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2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine Supported on Polystyrene (PS-BEMP) as an Efficient Recoverable and Reusable Catalyst for the Phenolysis of Epoxides under Solvent-Free Conditions

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Abstract: 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene (PS-BEMP) is an efficient catalyst for the ring-opening of epoxides with phenols (1.0 equiv.). Excellent yields have been obtained and in most of the cases the final products have been isolated in pure form without any additional purification step. E-factors associated to this protocol are small and further improvements were obtained by setting a cyclic continuous-flow reactor operating under solvent-free conditions (SolFC) that allowed us to minimize waste and reduce the E-factor by 95% compared to batch conditions. In addition the representative synthesis of a 2,3-dihydrobenzo[1,4]dioxepin-5-one has been realized. Optimization of this process was achieved by setting up an automated multi-step continuous-flow reactor based on a phenolysis process and a subsequent lactonization by thermal treatment of the reaction mixture. 3-Phenoxymethyl-2,3-dihydrobenzo[*e*][1,4]dioxepin-5-one was isolated in pure form and on a multi-gram scale in a very satisfactory 86% overall yield and an E-factor of 1.47.

Keywords: 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP); continuous-flow chemistry; epoxides; green chemistry; solvent-free conditions

Introduction

Epoxides are valuable intermediates in organic synthesis.[1] Their use has been even more established after the definition of highly efficient methods for their preparation in optically enriched form.[2] The variety of nucleophiles and the different promoters, reaction media and reaction conditions employed, make the ring opening of epoxide an immensely studied organic transformation.[1]

Among the different nucleophiles, alcohols and phenols react very poorly with epoxides.[3] However, this reaction is very important because it is the most direct access route for the preparation of β-alkyloxy and β-aryloxy alcohols.[4] To overcome the limitation related to the low reactivity of epoxides with alcohols, only few well established procedures are known.[5] Significant results have been obtained by Barluenga et al. by using a commercially available copper tetrafluoroborate salt.[5i] A recent related improvement has been reported by Baiker et al. by using a heterogeneous, recoverable copper(II) salt.[5a]

Efficient methods for the streoselctive ring-opening of epoxides by alcohols and phenols have been reported,[6] including kinetic resolution of terminal epoxides and desymmetrization of *meso*-epoxides.[7]

In the case of phenols as nucleophiles, basic conditions have been generally employed and the use of a large quantity of reactant and/or promoting base is somehow mandatory. As an alternative, an excess of the corresponding phenoxide salts is employed.[4a,5a,h,k]

Our research program is committed to the optimization of synthetic procedures by employing eco-friendly reaction protocols, including the use of water,[8] solvent-free conditions (SolFC),[9] and supported organocatalysts.[10]

We have been paying much attention to the reactivity of epoxides and we have developed several protocols for both their preparation and ring-opening by carbo- and heteroatomic nucleophiles such as azido ion, halides, amines and thiols, proving that the use of alternative reaction media such as water[11] or SolFC[12] is crucial for improving the efficiency of these processes. In our previous works we had not applied our strategy to the definition of a protocol for the reaction of epoxides with phenols.

We have reported that polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD) (10 mol%) is a sufficiently strong base able to promote the addition of phenol (**2a**) to styrene oxide **7** under SolFC.[10f] PS-TBD was chosen by considering its higher basicity among the commonly used nitrogen-containing organic bases (the pK_a of the conjugate acid of PS-TBD is >14 in water and 25.39 in MeCN).[13] Anyway, extension of the use of this base to other substrates gave unsatisfactory results.

Recently, our attention has been focused on 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene (PS-BEMP), a very strong base (in MeCN the pK_a is 27.63),[13] and a member of the class of Schwesinger's phosphazene bases, that have proved to be a widely useful uncharged auxiliary base.[13]

By using a catalytic amount of PS-BEMP, we have reported the nucleophilic addition of nitroalkanes to α,β-unsaturated carbonyl compounds under solvent-free conditions in batch conditions and also by using a cyclic continuous-flow reactor,[10b] as well as the addition of carbon nucleophiles to epoxides.[11a]

In consideration of its strong basicity we have chosen PS-BEMP as catalyst to define a novel and efficient procedure for the phenolysis of epoxides.

