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A catalytic approach to the base-promoted reaction of epoxides with activated methylenes

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ABSTRACT

This contribution reports the results obtained in the definition of a catalytic method for the nucleophilic ring opening of epoxides by activated methylenes promoted by a polymer-supported base. The attention has been focused on the use of polymer supported bases and the best results have been obtained by using 4-(dimethylamino)pyridine (PS-DMAP) and 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine both on polystyrene (PS-BEMP). Solvent-free conditions has been essential for reaching a sufficient reactivity to realize this process, in fact when a reaction medium is used, the processes are almost unfeasible.

1. Introduction

Organic bases are promising alternatives to metal-containing catalysts for a wide range of reactions.[1] In addition, they can be securely anchored on a solid support, solving the problem of their recovery and reuse and simplifying product isolation and purification.[2]

Our research is currently focused on the use of solid-supported catalysts[3] and we have showed that the efficiency of a polystyrene-supported basic or ionic catalyst is significantly improved under solvent-free conditions (SolFCs). The absence of a reaction medium is an effective strategy to regain the catalytic efficiency generally lost when a catalyst is anchored on a solid support. In fact, it is noteworthy that in several cases, the use of SolFC is necessary for the success of the process that can be dramatically slow or practically unfeasible by using an organic solvent.[3b,c,e] Highlights of our methodologies were chemical efficiency, simplified experimental procedures, and the minimization of the amount of organic solvent used which is employed only to facilitate the separation of the product from the heterogeneous catalyst.[3b–f]

Epoxides are useful reagents in organic synthesis, they generally react stereospecifically with several nucleophiles giving highly-functionalized molecules that can be further manipulated.

The nucleophilic ring-opening reactions of epoxides can be promoted by either acidic or basic catalysts, and efficient nucleophiles are heteroatomic reactants, such as water, alcohols, thiols, amines, halides, or pseudohalides.[4] In addition, they are easily prepared from a variety of substrates.

We have developed several protocols for both the preparation and the ring opening of epoxides by heteroatomic nucleophiles such as azide, halides, amines, and thiols, proving that the use of alternative reaction media such as water[5] and SolFC[6,3f,h] is crucial for improving the efficiency of these processes. In our previous works, we have not applied our strategy to the reactions of epoxides with activated methylenes.

Organometallic reagents like alkyllithium and Grignard reagents are known to undergo addition reactions to simple epoxides, but these reactions are complicated by a variety of competing processes,[7] such as deprotonation and disproportion, often requiring harsh conditions and the use of additives such as BF_3 and copper salts.[8]

Activated methylenes, such as 1,3-dicarbonyl compounds, can be easily deprotonated and alkylated and their reactions allow the access to highly functionalized compounds to be used as versatile intermediates to prepare complex molecules. Surprisingly, there are few examples that report the reaction of carbon nucleophiles (malonate, cyanoacetate, and acetylacetate esters) with epoxides. In this context, the reaction of styrene oxide with dialkyl malonates to give α,γ-substituted γ-lactones through a base-promoted ring-opening reaction followed by a lactonization of the resulting γ-hydroxy ester has been reported.[9] These reactions are usually performed in refluxing ethanol, with an overstoichiometric amount of base (NaOH or Na) giving moderate yields. The use of other carbon nucleophiles such as 1,3-diketones like acetylacetone or α-substituted malonate esters has never been reported.

Although it has been reported that more reactive aziridines smoothly react with activated methylenes in the presence of a catalytic amount of 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-

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perhydro-1,3,2-diazaphosphorine (BEMP),[10] to the best of our knowledge there are no reports of base-catalyzed protocols for the reaction of carbon nucleophiles with epoxides.

In this Letter, we present our results on the approach to a catalytic procedure for the reaction of activated methylenes with epoxides. Following our current interest based on the use of solid-supported catalysts under SolFC, we have compared the catalytic efficiency of different polystyrene-supported bases in the ring-opening reaction of epoxides **1a–h** by acetylacetone (**2**), dimethylmalonate (**5**), dimethyl methylmalonate (**7**), and dimethyl bromomalonate (**10**) under SolFC. Activated methylenes such as **2**, **7**, and **10** have never been used before as nucleophiles in epoxide ring-opening reactions.

