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An efficient protocol for regioselective ring opening of epoxides using sulfated tungstate: application in synthesis of active pharmaceutical ingredients atenolol, propranolol and ranolazine

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ABSTRACT

Sulfated tungstate was found to be a new and highly efficient catalyst for opening of epoxide rings by amines to give β-amino alcohols with high regioselectivity. Various advantages associated with this novel and environmental friendly protocol include solvent-free conditions, short reaction times, high product yields, simple workup procedure and easy recovery and reusability of the catalyst. This protocol has been applied for the synthesis of active pharmaceutical ingredients atenolol, propranolol and ranolazine.

Epoxides are well-known carbon electrophiles capable of reacting with several nucleophiles to provide 1,2-difunctional products. Regioselective ring-opening of epoxides with amines is an important reaction for synthetic organic and medicinal chemists as the resultant β-amino alcohols represent a wide range of β-adrenergic blockers (Fig. 1) used in the management of cardiovascular disorders.[1] The versatility of this transformation is well recognized, as it constitutes a key step the for synthesis of β_2-adrenoceptor agonists,[2] anti-HIV agents,[3] glycosidase inhibitor,[4] 4-demethoxydaunomycine,[5] antimalarial agents,[6] liposidomycin B class of antibiotics,[7] taxoid side chain,[8] protein kinase C inhibitor balanol,[9] naturally occurring brassinosteroids[10] and a wide range of biologically active natural and synthetic products,[11] unnatural amino acids[12] and chiral auxiliaries for asymmetric synthesis.[13]

Classical synthetic approaches towards β-amino alcohols involve heating of epoxides in the presence of excess of amines. There are several limitations to this classical approach such as, requirement of elevated reaction temperatures in case of less reactive amines, and lower reactivity arising out of sterically crowded amines/epoxides. In addition, these reactions are accompanied by poor regioselectivity of the ring opening. To overcome these problems, several profitable promoters or catalysts for ring opening of epoxides have been reported. These include phosphomolybdic acid, (PMA)-Al_2O_3,[14] $(TBA)_4PFeW_{11}O_{39}\cdot 3H_2O$,[15] silica gel,[16] Amberlite,[17] Mesoporous aluminosilicate,[18] sulfamic acid,[19] montmorillonite K10,[20] sulfated zirconia,[21] zinc(II) and copper(II),[22] DIPAT,[23] *N*,*N*-bis[3,5bis(trifluoromethyl)phenyl] -thiourea,[24] $[Ti(o\text{-}i\text{-}pr)_4]$,[25] trifluoroethanol,[26] metal triflates such as $Sn(OTf)_2$,[27] $Sm(OTf)_3$,[28] $Al(OTf)_3$,[29] $Er(OTf)_3$,[30] metal halides such as $InCl_3$,[31] $BiCl_3$,[32] $SbCl_3$,[33] $ZnCl_2$,[34] $InBr_3$,[35] $CoCl_2$[36] and $SmCl_3\cdot 6H_2O$.[37] In spite of a broad set of available activators, because of the existence of some defects in these methods such as high temperatures, low yields, rearrangement of epoxides and formation of by-products, long reaction times and need of high amount of catalysts, there is a scope for newer methods.

Recently, our group has introduced sulfated tungstate, a mild solid acid, as heterogeneous catalyst and has shown its usefulness in bringing about a variety of transformations, including amidation, by condensation between carboxylic acids and amines,[38] amidation by Ritter reaction[39] and N-formylation,[40] Biginelli,[41] Kindler,[42] Willgerodt–Kindler,[43] Strecker reactions,[44] and N-alkylations.[45] Key observation in all these investigations is that sulfated tungstate has good affinity towards oxygen containing substrates compared to amines, leading to selective activation and catalysis. These observations encouraged us to investigate epoxide opening reaction with amine in the presence of sulfated tungstate as catalyst and results are presented here. Preliminary investigations were carried out using cyclohexene oxide and aniline towards finding suitability of sulfated tungstate as a catalyst (Scheme 1) and optimize reaction conditions. The details of these investigations are presented in Table 1.