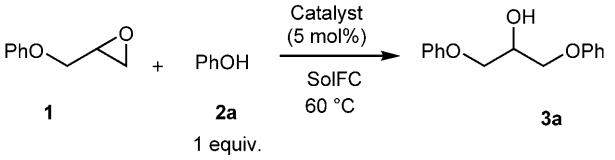
Results and Discussion

In this article, we report our results in the use of PS-BEMP as an efficient, recoverable and reusable solid basic catalyst able to promote the reaction of epoxides (**1**, **4**–**7**) with a variety of phenols (**2a**–**k**) under solvent-free conditions.

In preliminary studies, the efficiency of PS-BEMP was compared to that of PS-TBD in the reaction of phenyl glycidyl ether (**1**) and phenol (**2a**). The results are illustrated in Table 1.

At 60 °C, PS-BEMP showed a higher catalytic efficiency than PS-TBD (Table 1, entry 3 *vs.* 4) and when PS-BEMP was used, a complete disappearance of the reactants was observed after 20 h. Isolation of **3a** was quantitative and no trace of its regioisomer coming from the α-attack of **2a** to the epoxide **1** was observed. This result is also in agreement with the higher efficiency of non-supported BEMP compared to that of non-supported MTBD (Table 1, entry 5 *vs.* 7).

Table 1. Optimization of the base-catalyzed phenolysis of phenyl glycidyl ether (**1**) and phenol (**2a**) under SolFC.



1 **2a** (1 equiv.) **3a**

Entry	Catalyst[a]	Time [h]	C [%][b]	Yield [%][c]
1		3	50	–
2	PS-BEMP	15	98	–
3		20	>99	99
4	PS-TBD	20	88	–
5	BEMP	3	88	–
6		8	>99	–
7	MTBD[d]	3	79	–
8	PS-BEMP in MeCN	20	12	–
9	PS-BEMP in DCE or DCM	20	–	–
10	PS-BEMP reused for 10 times	20	always >99	98–99

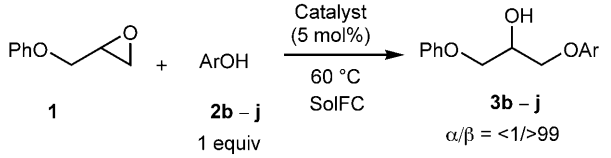
[a] PS = 200–400 mesh polystyryl with 2% of divinylbenzene as cross-linker.
[b] Conversion to **3a** measured by GLC analyses, the remaining material was the equimolar unreacted mixture of **1** and **2a**.
[c] Isolated yield of the pure product **3a** after filtering the solid catalyst using 5 mL mmol^{-1} of EtOAc and after vacuum evaporation of the latter (see Experimental Section for further details).
[d] 7-Methyl-TBD.

The influence of the reaction medium is dramatic. Although we have used the best organic solvents for swelling PS-BEMP,[13] the results obtained were completely unsatisfactory compared to SolFC. In fact, in the presence of 2 mL/mmol of DCM or DCE no conversion to **3a** was observed at all, while a poor 12% **3a** was formed when MeCN was used (Table 1, entries 8 and 9).

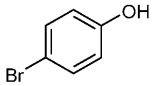
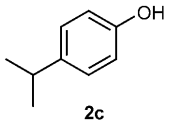
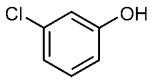
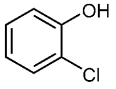
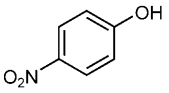
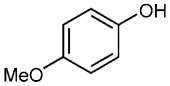
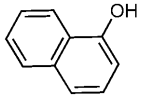
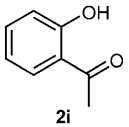
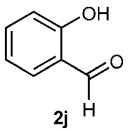
According to our intention to define a simple and efficient protocol with minimization of waste, we have used equimolar amounts of **1** and **2a**. In all the cases a conversion of 50% or more was reached in a relatively short time (3 h), while completion of the reaction requires a much longer time (Table 1, entries 1, 5, and 7). This is just presumably due to the reduced concentration of **1a** and **2a** in the reaction mixture and cannot be attributed to a decreased efficiency of the catalyst, that was recovered and reused several times (at least 10) with no decrease of its efficiency allowing always the isolation of 1,3-diphenoxy-2-propanol (**3a**) in almost quantitative yields (Table 1, entry 10).

To verify the application range of the use of PS-BEMP in the phenolysis of epoxides, other substrates were considered. The results of the reactions of equimolar amounts of epoxides **1, 4–7** and phenols **2a–j** are reported in the Table 2, Table 3, and Scheme 1.