According to our previous works, we have chosen as representative solid bases the polystyrene-supported 4-(dimethylamino)pyridine (PS-DMAP), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD),[3a–f] and the very strong Schwesinger's phosphazene base 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP).[3b,11] For all these bases, the solid polymeric support was 200–400 mesh polystyrene co-polymerized with 2% of divinylbenzene.

As a weak nucleophilic base a solid source of fluoride, Amberlyst-F (Amb-F)[3a,c,e,12] was chosen as supported organic base.

2. Results and discussion

We have initially studied the reaction between *O*-phenyl glycidol (**1a**) and acetylacetone (**2**), in equimolar quantities, under solvent-free conditions, at 80 °C, and in the presence of 5 mol % of PS-BEMP, PS-DMAP, PS-TBD, or Amb-F (Table 1).

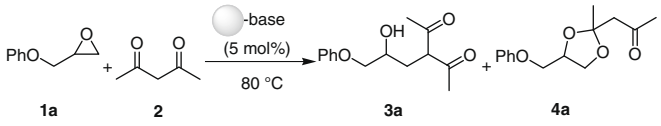
The epoxide **1a** reacted exclusively at the β-position, but together with the expected γ-hydroxydiketone product **3a**, the 1,3-dioxane **4a** was also detected. The latter comes from the attack of the harder oxygen of the acetylacetone anion and consequent ring closure by intramolecular Michael addition (Fig. 1). The ring-opening reaction was efficiently catalyzed by PS-DMAP, PS-TBD, and PS-BEMP, (Table 1, entries 1, 2, and 4) while the mild, ionic base Amb-F (Table 1, entry 3) was less active. The phosphazene base PS-BEMP was the best catalyst for this reaction, giving complete conversion of **1a** after 18 h, probably because of its stronger basicity.[11] PS-DMAP revealed to be more active than PS-TBD, despite DMAP being less basic than TBD, which is probably due to its minor steric hindrance.

In the presence of toluene or acetonitrile as reaction medium, PS-BEMP showed a reduced activity, but the products' distribution was not significantly influenced by the polarity of the medium (Table 1, entries 5 and 6).

The use of PS-BEMP was then extended to epoxides **1b–h**. The results are illustrated in Table 2.[13]

Under SolFC and with 5 mol % of PS-BEMP, at 80 °C, acetylacetone (**2**) was able to react only with activated epoxides such *O*-protected glycidols and chloromethyl epoxide (**1a** and **1d–g**). Under these reaction conditions, *n*-octene oxide (**1c**) did not yield any product, while styrene oxide (**1b**) decomposed. Glycidols functionalized with a leaving group such as **1h** were known to react with activated methylenes in the presence of a stoichiometric quantity of base, giving a nucleophilic substitution followed by ring-open-

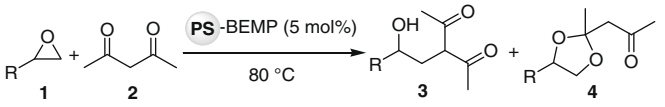
Table 1
Ring opening of epoxide **1a** with acetylacetone (**2**) under SolFC at 80 °C catalyzed by organic supported bases

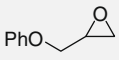
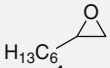
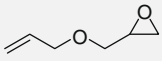
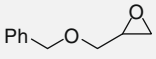
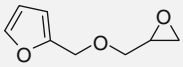
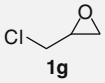
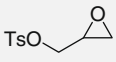


Entry	Medium	Base	*T* (h)	Conversion[a] (%)	**3a**/**4a**
1	SolFC	PS-DMAP	24	92	72/28
2	SolFC	PS-TBD	24	86	79/21
3	SolFC	Amb-F	24	54	76/24
4	SolFC	PS-BEMP	18	>99	71/29
5	PhMe(0.5 M)	PS-BEMP	24	7	57/43
6	MeCN(0.5 M)	PS-BEMP	24	13	77/23

[a] The remaining material was unreacted **1a** and **2**; measured by NMR analyses.

