d** in good yields in short reaction times (Table 2, entries 10–12). In the case of dihydroxysulfonamide **7g** derived from glycidol (**1d**), the reaction was slower affording 2-hydroxymethyl benzoxazine **4d** in only 63% yield. However, **4d** can also be isolated in high yield from **4c** by removal of the *t*-butyl moiety in quantitative yield by treating with trifluoroacetic acid at 0 °C.

Enantiopure 2-substituted benzoxazines can be easily obtained from chiral epoxides, as proved in the case of benzoxazine (*R*)-**4a** which has been isolated in 73% overall yield by the ring opening of (*R*)-1,2-epoxy-3-phenoxypropane (*R*)-**1a** [18] with **6c**, followed by CuI catalyzed cyclization as previously described.

The tosylate group is known to be a good leaving group in aliphatic and also aromatic nucleophilic substitution [19]. Therefore, it was investigated for a possible leaving group for the cyclization to benzoxazines. We were pleased to find that excellent yields of 2-phenoxymethyl-benzoxazine **4a** could be obtained through the tosylate group displacement in **7d** under SL-PTC conditions, by using solid NaOH in dioxane at 90 °C without copper(I) catalyst (Table 2, entry 8). The same reaction proceeded only in moderate yield when 50% aqueous NaOH was used in the presence of *n*-$C_{14}H_{29}Me_3N^+Cl^-$ as PT catalyst in order to carry out the reaction in the absence of organic solvent (Table 2, entry 9).

4. Conclusions

In summary 2-substituted benzoxazines **4** can be produced in an efficient and economical manner by employing inexpensive, safe and commercially available reagents under SL-PTC conditions. The addition of catalytic amounts of copper(I) salts to the SL-PTC reaction mixture made the cyclization of bromo- and iododerivatives **7** feasible under ligandless conditions. The tosylate group also proved to be a good leaving group for the S_NAr, providing excellent yields of benzoxazines under standard SL-PTC conditions without copper(I).

This new procedure enables 2-bromo- and 2-iodoanilines, as well as 2-aminophenols, to be employed as starting materials alternative to 2-fluoroanilines, therefore greatly expanding the reaction scope. A large number of enantiomerically pure 2-substituted 3,4-dihydro-*2H*-1,4-benzoxazines can thus be easily prepared from a variety of anilines or phenols using chiral epoxides.

Moreover, the nitrogen protective group of benzoxazines **4a**–**d** can be efficiently removed with one of the standard detosylation protocols such as 40% HBr/AcOH in the presence of phenol as bromine scavenger, Na/naphthalene or Red-Al, as previously reported [6,7b].

This procedure appears attractive from an environmental point of view since benzoxazines **4** can also be obtained under solventless conditions through a two-step PTC protocol operating through the ring opening of epoxides with sulfonamide **6c**, followed by ring closure of the resultant iodinated hydroxysulfonamides using 50% NaOH under SL-PTC conditions in the presence of a copper(I) catalyst, without any added ligand. On the other hand a copper(I) free, almost solventless protocol has been developed through the ring opening of epoxides with sulfonamide **6d**, followed by cyclization with solid NaOH and $Bu_4N^+Br^-$ in the presence of a small amount

of dioxane in order to maintain an efficient stirring of the reaction mixture.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2008.03.017.

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