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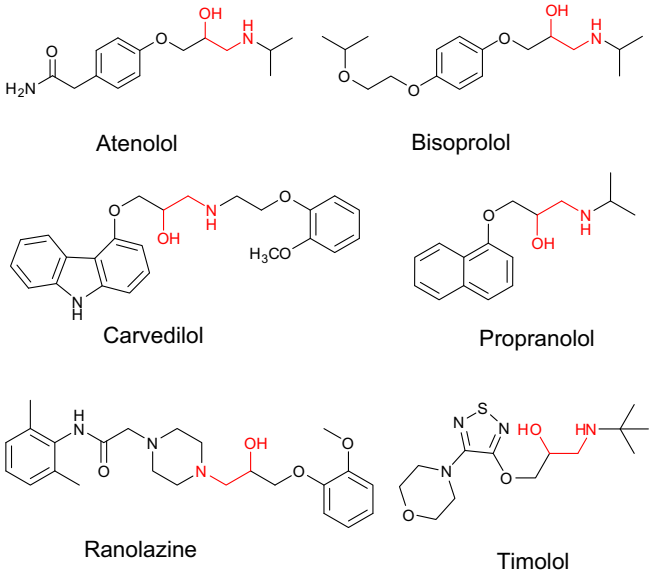
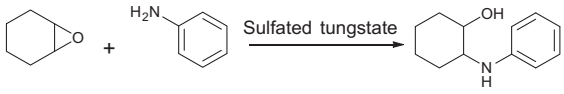


Figure 1. Examples of active pharmaceutical ingredients containing a β-amino alcohol unit.



Scheme 1. Epoxide opening of cyclohexene oxide with aniline.

Table 1
Results of optimization studies[a]

Entry	Solvent	Sulfated tungstate (wt%)	Time (min)	Yield[b] (%)
1	Neat	—	720	15
2	Neat	1	60	19
3	Neat	5	60	69
4	**Neat**	**10**	**15**	**96**
5	Neat	20	15	96
6	Ethyl acetate	20	60	90
7	Chloroform	20	60	62
8	Ethanol	20	60	79
9	Toluene	20	60	58

[a] Reaction conditions: cyclohexene oxide (1 g, 10.18 mmol) and aniline (0.95 g, 10.18 mmol) at 25 °C.
[b] Isolated yield.

Thus, when a mixture of cyclohexene oxide (1 equiv), aniline (1 equiv) and sulfated tungstate (10 wt%) was stirred at rt, a fast reaction ensued and got completed in just 15 min to give 96% yield of 2-(phenylamino)cyclohexanol (Table 1, entry 4). A control experiment was performed in the absence of catalyst and the reaction did not occur (Table 1, entry 1) thus proving the catalytic role of sulfated tungstate. Next, experiments were conducted to optimize quantity of sulfated tungstate and found that use of just 10 wt% of catalyst is sufficient to produce an excellent yield of the product in short reaction time (Table 1, entries 2–5). Regarding the use of solvent, ethyl acetate was found to be most suitable (Table 1, entry 6) and whereas other solvents such as chloroform, ethanol and toluene were found to be relatively inferior in terms of yield and time taken for the completion of reaction (Table 1, entries 7–9).

To assess the standing of sulfated tungstate among other catalysts for the formation of 2-(phenylamino)cyclohexanol, comparative experimental data were taken from the literature and is compiled in Table 2. Among the various catalysts *viz* amberlite, mesoporous aluminosilicate, sulfamic acid, montmorillonite K10 and sulfated zirconia, only sulfated tungstate was found to be the most efficient in terms of amount required, time and yield (Table 2, entries 1–6).