Table 2. Phenolysis of phenyl glycidyl ether (**1**) catalyzed by 5 mol% of PS-BEMP at 60 °C under SolFC.

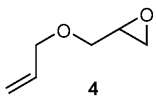
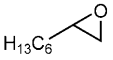
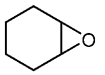
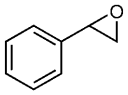


1 **2b – j** (1 equiv) **3b – j** α/β = <1/>99

Entry	Phenol	Time [h][a]	Yield [%][b]
1	 **2b**	34	99
2	 **2c**	18	99
3	 **2d**	40	99
4	 **2e**	28	99
5	 **2f**	70	87
6	 **2g**	20	99
7	 **2h**	36	96
8	 **2i**	55	97
9	 **2j**	45	94[c]

[a] Time for the complete conversion of **1** to **3**.
[b] Isolated yield of the pure product **3** (see Experimental Section for further details).
[c] Reaction performed at 80 °C.

Table 3. Phenolysis of epoxides **4–7** catalyzed by 5 mol% of PS-BEMP under SolFC at 60 °C.

Entry	Epoxide	ArOH	Time [h]	Yield [%][a]	α/β ratio[b]
1	 **4**	**2a**	24	94[c]	<1>99
2		**2b**	60	97	<1>99
3		**2d**	60	98	<1>99
4		**2g**	38	98	<1>99
5	 **5**	**2a**	96	98	4/96
6		**2b**	34	96[d]	8/92
7		**2d**	40	95[d]	10/90
8		**2g**	40	96[d]	8/92
9	 **6**	**2a**	96	82[c]	–
10		**2b**	34	85[c,d]	–
11		**2d**	38	77[c,d]	–
12			7	95[d,e]	–
13		**2g**	38	92[c,d]	–
14	 **7**	**2a**	45	94	68/32
15		**2b**	60	78	80/20
16		**2d**	60	69[c],	84/16
17			20	94[f]	67/33
18		**2g**	60	89	58/42

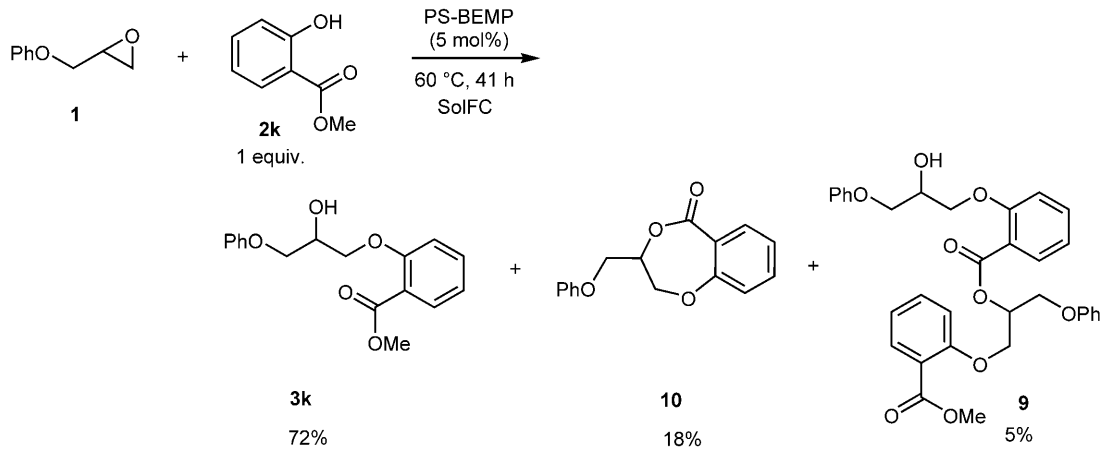
[a] Overall isolated yield of the pure products (see Experimental Section for further details).
[b] Measured by GLC analyses; in the cases when α- and β-isomers were formed they were isolated as pure products by silica gel column chromatography.
[c] Column chromatographic purification of the reaction mixture was necessary.
[d] Reaction performed at 80 °C.
[e] 2 equiv. of **6**.
[f] 2 equiv. of **7**.

An extension to alkyl alcohols was not investigated at this stage considering that generally large amounts of alcohols must be used to avoid a bis-product formation.

