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A Catalytic Approach to the Metal-Free Reaction of Epoxides with Ketene Silyl Acetals for Accessing γ-Lactones

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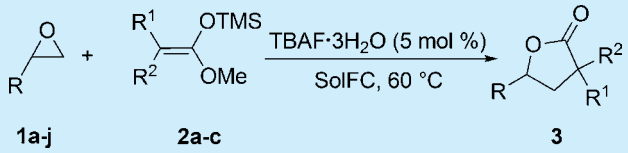
Supporting Information

ABSTRACT: The first catalytic approach to the nucleophilic addition of silyl ketene acetals **2** to epoxides **1** is reported. The defined protocol is metal-free using tetrabutylammonioum fluoride as the catalyst. It works in a very efficient manner under solvent-free conditions (SolFC) allowing γ-lactones **3** to be directly obtained with high regioselectivities and yields.



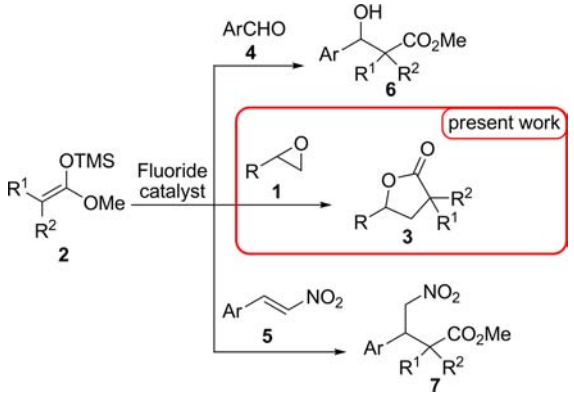
Epoxides **1** are valuable intermediates in organic synthesis, and their preparation and use have been widely investigated. In particular, the nucleophilic addition to form 1,2-disubstituted products has been one of the most thoroughly studied transformations of these compounds.[1] Our group developed several protocols for the ring opening of epoxides by heteroatomic nucleophiles such as azido and halide ions, amines, and thiols, proving that the use of alternative reaction media such as water[1a,2] and SolFC[3] is often crucial for improving the efficiency of these processes allowing in some cases unique chemical outcomes. In the case of carbon nucleophiles our research was limited to activated methylenes.[3d]

The reactions of epoxides and carbon nucleophiles is a truly important transformation in the synthesis of biologically significant targets.[1f,h,4] In particular, our attention has been directed to the ring opening of epoxides **1** with ketene silyl acetals (KSA) **2** which is a very interesting process that allows the straightforward preparation of γ-lactones,[5] a commonly important class of widely biologically active compounds (Scheme 1). The importance of this process prompted us to investigate the possibility of defining a catalytic protocol (preferentially metal-free) for the reactions of epoxides and carbon nucleophiles such as ketene silyl acetals (KSA).

To date, few reports exist on this process and in all cases Lewis acids such as $BF_3{\cdot}OEt_2$,[6] $TiCl_4$,[7] and $LiClO_4$[8] need to be used as promoters (1.5–3.0 equiv). The main limitations are just related to the use of overstoichiometric quantities of nucleophiles and Lewis acids, to the need for working at low temperatures, and also to the substrate scope that is limited to a specific class of epoxides (epihalohydrins, 1,1-dibromo-3,4-epoxy-1-alkenes).

Considering our ongoing studies in the field of fluoride catalysis to activate silylated nucleophiles,[3a,9] we have also applied this approach to the Si–O bond activation of KSA **2** that may allow the reactions with a variety of electrophiles and access to different classes of target molecules.

Scheme 1. Fluoride Activation of Ketene Silyl Acetals Si–O Bonds Investigated by Our Group



Examples of Si–O bond activation were provided by our group in the reactions that involved the nucleophilic addition of methyl trimethylsilyl dimethylketene acetal **2a** to aldehydes **4** (Mukaiyama aldol reaction)[9d,e] and to β-nitrostyrenes **5** (Michael-type addition)[9f] to synthesize β-hydroxyesters **6** and γ-nitroesters **7** respectively (Scheme 1).

We have planned the synthesis of γ-butyrolactones **3** via addition of epoxides **1** with KSA **2** and subsequent *in situ* cyclization of the resulting adduct. Our goal is to combine solvent-free conditions (SolFC) and fluoride catalysis to both reach sufficient reactivity and avoid large quantities of metal catalysts.

In this work we report our simple and efficient protocol for the metal-free synthesis of several γ-lactones **3** based for the first time on a catalytic approach.