Table 2
Comparison of different catalysts for the formation of 2-(phenylamino)cyclohexanol[a]

Entry	Catalyst	Wt[b] (%)	Solvent	Temperature / Time in min	Yield[c] (%)
1	Amberlite	40	DCM	25 °C /150	89
2	Mesoporous aluminosilicate	60	DCM	25 °C /360	85
3	Sulfamic acid	16	Neat	70 °C /120	95
4	Montmorillonite K10	12	Neat	25 °C /60	95
5	Sulfated zirconia	17	Neat	25 °C /60	94
6	Sulfated tungstate	10	Neat	25 °C /15	96

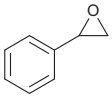
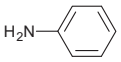
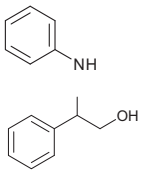
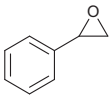
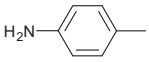
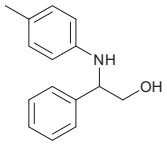
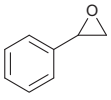
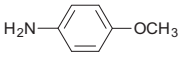
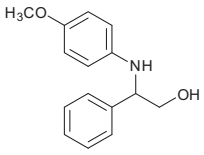
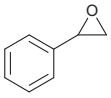
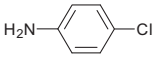
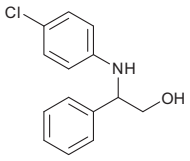
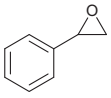
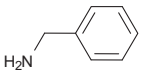
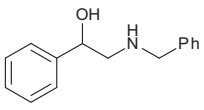
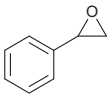
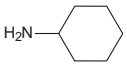
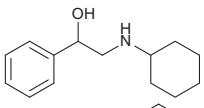
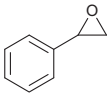
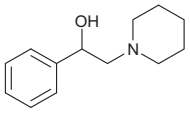
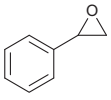
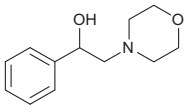
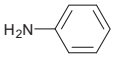
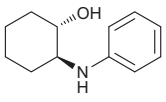
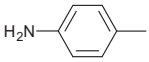
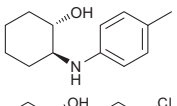
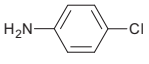
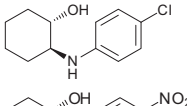
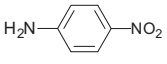
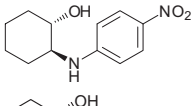
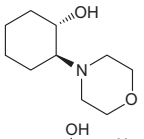
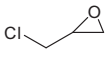
[a] Data were taken from the literature (Refs. 17–21).
[b] For ready comparison converted into wt %.
[c] Isolated yield.

With the optimized conditions in hand, a number of structurally diverse epoxides and amines were screened to demonstrate general applicability and efficacy of this protocol[46] and results are summarized in Table 3. To determine the regioselectivity, styrene oxide was used as a representative unsymmetrical epoxide and was treated with various aromatic and aliphatic amines in the presence of sulfated tungstate. During the reaction with aromatic amines, an exothermic reaction occurred, and the reaction was completed within 15 min (Table 3, entries 1–4) affording 86–92% yields of the β-amino alcohols. However in case of aliphatic amines, the reaction was slow and required heating to give β-amino alcohols in 87–90% yields at 70 °C for 30 min (Table 3, entries 5–8). This is attributed to interaction of strongly basic aliphatic amines with the catalyst resulting in reduced nucleophilicity. As far as regioselectivity of epoxide opening is concerned a complementarity was observed with aromatic and aliphatic amines. Reaction with aromatic amines afforded β-amino alcohols from nucleophilic attack at the benzylic position of the epoxide ring as the major products (Table 3, entries 1–4), whereas in case of aliphatic amines, the major/exclusive product was the regioisomeric amino alcohol produced by nucleophilic attack at the less hindered carbon atom of the epoxide ring (Table 3, entries 5–8). The ring opening of cyclohexene oxide was attempted with various aromatic and aliphatic amines. Excellent results were obtained in each case affording in high yields of the corresponding *trans*-2-aryl/alkylaminocyclo hexanols. The reactions were, in general, faster (15–45 min, rt) with aromatic amines compared to that for cyclic aliphatic amines (60 min, 70 °C) (Table 3, entries 9–13). Epichlorohydrin (Table 3, entries 14–17) and glycidyl ethers (Table 3, entries 18–20) reacted smoothly with amines to afford the corresponding β-amino alcohols in excellent yields with high regioselectivity. In both cases the main product was regioisomer arising out of attack at the less hindered carbon atom of the epoxide ring. The reaction with epichlorohydrin provided an example of excellent chemoselectivity and no product derived from nucleophilic substitution of the chlorine was formed.