At 60 °C and by using 5 mol% of PS-BEMP, yields were excellent in all the cases and reaction proceeded to completeness in 18–70 h giving only the β-products **3b–j** starting from the corresponding equimolar mixtures of **1a** and **2b–j**. Products were isolated in high purity without any additional purification procedure.

The use of PS-BEMP was then extended to epoxide **4–7** and the representative phenols **2a**, **2b**, **2d**, and **2g**.

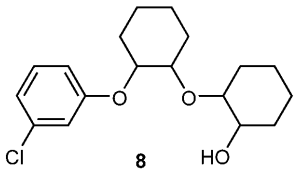
Allyl glycidyl ether (**4**) reacted satisfactorily giving the corresponding products in very good yields and complete β-regioselectivity. Also in the cases of octene oxide (**5**) selected as a representative terminal epoxide, cyclohexene oxide (**6**) as a commonly used bicyclic epoxide, and styrene oxide (**7**) as a representative aryl-substituted epoxide, the corresponding products were isolated in very high yields. Epoxides **5** and **6**, were much less reactive than **1** and **4** and required a higher reaction temperature (up to 80 °C), except in the case of phenol **2a** where 60 °C was sufficient to complete the ring opening process.



Scheme 1. Reaction of **1** with methyl salicylate (**2k**) leading to transesterification by-product **9** and 2,3-dihydrobenzo[*e*]-[1,4]dioxepin-5-one **10**.

As expected, in the case of **5** the regioselectivity of the reaction favored the less substituted β-carbon, while the α-product was the major one in the case of **7**. All the α- and β-isomers were isolated as pure products by silica gel column chromatography.

In the reactions of 3-chlorophenol (**2d**) with cyclohexene oxide (**6**) and styrene oxide (**7**), formation of a side product was observed when equimolar amounts of reactants were used. By-product **8** formed in the case of epoxide **6** could be isolated only in mixture with **2d** and its stereochemistry could not be assigned while its structure was confirmed by representative ^{1}H NMR signals (see Supporting Information) (Figure 1). This product arises from the attack of the



8

Figure 1. By-product formed in the case of the reaction of **6** with **2d**.

ring-opened product to another molecule of epoxide **6**. To avoid formation of this bis-product, we used 2 or 4 equivalents of **2d**, but the amount of **8** formed was approximately identical or even bigger. Instead, the use of 2 equivalents of epoxide did not lead to the formation of **8** and the reaction was completed in 7 h. Excess of cyclohexene oxide (**6**) was removed under reduced pressure, to give the product in 99% yield. In addition, reactions of **6** and **7**, were successfully performed on a 100-mmol scale and in this case it was possible recover the excess of epoxide by distillation in 93% yield.

PS-BEMP has proved to be an efficient catalyst for the phenolysis of epoxides under SolFC and the corresponding β-aryloxy alcohols products were generally prepared in high yields and purity without further purification. In the presence of a reaction medium PS-BEMP is not efficient at all and therefore adoption of SolFC was necessary.

However, addition of an organic solvent (EtOAc) was still necessary at the end of the ring-opening process in order to isolate the products by filtering off the PS-BEMP that is still fully efficient in further processes.

The use of equimolar amounts of reactants, the recovery and reuse of the catalyst allowed the minimization of waste which results in a very low E-factor[14] associated with our protocol.

As an example, in one of the best cases when **1** reacted with **2a** (Table 1, entry 3), the E-factor is 18.6. In the case of the reaction of **7** with **2d**, when the use of 2 equivalents of epoxide was necessary and the isolated yield of the product was 94% (Table 3, entry 17), the E-factor associated with this process was 19.6, and this value becomes 19.1 if we consider that the starting epoxide can be recovered in 93% yield when the process was performed on a large scale (100 mmol) (see Supporting Information).

In order to improve the efficiency of solvent-free conditions, we have set-up a protocol by using a cyclic continuous-flow reactor operating under SolFC on a 100-mmol scale in the case of the reaction of **4** with **2b** (Figure 2, the thermostat box is not showed for clarity).