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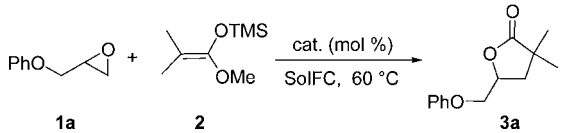
Table 1. Addition of KSA 2a to Phenyl Glycidyl Ether (1a) under SolFC Using Different Catalysts[a]



1a 2 3a

entry	catalyst (mol %)	time (h)	conversion[b] (%)
1	–	96	0
2	KF (5)	24	0
3	KF/alumina (5)	24	0
4	TBAF·3H$_2$O (5)	0.17	99[c]
5	TBAF/silica (5)	0.17	88[d]
6	Amb-F (5)	96	76
7	Amb-F[e] (5)	96	88
8	Amb-F[e] (20)	96	99
9	TBAF·3H$_2$O (0.5)	1	99
10	TBAF/silica (0.5)	1	50[f]

[a]Reaction conditions: epoxide **1** (1 mmol), KSA **2** (1.5 mmol), 60 °C. [b]Determined by ^{1}H NMR analysis. [c]Pure product **3a** was isolated in 92% yield; the reaction performed under the same conditions but in organic solvents (2 mL/mmol) was slower giving incomplete conversions to **3a**, due to the inevitable consumption of KSA. [d]Complete conversion was reached after 1 h. [e]Dried Amb-F. [f]Complete conversion was reached after 7 h.

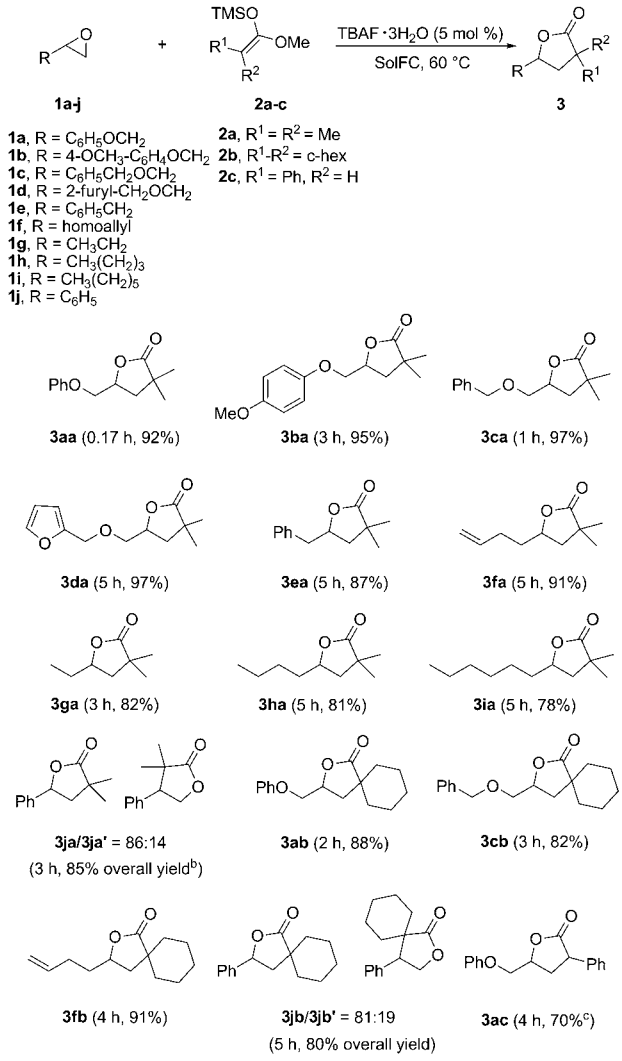
We started our investigation with the model reaction between phenyl glycidyl ether **1a** and KSA **2a** in SolFC at 60 °C. The results are summarized in Table 1.