Reusability study of the catalyst was performed, by following standard protocol previously reported by us,[39] and found that the catalyst was stable and reusable four times without any significant loss of activity with marginal drop in yield from 96% to 92% with respect to fresh and fourth recycle respectively (Table 4).

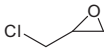
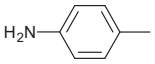
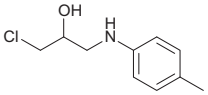
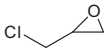
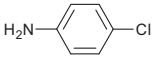
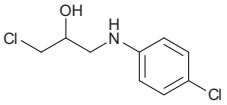
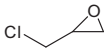
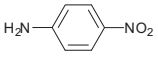
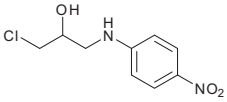
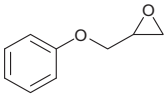
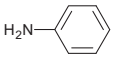
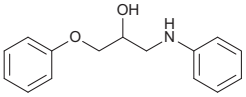
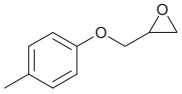
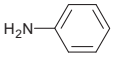
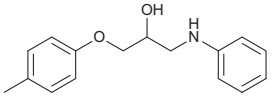
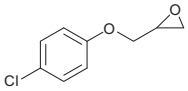
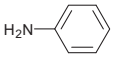
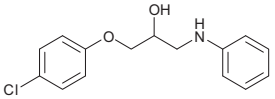
Applicability of the methodology is demonstrated for the synthesis of various β-adrenergic blocking agents such as atenolol, propranolol and ranolazine (Fig. 1). β-Adrenergic blocking agents are effective life-saving medicines in the management of cardiovascular disorders, including hypertension, angina pectoris, cardiac

Table 3
Epoxide opening reaction of various epoxide and amines in presence of sulfated tungstate[a]

Entry	Epoxide	Amine	Product	Temp/Time (min)	Yield[b]
1				25 °C/15	92
2				25 °C/15	91
3				25 °C/15	90
4				25 °C/15	86
5				70 °C/30	90
6				70 °C/30	89
7				70 °C/60	84
8				70 °C/60	87
9				25 °C/15	96
10				25 °C/15	95
11				25 °C/15	96
12				25 °C/45	82
13				70 °C/60	85
14				25 °C/15	92

(*continued on next page*)

Table 3 (*continued*)

Entry	Epoxide	Amine	Product	Temp/Time (min)	Yield[b]
15				25 °C /15	90
16				25 °C/15	89
17				25 °C/45	82
18				25 °C/15	92
19				25 °C/15	90
20				25 °C/15	92

[a] Reaction Conditions: epoxide (1 equiv), amine (1 equiv) and sulfated tungstate (10 wt%) under solvent-free at different temperatures.
[b] The major regioisomeric alcohol formed during the reaction of epoxide with amines was isolated by column chromatography. All the products are known and were identified by their melting point, IR and ^{1}H NMR spectra according to the literature.

Table 4
Reusability study[a]

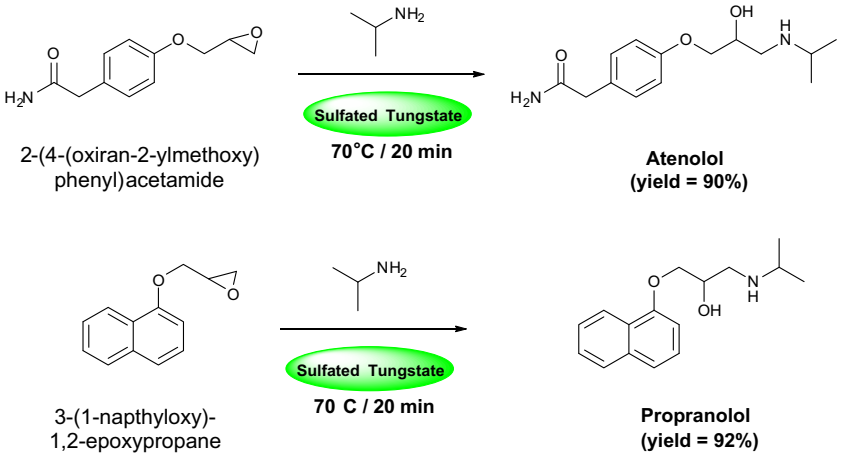
Run no[b]	Yield of 2-(phenylamino)cyclohexanol (%)
Fresh	96
First recycle	95
Second recycle	94
Third recycle	94
Fourth recycle	92