The reaction mixture at 60 °C was continuously pumped for 60 h through the catalytic amount of solid PS-BEMP until conversion was complete. At this point the pump is left to run in order to recover the final product into the reservoir allowing 21.5 g (75% yield) of 1-allyloxy-3-(4′-bromophenoxy)-propan-2-ol

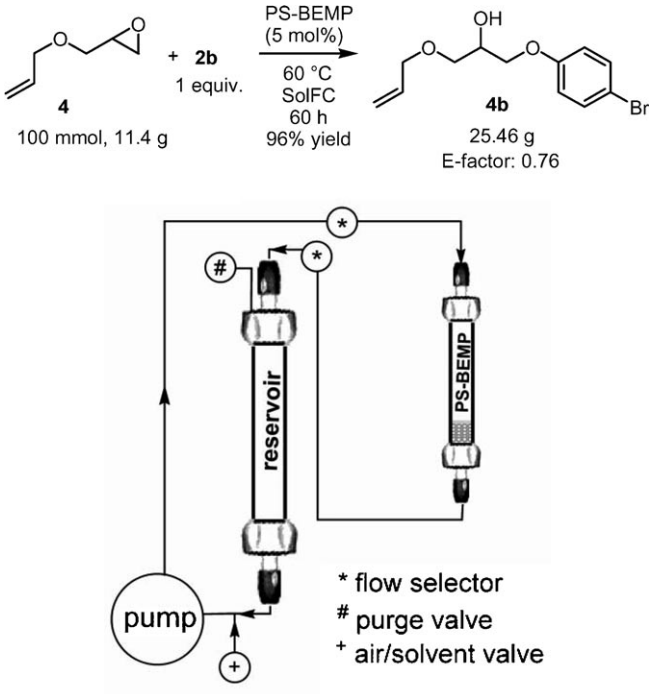


Figure 2. Schematic diagram of the cyclic continuous-flow reactor operating under SolFC.

(**4b**) to be isolated without using any organic solvent at all. At this point, some EtOAc was added in three portions (3×6 mL)[15] to wash the catalyst and the reactor and recover additional 4.0 g of product **4b** to give an overall 96% yield after vacuum removal of the organic solvent.

In this case E-factor was further reduced from the 16.2 obtained under batch conditions to 0.76 obtained by using the SolFC reactor (a reduction of 95%).

The catalyst was completely recovered without problems related to mass loss because it is kept in the sealed glass column all the time.

We have then planned to exploit the catalytic efficiency of PS-BEMP in the phenolysis of epoxide **1** under SolFC for the preparation of 2,3-dihydrobenzo[*e*][1,4]dioxepin-5-one **10** *via* the reaction of **1** with methyl salicylate (**2k**) and subsequent lactonization of **3k** (see Scheme 1). In addition, to reach this goal, we intended also to define a protocol that should allow an easy scaling-up and E-factor minimization.

The reaction conditions previously used (60 °C, 5 mol% of PS-BEMP, SolFC) proved to be efficient also in the case of the phenolysis of **1** with **2k**. However, under the reaction conditions, product **3k** was poorly converted to the desired 2,3-dihydrobenzo[*e*]-[1,4]dioxepin-5-one **10** (18%), and in addition a transesterification between two molecules of **3k** led also to the formation of by-product **9** (5%).

To satisfactorily achieve the preparation of **10**, we have investigated several reaction conditions for realizing the direct lactonization of **3k** and by-product **9** by avoiding any additional protection/deprotection or activation step that would reduce the overall efficiency of the process making more difficult the scaling-up procedures.

Lactonization and esterification reactions are important processes and have been largely investigated to find mild catalysts and efficient conditions for 100% conversion of equimolecular amounts of carboxylic acids and alcohols.[16]

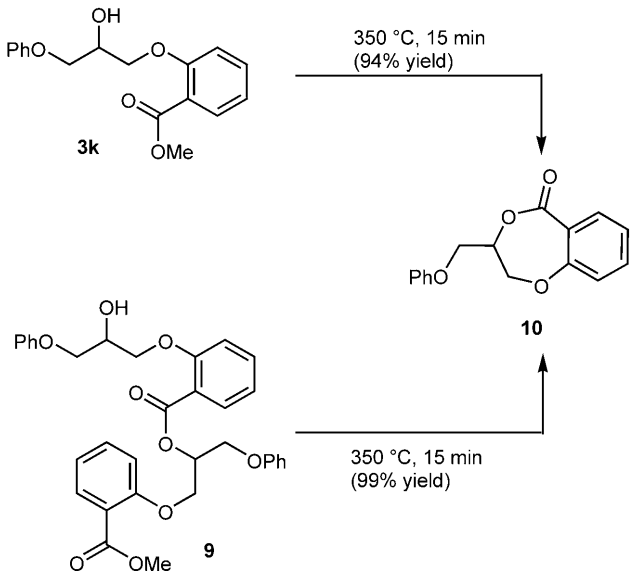
Unfortunately, in our case all the conditions used led to decomposition processes (see Supporting Information).