By this preliminary screening we wanted to test various fluoride sources, organic and inorganic, supported and unsupported. As it is evident from the data in Table 1, the best results were accomplished with the use of 5 mol % of "free" tetrabutylammonium fluoride (TBAF)·3H$_2$O or TBAF on silica (Table 1, entries 4–5). KF as an inorganic fluoride sources, was unable to promote the reaction (Table 1, entries 2–3). Commercially available polymer-supported ammonium fluoride (Amb-F),[10] which is a hygroscopic solid showed better efficiency if dried under vacuum (Table 1, entry 6 vs 7). To obtain a complete conversion of the epoxide **1a** to the desired product **3a**, harsh reaction conditions (20 mol % of dry Amb-F and 4 days of reaction time) are required (Table 1, entry 8). In all cases, the reaction revealed to be completely regioselective with the nucleophilic attack at the β-carbon of the epoxide, according to the expected S_N2 mechanism. Moreover, and somehow according to our previous related results in a related process for the synthesis of benzo[*e*]1,4-oxathiepin-5-ones from epoxides under SolFC,[11] in our reactions we observed only the formation of γ-butyrolactone **3a** deriving from the ring opening of the epoxide **1a** and direct in situ cyclization. This result differs from the previously mentioned procedures,[6,7] for which, after Lewis acid promoted ring opening of the epoxide, addition of *p*-TsOH to the reaction mixture is needed to obtain the cyclized product **3**. This result suggests the double role of fluoride as a Si–O bond activator in the first step and then as a basic catalyst for the lactonization step.

In our case the use of the fluoride catalyst at 60 °C paved the way toward a straightforward experimental protocol and also to a very efficient synthetic tool that does not require the use of wasteful overstoichiometric amounts of promoters and additional additives.

Considering the value of using supported catalysts instead of homogeneous ones, we tried to recover and reuse TBAF on silica,

Scheme 2. TBAF·3H$_2$O Catalyzed Ring Opening of Epoxides 1a–j with KSA 2a–c[a]



[a]Reaction conditions: epoxide **1** (2 mmol), KSA **2** (3 mmol), catalyst (5 mol %), 60 °C. [b] 3 equiv of nucleophile were used. [c] The lactone product was obtained as a 1:1 mixture of diastereoisomers (^{1}H NMR analyses), in 70% overall yield, after an additional 1.5 h at 270 °C.

but unfortunately after the first recycle run no reaction at all was observed. Elemental analysis of the recovered catalyst after the first run exhibited only traces of nitrogen content, revealing that catalyst TBAF on silica, which is not covalently linked to the inorganic support, in the course of the reaction is completely leached. Therefore, also in this case the reaction proceeds as in the presence of "free" TBAF. This result also accounts for the unusual comparable activity of the supported and the homogeneous catalysts.

On the basis of our previous work on polymer-supported fluoride catalysts,[9] we have also compared different heterogeneous fluoride sources prepared by our group, differing in the support (gel-type, porous, and macroporous) and in the ammonium tag, but none of these catalysts allowed the same results as in the case of TBAF (see Table S1 in the Supporting Information).

To verify the application range, the optimized protocol (Table 1, entry 4) was extended to epoxides **1b–j**. In all the cases, with both aromatic and aliphatic epoxides, only the corresponding

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lactone products were isolated in high to excellent yields (78−97%). Complete β-regioselectivity was achieved except for styrene epoxide **1j**. As expected, in this case a mixture (86:14) of the two regioisomers **3ja** and **3ja′**, deriving from the nucleophilic attack at the β- and α-position respectively, has been isolated (Scheme 2).

Our procedure was also tested with two additional KSA **2b** and **2c**. Despite its higher steric hindrance, **2b** reacted with epoxides **1a**, **1c**, **1f**, **1j** in short times (2−5 h) giving only cyclized products **3ab**, **3cb**, **3fb**, **3jb**/**3jb′** (81:19) in good yields (80−91%). KSA **2c** behaved differently, and a different outcome was observed. In fact, after 4 h at 60 °C, the reaction with **1a** lead to the formation of the ring opened product deriving from the attack of **2c** to the epoxide **1a**. To obtain the desired lactonization product **3ac**, a thermal treatment of the reaction mixture was needed and the γ-lactone was prepared in 70% yield after an additional heating at 270 °C for 1.5 h (Scheme 2).

In conclusion, for the first time we have reported a catalytic approach to the reaction of epoxides **1** with KSA **2**. TBAF·3H_2O was found to be the most efficient fluoride catalyst, and the efficiency of the process could be reached by adopting SolFC. The general procedure described herein can be applied to both aryl and alkyl epoxides leading in all cases to the preparation of γ-lactones **3** in good to excellent yields. Moreover, the use of the fluoride catalyst with SolFC allowed the final products to be obtained without any additives (i.e., *p*-TsOH for the lactonization of the epoxide ring-opening product).

The chemical efficiency, simple experimental procedure, absence of metal species, and use of an inexpensive and mild catalyst make this process particularly attractive. Further studies will be devoted to the design and synthesis of novel and more efficient heterogeneous fluoride sources to be used as recoverable catalysts.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data and copies of the ^{1}H and ^{13}C NMR spectra for all compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) 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".

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