Table 2
PS-BEMP-catalyzed ring-opening reaction of epoxides **1a**–**h** by acetylacetone (**2**) under SolFC at 80 °C



Entry	Epoxide	*T* (h)	Yield[a] (%)	3/4[b]
1	 **1a**	18	92	71/29
2	 **1b**	24	–	–
3	 **1c**	48	–	–
4	 **1d**	24	72	72/28
5	 **1e**	48	80	66/34
6	 **1f**	48	80	64/36
7	 **1g**	24	75	63/37
8	 **1h**	24	–	–

[a] Overall isolation yield of both **3** and **4**.
[b] Measured by NMR analyses.

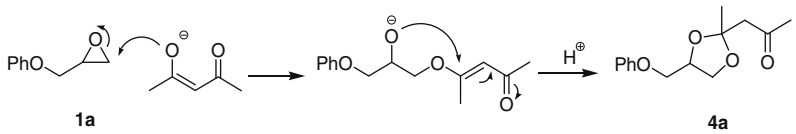
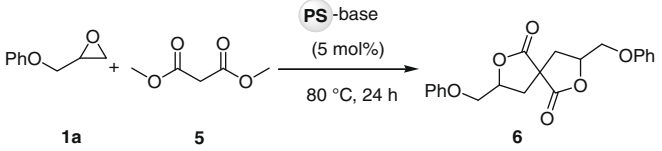


Figure 1. Formation of 1,3-dioxane **4a**.

Table 3
Ring opening of epoxide **1a** with dimethyl malonate (**5**) under SolFC at 80 °C catalyzed by organic supported bases



Entry	PS -Base	Yield of **6** (%)
1	PS-DMAP	45
2	PS-TBD	10
3	PS-BEMP	89
4	PS-BEMP in PhMe	—

ing reaction with the formation of the corresponding cyclopropanes.[10a,14] In our case we did not observe any reaction.

It was also found that *O*-phenyl glycidol (**1a**) reacted under SolFC at 80 °C in 24 h with dimethyl malonate (**5**), in equimolar quantities and in the presence of a supported base, giving spirolactone **6**. These results are illustrated in Table 3.

According to the previous results, PS-BEMP was the best catalyst, giving product **6** in 89% yield under SolFC, while in toluene the reaction did not occur at all (Table 3, exp 3 vs 4). Again, PS-DMAP was more active than PS-TBD to promote the ring-opening reaction (Table 3, exp 1 vs 2). With the intention of isolating the product γ-lactone coming from the attack of **5** to **1a** and consequent lactonization, various reaction conditions and **1a**/**5** ratios were tested but with no result. This outcome is probably due to the higher acidity of the γ-lactone compared to that of dimethyl malonate (**5**)[15] that under reaction conditions is promptly deprotonated reacting as soon as it is formed with another molecule of **1a**.

To avoid the formation of the corresponding spiro product, α-substituted malonates **7** and **10** were considered. Initially, we have studied the reaction between *O*-phenylglycidol (**1a**) and dimethyl methylmalonate (**7**) under SolFC in the presence of PS-DMAP or PS-BEMP (Table 4).

Surprisingly, PS-DMAP revealed to be an active catalyst, while PS-BEMP showed no catalytic activity. This can be tentatively explained by invoking steric factors considering the bulkiness of PS-BEMP. PS-DMAP promoted this reaction under SolFC at 80 °C to give a mixture of **8** and **9** that was first purified and treated with LiI in aqueous DMF to give pure α-lactone **9** as a mixture of diastereoisomer with an overall 44% yield.