[a] Reaction conditions: cyclohexene oxide (1 g, 10.18 mmol) and aniline (0.95 g, 10.18 mmol) at 25 °C.
[b] Loss of catalyst (<5%) during handling.

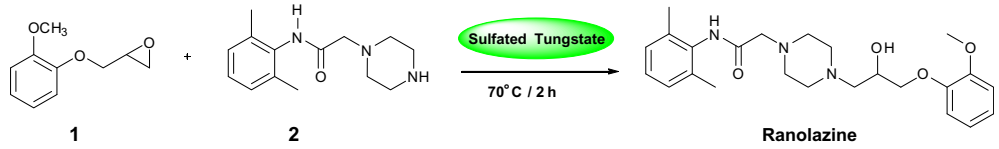
arrhythmias and other disorders related to the sympathetic nervous system and have had widespread and generally safe use for more than 25 years. Atenolol and propranolol are two of the top five best-selling drugs in the world today for the treatment of hypertension, angina pectoris and in the treatment of post myocardial infarction. We have extended our new protocol for epoxide ring opening with isoproylamine for a synthesis of atenolol and propranolol with yield of 90% and 92% respectively (Scheme 2).

Ranolazine offers a new approach for treating chronic angina pectoris. It was approved by the US FDA in January 2006 and launched in the US in March 2006 for patients who do not show adequate response to other anti-anginals and is the first drug of a novel class to be approved in the US in more than 20 years for treatment of this disease condition.[47] We employed our novel methodology based on sulfated tungstate for epoxide intermediate **1** opening by piperazine intermediate **2** to give ranolazine with a yield of 85% (Scheme 3).

The catalytic potential of sulfated tungstate for epoxide ring opening by amines to form β-amino alcohols has been assessed



Scheme 2. Synthesis of atenolol and proponolol.



Scheme 3. Synthesis of ranolazine.

and found to be a new and highly efficient catalyst. The notable features of this procedure are mild reaction conditions, excellent regioselectivity, cleaner reactions, high yields and simplicity in operation, which makes it a useful and attractive process for the synthesis of β-amino alcohols of biological and synthetic importance. Extension of this methodology was demonstrated for the synthesis of active pharmaceutical ingredients such as atenolol, propranolol and ranolazine.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.065.

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46. *Preparation of sulfated tungstate:* Anhydrous sodium tungstate (32.9 g, 0.1 mol) was added gradually, maintaining the temperature between 0 and 5 °C, to a stirred solution of chlorosulfonic acid (23.2 g, 0.2 mol) in chloroform (150 ml) contained in a 250 ml round bottomed flask placed in an ice bath. After completion of addition, the mixture was stirred further for 1 h. A yellowish-white solid obtained was filtered, washed repeatedly with deionized water until the filtrate was neutral and free from chloride ions (detected by $AgNO_3$ test) and dried in an oven for 2 h at 100 °C to get 34 g of sulfated tungstate. *General procedure for epoxide opening reaction:* Sulfated tungstate (10 wt%) was added to a solution of cyclohexene oxide (1 g, 10.18 mmol) and aniline (0.95 g, 10.18 mmol) in solvent-free condition and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate (15 ml) and filtered to recover the catalyst. Organic layer washed with water (10 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product which was purified by chromatography on silica gel (#60–120) with hexane-ethyl acetate (8:2) as eluent to get pure 2-(phenylamino) cyclohexanol as a white solid (Table 3, entry 9).
47. FDA labelling information, (a) http://www.fda.gov/News Events/Newsroom/PressAnnouncements/2006/ucm108587.htm; (b) http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021526s004lbl.pdf.