This somewhat correlates to our earlier observations in the preparation of the benzo[*e*]1,4-oxathiepin-5-one ring, *via* lactonization of hydroxy-thiocarboxylic acids.[12b] In this paper, we reported that thermal treatment was the only efficient method for completing this transformation and to avoid further manipulation of a product coming from the epoxide ring-opening by the corresponding thiol.[12b]

Therefore, thermal treatment was applied to **3k** and to **9** separately. After a long time (40 h) at 200 °C only 60% was converted to **10** while **9** gave no reaction (see Supporting Information).

Raising the temperature to 450 °C for several minutes led to partial conversion of both **3k** and **9** to **10**, proving that also the conversion of **9** to **10** was possible. Prolonging this treatment for longer time (30 min) caused charring of the reaction mixture.

The optimal conditions were found for both substrates at 350 °C for 15 min. Under these conditions



Scheme 2. Optimized lactonization of **3k** and **9** to 2,3-dihydrobenzo[*e*][1,4]dioxepin-5-one **10**.

3k converted in 94% yield while for **9** conversion to **10** was quantitative (Scheme 2).

As alternative, we have also tried to cyclize **3k** by using microwaves (250 W, 200 °C) but after 15 min conversion to **10** was 58% and reduced over the time (1 h, 31% and 2 h, 22%), proving that this approach was not suitable.

Finally, by treating the crude reaction mixture directly coming from the reaction of **1** with **2k** at 350 °C for 15 min, the complete conversion to **10** was achieved and pure 3-phenoxymethyl-2,3-dihydrobenzo[*e*][1,4]dioxepin-5-one (**10**) was obtained in 90% overall yield after purification over a silica gel pad to remove some burned material.

We have then scaled-up and automated the preparation of **10** starting from **1** and **2k** by coupling a cyclic continuous-flow reactor and a flow-through reactor as illustrated in Figure 3 (the thermostat box is not showed for clarity).

At the end of the phenolysis of **1** with **2k**, performed in the cyclic continuous-flow reactor, the resulting reaction mixture was pumped to a 3-meter × 1.2 mm ø wire heated at 350 °C at a constant flow of 0.5 mL min^{-1}.[17]

To completely transfer the remaining reaction mixture of **3k** and **9** from the phenolysis reactor to the heating wire (*ca* 25% of the total), EtOAc was used (3 × 6 mL).[15]

For the success of this large-scale two-step protocol, the choice of the diameter of the tube used for the wires is crucial. Several attempts were made but reproducible results can be obtained only if the tube used has a diameter of at least of 1.0–1.2 mm. In the case of smaller tubes, the solvent used for transferring the final portion of reaction mixture and washing the catalyst and the glass reactor, when suddenly heated at 350 °C causes a very accelerated flow reducing the time of the thermal treatment and therefore resulting in the incomplete conversion to the desired **10**. By using a larger tube this phenomenon is reduced and reproducible results were obtained over three consecutive experiments.

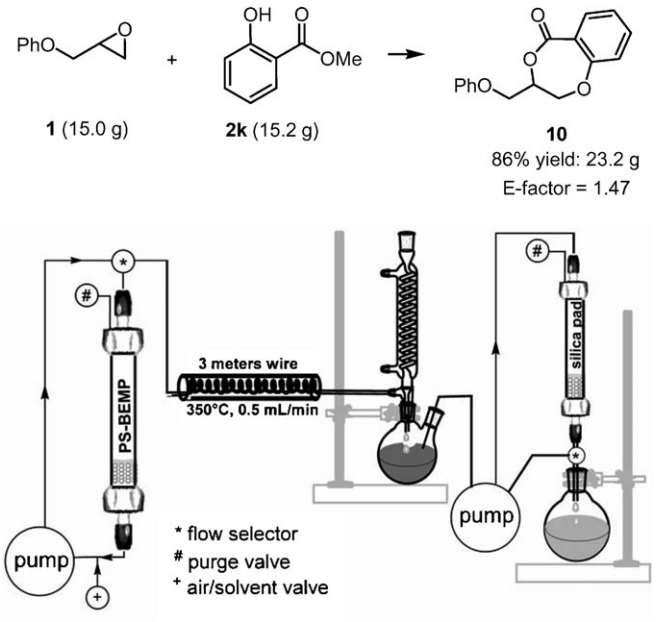


Figure 3. Schematic diagram of the continuos-flow/flow-through reactor for the automated synthesis of 2,3-dihydrobenzo[*e*][1,4]dioxepin-5-one **10**.