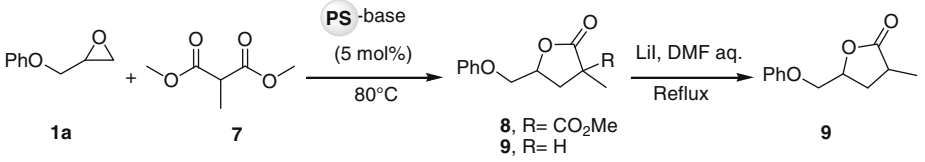
Under the same conditions, the reaction between *O*-phenylglycidol (**1a**) and dimethyl bromomalonate (**10**) gave different results (Table 5). Bromomalonate anion reacted with **10** and after subsequent elimination of HBr led to tetramethyl ethene–tetracarboxylate (**12**). Epoxide **1a** under these conditions in the presence of HBr gave the corresponding bromohydrine (**11**).

The stronger base PS-BEMP was again the best catalyst for this transformation, giving shorter reaction time, while yields were similar to those obtained with PS-DMAP.

3. Conclusions

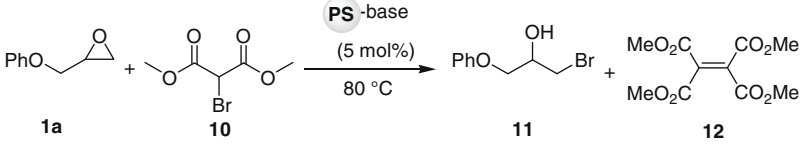
In conclusion, we have investigated the nucleophilic ring opening of epoxides by activated methylenes **2**, **5**, **7**, and **10** under solvent-free conditions by using polystyrene-supported bases as catalysts and stoichiometric quantities of reagents. The best results have been obtained by using 5 mol % of PS-BEMP or PS-DMAP. Swelling problems, related to the access to reactive sites of the polymer-supported catalysts, can be overcome under SolFC, where, apparently, the reactants flow through the polymer network more easily than in the presence of an additional reaction medium. These results are promising and represent the first effort to define

Table 4
Ring opening of epoxide **1a** with dimethyl methylmalonate (**7**) under SolFC at 80 °C in the presence of organic supported bases



Entry	PS -Base	*T* (h)	Yield of **9a** (%)
1	PS-DMAP	24	44
2	PS-BEMP	48	—

Table 5
Ring opening of epoxide **1a** with dimethyl bromomalonate (**10**) under SolFC at 80 °C catalyzed by organic supported bases



Entry	PS -Base	*T* (h)	Yield of **11**[a] (%)	Yield of **12**[b] (%)
1	PS-DMAP	120	83	70
2	PS-BEMP	36	79	82

[a] Isolation yield calculated on **1a**.
[b] Isolation yield calculated on **10**.

a catalytic approach to this type of reactions that are generally performed by using large amounts of base. Further studies are directed to the preparation of novel solid supports to improve the efficiency of this process.

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Supplementary data

Supplementary data (all the procedures and the spectroscopic data for known (**8**, **11** and **12**) and new compounds (**3a**, **3d–g**, **4a**, **4d–g** and **6**)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.055.

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12. Amberlite IRA900F is a trimethylammonium fluoride on macroreticular polystyrene resin which is commercially available from Aldrich as 'Fluoride on polymer support' or as 'Fluoride on Amberlyst A-26'. Commercially available Amb-F is a hygroscopic solid which contains ca. 20 wt % of water. In general we have used water-free Amb-F which was obtained by drying the commercial product under vacuum.
13. *General procedure*: The reaction of **1a** with **2**: In a screw-capped vial equipped with a magnetic stirrer, PS-BEMP (0.070 g, 0.15 mmol, 2.1 mmol/g), phenyl glycidyl ether (**1a**) (0.405 g, 3 mmol), and acetylacetone (**2**) (0.306 mL, 3 mmol) were consecutively added and the resulting mixture was left under stirring at 80 °C. After 18 h AcOEt (2 mL) was added, the catalyst was filtered off and the solvent was removed under vacuum. The crude mixture was purified by silica gel flash chromatography (eluent: Petroleum ether/EtOAc, 8:2) to give two products (**3a** and **4a**) as a colorless oil (0. 687 g, 92% total yield).
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