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Efficient and regioselective ring-opening of arylaziridines with alcohols, thiols, amines and *N*-heteroaromatic compounds using sulphated zirconia

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ABSTRACT

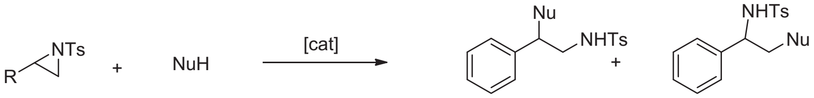
Sulphated zirconia is an efficient catalyst for the regioselective ring-opening of aryl-substituted aziridines. This heterogeneous catalyst can be used several times without loss of activity and is compatible with a variety of acid sensitive and slightly basic nucleophiles.

The interest of aziridines as valuable intermediates in synthetic organic chemistry[1] is associated to their regioselective ring-opening, which is particularly interesting in the case of asymmetrically substituted aziridines. Both processes, namely aziridination and ring-opening, constitute an important tool in synthetic organic chemistry, and a large variety of biologically important compounds have been prepared using this methodology.[2] However, the ring-opening of aziridines presents some limitations: (i) hazardous or expensive reagents are required, (ii) tedious workup procedures are necessary, (iii) in most cases an excess of nucleophile is required, and (iv) in some cases drastic reaction conditions have to be used.

In practice, aziridines are commonly opened using Lewis acids in homogeneous phase such as $Cu(OTf)_2$,[3a,b] $CeCl_3$,[3c] $LiClO_4$,[3d] $ZnCl_2$,[3e] $Sn(OTf)_2$,[3f,g] $BF_3{\cdot}OEt_2$,[3f] $Sn(OTf)_2$-$BF_3{\cdot}OEt_2$,[3g] $Sc(OTf)_3$,[3h] $[Ag(COD)_2]PF_6$,[3i] and $InCl_3$[3j,k] (Scheme 1).

Recently, the use of solid acids such as ammonium-12-molybdophosphate,[4a] phosphomolybdic acid,[4b] or montmorillonite[4c] has been studied. These solid acids are expected to exhibit several advantages over homogeneous reagents in chemical industry processes: (i) an easy separation from the reaction mixture potentially allowing continuous flow operation, (ii) the possibility of regeneration of the solid catalyst, (iii) they are not corrosive for the reaction vessel, and (iv) they avoid environmental issues in terms of disposal of the used catalyst.[5]

The superacid activity of sulphated zirconia[6] makes it an excellent candidate as catalyst for the ring-opening of aziridines. An additional advantage of zirconia is that the acidity of this material can be modulated, opening the possibility to also fine tune its activity as catalyst. In this context, Reddy and co-workers have demonstrated that sulphated zirconia catalyzes the ring-opening of aryl- and also aliphatic-aziridines with thiols and isothiocyanates (Scheme 1, NuH = R′SH) with excellent regioselectivities and yields.[6c] Herein, we show that sulphated zirconia of controlled acidity is a selective catalyst for the ring-opening of aryl-*N*-tosylaziridines with a large variety of nucleophiles, and that under the reaction conditions, many functional groups are compatible.



Scheme 1. Nucleophilic opening of tosylaziridines.

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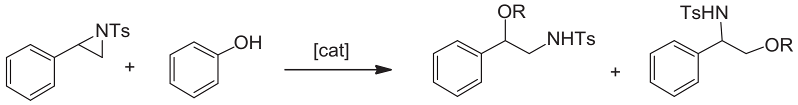
Table 1
Opening of aziridine **1** with phenol. Optimization of reaction conditions[a]



1 **2** **3** R=Ph **4** R=Ph
5 R=H **6** R=H

Entry	Catalyst loading (%)	Time (h)	Conv[c,d] (%)	Ratio[c,d,e] (**3** + **4**)/(**5** + **6**)
1	20	2	>98	80:20
2	10	2	>98	85:15
3	5	3	>98	90:10
4[b]	5	3	>98	>98:<2
5[b]	2.5	12	64	>98:<2

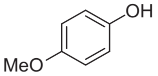
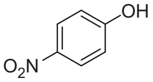
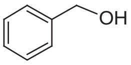
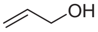
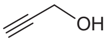
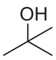
[a] 0.1 M in CH_2Cl_2. The reaction was run at room temperature and it was monitored by TLC.
[b] The catalyst was kept at 110 °C before use.
[c] As average of at least two experiments.
[d] Determined by ^1H NMR.
[e] Ratio 3:4 = 1:1.

In a first series of experiments, the catalyst loading of the sulphated zirconia to open aziridine **1** with phenol was optimized.[7,8] A catalyst loading of 5% was necessary to obtain the product in a quantitative conversion at room temperature in 3 h (Table 1). However, together with the expected products **3** and **4**, significant amounts of the hydrolysed products **5**, **6** were obtained (Table 1, entries 1–3). The formation of products resulting from the hydrolytic opening was suppressed by storing zirconia at 110 °C before use (Table 1, entries 4 and 5). In all cases, a 1:1 ratio of compounds **3** and **4** was obtained.

After these preliminary attempts, we treated aziridine **1** with different aryl, alkyl, allyl, or propargyl alcohols as nucleophiles under the optimized conditions (Table 2). *p*-Methoxy- and *p*-nitrophenol afforded the ring-opening products in quantitative conversions and moderate regioselectivities; obtaining a mixture of products **7**, 15 and **8**, 16 in a 64:36 and 71:27 ratio, respectively (Table 2, entries 1 and 2). Benzylalcohol afforded a complete conversion in a similar reaction time and in this case the selectivity increased to 83:17, compound **9** being the major product, resulting from the nucleophilic attack at the benzylic position of the phenylaziridine (Table 2, entry 3). Methanol, allyl-, and propargyl alcohol also gave quantitative conversion and compounds **10**, **11**, and **12** were obtained in excellent yields and interestingly, in high regioselectivities (>87:<13) (Table 2, entries 4–6), showing that the reaction conditions

Table 2
Opening of aziridine **1** with alcohols and phenols[a]

1 **7-14** **15-22**

Entry	Nucleophile (ROH)	Product	Conv[b,c] (%)	Selectivity[b,c] (**7**–**14**):(**15**–**21**)	Yield[d] (%)
1		**7**, **15**	>98	64:36	54
2		**8**, **16**	>98	73:27	67
3		**9**, **17**	>98	83:17	73
4	MeOH	**10**, **18**	>98	>98:<2	97
5		**11**, **19**	>98	96:4	90
6		**12**, **20**	>98	88:12	83
7		**13**, **21**	78	87:13	60
8[e]	H_2O	**14**, **22**	65	80:20	42

[a] 0.1 M in CH_2Cl_2, catalyst was kept at 110 °C before using. The reaction was run at room temperature and it was monitored by TLC.
[b] Determined by ^1H NMR.
[c] As average of at least two experiments.
[d] Isolated yield of major product (**7**–**14**).
[e] The reaction was run in THF.