At this point, the highly concentrated solution of **10** in EtOAc was flowed through a silica pad. Additional EtOAc was used (3 × 4 mL)[15] to wash the silica. After removal of the organic solvent under vacuum, the pure 3-phenoxymethyl-2,3-dihydrobenzo[*e*]-[1,4]dioxepin-5-one (**10**) was isolated in an overall 86% yield.

The E-factor of this synthetic two-step large-scale procedure for the preparation of **10** is a very good 1.47 (see Supporting Information). Further improvements of the E-factor can be obtained by recovery of the EtOAc by distillation.

Conclusions

In conclusion, we have reported that under SolFC PS-BEMP is an efficient catalyst for the phenolysis of epoxides **1**, and **4–7** with phenols **2a-k**. Excellent yields have been obtained and in most of the cases the final products have been isolated in pure form without any additional purification step.

The efficiency of this protocol is strictly related to the use of SolFC that is necessary for the feasibility of the reactions and also allows us to minimize the use of organic solvent. As a consequence waste associated with the batch protocol is very little and E-factors are significantly small. Further improvements were obtained by setting up a cyclic continuous-flow reactor operating under SolFC that allowed us to further reduce the E-factor by 95% compared to batch conditions.

Finally, we have exploited the phenolysis protocol by realizing the synthesis of 2,3-dihydrobenzo [1,4]dioxepin-5-one **10**. Optimization of this process was achieved by setting up an automated multistep continuous-flow reactor based on the phenolysis of **1** with **2k** and subsequent lactonization by thermal treatment of the reaction mixture. 3-Phenoxymethyl-2,3-dihydrobenzo[*e*][1,4]dioxepin-5-one (**10**) was isolated in pure form and on a multigram scale in a very satisfactory 86% overall yield. The E-factor of 1.47 associated with this procedure makes the synthesis of this heterocycle highly environmentally efficient.

Experimental Section

General Remarks

All chemicals were purchased and used without any further purification. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100.6 MHz, respectively, using a convenient deuterated solvent (reported in the characterization charts) and the residual peak as internal standard, or TMS in the case of $CDCl_3$. Column chromatographies were performed by using silica gel 230–400 mesh and eluting as reported in the following characterization charts. PS-BEMP was purchased from Aldrich.

Compounds **3a**, **b**,[5f] **3d**,[18] **3e**,[19] **3f**, **g**,[5f] **4a**,[20] **4b**,[19] **5a** (β-product),[21] **5b** (β-product),[21] **6a**, **b**,[22] **6g**,[22] **7a** (α- and β-products),[23] **7g** (α- and β-products),[24] are known compounds, while compounds **3c**, **3h**, **3i**, **3k**, **4d**, **4g**, **5a** (α-product), **5b** (α-product), **5d** (α- and β-products), **5g** (α- and β-products), **6d**, **7b** (α- and β-products), **7d** (α- and β-products), **8**, **9**, and **10** are new compounds.

Characterization data and copies of the ^{1}H and ^{13}C NMR spectra for all compounds **3a–k**, **5a–d**, **6a–d**, **7a–d**, and **8–10** are given in the Supporting Information.

Representative Batch Experimental Procedure

In a screw-capped vial equipped with a magnetic stirrer PS-BEMP (0.048 g, 0.1 mmol, 2.1 mmol/g), 4-bromophenol (**2b**) (0.346 g, 2.0 mmol) and phenyl glycidyl ether (**1**) (0.300 g, 2.0 mmol) were consecutively added and the resulting mixture was left under stirring at 60 °C. After 34 h EtOAc (2 mL) was added and the reaction mixture filtered. The catalyst was washed using additional 4×2 mL of EtOAc. Organic layers were collected and solvent was removed under vacuum to give 1-(4-bromophenoxy)-3-phenoxypropan-2-ol (**3b**) as a white solid; yield: 0.641 g (99%).

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